

RESEARCH MONOGRAPH . COMPOUND PROFILE

Urolithin-B

A monohydroxylated dibenzo[b,d]pyran-6-one produced by colonic microflora from dietary ellagitannins and ellagic acid, distinguished from the structurally related urolithin A by selective promotion of skeletal muscle protein synthesis via androgen receptor and mTORC1 signaling, and by protective activity against islet amyloid polypeptide proteotoxicity.

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ABSTRACT

Urolithin B (3-hydroxy-6H-dibenzo[b,d]pyran-6-one; CAS 1139-83-9) is one of the two principal terminal metabolites generated by human colonic microflora from dietary ellagitannins and ellagic acid, polyphenolic compounds abundant in pomegranates, walnuts, raspberries, strawberries, and certain tree nuts. Unlike its dihydroxylated isomer urolithin A (3,8-dihydroxyurolithin), which has advanced into human clinical trials primarily on the basis of mitophagy induction and mitochondrial quality control, urolithin B is distinguished by a pharmacological profile centered on skeletal muscle anabolism, neuroprotection through PI3K/Akt survival signaling, anti-inflammatory activity through NF-kappaB and NLRP3 inflammasome suppression, and a unique capacity to attenuate islet amyloid polypeptide (IAPP) proteotoxicity relevant to type 2 diabetes pathogenesis. The skeletal muscle activity, formally characterized by Rodriguez et al. (2017), demonstrated that urolithin B at 15 micromolar enhanced C2C12 myotube protein synthesis by 96.1 percent, increased myotube diameter and fusion index, suppressed the ubiquitin-proteasome degradation pathway, and operated through an androgen receptor to mTORC1 signaling axis independent of Akt phosphorylation. In vivo, 28-day subcutaneous delivery at 10 micrograms per day produced 11.9 percent increases in tibialis anterior muscle fiber cross-sectional area and significant preservation of muscle mass in denervation-induced atrophy models. The neuroprotective profile, characterized by Chen et al. (2021) in D-galactose-induced aging mice, demonstrated dose-dependent rescue of spatial and working memory deficits at oral doses of 50 to 150 mg/kg/day for 8 weeks, mediated by PI3K/Akt pathway activation, inhibition of

JNK/p38 apoptotic signaling, suppression of cytochrome c mitochondrial release, and restoration of hippocampal synaptic density markers PSD95 and synapsin I. Anti-inflammatory mechanisms, characterized in BV2 microglial cells by Lee et al. (2019), include suppression of NF-kappaB activation through reduced IkappaBalpha phosphorylation and degradation, attenuation of JNK, ERK, and Akt phosphorylation, enhancement of AMPK phosphorylation, and upregulation of heme oxygenase-1 through Nrf2/ARE signaling. Anticancer activity has been demonstrated in hepatocellular carcinoma (through Wnt/beta-catenin inactivation), osteosarcoma (G2/M arrest and MMP-2/-9 targeting), bladder cancer, leukemia, triple-negative breast cancer, and esophageal cancer cell lines. Bone-protective activity was reported in ovariectomy-induced osteoporosis models through inhibition of osteoclast formation via ERK/NF-kappaB suppression. The compound is produced endogenously only by individuals with the urolithin metabotype B (UM-B) gut microbiota profile, estimated at approximately 10 to 50 percent of the population depending on ethnicity and dietary pattern. Urolithin B undergoes extensive hepatic phase II conjugation to glucuronide and sulfate metabolites; circulating total urolithin concentrations in UM-B individuals following ellagitannin consumption range from 0.003 to 5.2 micromolar, with urinary excretion reaching up to 50 micromolar. No human clinical trials of exogenous urolithin B supplementation have been completed as of monograph preparation. The compound is available as a research-grade preparation from multiple chemical suppliers at greater than 95 percent purity. This monograph reviews the chemistry, biosynthesis, and structural class of urolithin B; the molecular pharmacology across muscle, neuronal, inflammatory, metabolic, and oncologic systems; the preclinical evidence base;

the pharmacokinetic and metabotype considerations; sourcing and quality verification; reconstitution and handling; stack interactions; adverse events and safety signals; and a comparative assessment of five structurally or functionally related compounds against urolithin B on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Systematic name: 3-Hydroxy-6H-dibenzo[b,d]pyran-6-one.

Common names: Urolithin B, Uro B, UB.

Chemical Abstracts Service registry number: 1139-83-9.

PubChem Compound Identifier: CID 5380406.

International Union of Pure and Applied Chemistry name: 3-hydroxy-6H-dibenzo[b,d]pyran-6-one. The compound belongs to the dibenzopyranone (benzo[c]chromenone) structural class and is classified as a coumarin derivative in the broader sense, though it lacks the 2H-chromen-2-one core of simple coumarins [1].

Other identifiers: The compound is referenced in the literature as 3-hydroxybenzo[c]chromen-6-one and as 3-hydroxycoumestan in some older classification schemes, though the coumestan designation is structurally imprecise. The InChI key is WXUQMTRHPNOXBV-UHFFFAOYSA-N. The SMILES string is O=C1OC2=C(C3=C1C=CC=C3)C=CC(O)=C2.

1.2 Structural class and chemistry

Urolithin B is a monohydroxylated dibenzo[b,d]pyran-6-one, the simplest of the urolithin family of gut microbiota metabolites. The urolithin class comprises a series of hydroxylated 6H-dibenzo[b,d]pyran-6-one derivatives produced by successive dehydroxylation of the ellagic acid lactone ring system by colonic bacteria [2]. The family includes urolithin D (tetrahydroxylated), urolithin C (trihydroxylated), urolithin A (3,8-dihydroxylated), isourolithin A (3,9-dihydroxylated), and urolithin B (3-monohydroxylated), with urolithin B representing the most extensively dehydroxylated terminal metabolite [3].

Molecular formula: C₁₃H₈O₃.

Exact mass: 212.0473 g/mol (monoisotopic).

Molecular weight: 212.20 g/mol.

Physical properties: Off-white to pale yellow crystalline powder. Soluble in dimethylformamide (30 mg/mL), dimethyl sulfoxide (30 mg/mL), and ethanol (30 mg/mL); sparingly soluble in water. Absorption maxima at 231, 279, and 304 nm in ethanol [4].

Stereochemistry: Urolithin B contains no stereocenters. The planar dibenzopyranone ring system is achiral, and the compound exists as a single constitutional isomer without enantiomeric or diastereomeric forms. This simplifies analytical verification relative to chiral natural products.

1.3 Biosynthesis and metabolic origin

The endogenous production of urolithin B occurs exclusively through gut microbiota catabolism of dietary ellagitannins and ellagic acid. The biosynthetic pathway proceeds through several stages [2, 3]:

First, dietary ellagitannins (punicalagin from pomegranate, pedunculagin from walnuts, sanguiin H-6 from raspberries, and related structures) undergo acid hydrolysis in the stomach and enzymatic hydrolysis in the small intestine to release free ellagic acid.

Second, ellagic acid reaches the colon largely intact owing to poor absorption in the upper gastrointestinal tract. In the colon, specific bacterial taxa (principally members of the Eggerthellaceae family, including *Gordonibacter*, *Ellagibacter*, and related genera) catalyze the sequential loss of one lactone ring and progressive dehydroxylation [5]. The pathway proceeds from ellagic acid through urolithin M-5, urolithin M-6, urolithin D, urolithin C, urolithin A, isourolithin A, and finally urolithin B.

Third, the capacity to produce urolithin B defines a specific gut microbiota metabotype designated UM-B [5]. Individuals with UM-B microbiota produce both urolithin A and urolithin B (and often isourolithin A), while UM-A individuals produce predominantly urolithin A without significant urolithin B. A third group, UM-0, produces no detectable urolithins. The UM-B phenotype is estimated to represent approximately 10 to 50 percent of the population depending on ethnicity, diet, and age [5]. The bacterial genera associated with UM-B metabolism include *Ellagibacter*, *Senegalimassilia*, *Slackia*, and *Adlercreutzia*, all members of the Eggerthellaceae family.

1.4 Chemical synthesis

Chemical synthesis of urolithin B has been accomplished through several approaches. The most straightforward route proceeds from commercially available starting materials through intramolecular lactonization of appropriately substituted 2-(2-hydroxyphenyl)benzoic acid precursors. The dibenzopyranone ring closure can be achieved under Friedel-Crafts conditions or through palladium-catalyzed intramolecular C-H activation. Yields are moderate to good (50 to 80 percent for the cyclization step) [6]. Regioselective glucuronidation of synthetic urolithin B has been optimized for the preparation of phase II metabolite standards, with high yields reported for the O-beta-D-glucuronide conjugate [7]. The compound is commercially available from multiple suppliers in milligram to gram quantities at greater than 95 percent purity, making total synthesis unnecessary for most research applications.

2. Abstract

Urolithin B (3-hydroxy-6H-dibenzo[b,d]pyran-6-one) is a monohydroxylated dibenzopyranone generated by sequential microbial dehydroxylation of ellagic acid in the human colon, representing the terminal and most extensively modified metabolite in the urolithin family [2, 3]. The compound has emerged as a research target of considerable interest across several pharmacological domains, distinguished from the better-studied urolithin A by a unique profile of skeletal muscle anabolic activity, IAPP amyloid inhibition, and neuroprotective signaling that does not depend on the mitophagy induction pathway central to urolithin A pharmacology.

The skeletal muscle application is the most rigorously characterized. Rodriguez et al. (2017) demonstrated that urolithin B at 15 micromolar increased C2C12 myotube protein synthesis by 96.1 percent (comparable to the 61.5 percent increase produced by insulin), enhanced myotube diameter and fusion index, and repressed the ubiquitin-proteasome protein degradation pathway through downregulation of the muscle-specific E3 ligases MAFbx and MuRF1 [8]. The mechanism operates through the androgen receptor (genetic knockdown and pharmacological blockade with bicalutamide abolished the effect) with downstream activation of mTORC1 and rpS6 phosphorylation, independent of Akt. In vivo, 28-day subcutaneous delivery at 10 micrograms per day in mice produced significant hypertrophy of the tibialis anterior (11.9 percent increase in fiber cross-sectional area), quadriceps, and soleus muscles, and reduced denervation-induced atrophy across multiple muscle groups [8]. Notably, urolithin A at identical concentrations produced no effect on myotube diameter or protein synthesis, establishing a clear isomer-specific pharmacological distinction.

The neuroprotective application was characterized by Chen et al. (2021) in D-galactose-induced aging mice, where oral urolithin B at 50 to 150 mg/kg/day for 8 weeks produced dose-dependent rescue of Morris water maze, Y-maze, and open field performance, restored hippocampal neuronal density and synaptic marker expression (PSD95, synapsin I), and activated PI3K/Akt survival signaling while suppressing JNK/p38 apoptotic pathways and cytochrome c release [9]. The anti-inflammatory mechanism in the central nervous system was further detailed by Lee et al.

(2019) in LPS-stimulated BV2 microglial cells, demonstrating NF-kappaB suppression through IkappaBalpha stabilization, AMPK activation, and Nrf2/ARE-dependent upregulation of heme oxygenase-1 [10].

The anti-diabetic application was characterized by Savastano et al. (2022), who demonstrated that urolithin B, but not urolithin A at equivalent concentrations, conferred protection against IAPP proteotoxicity by reshaping low-order oligomeric species into less toxic aggregates and by activating autophagy, mitochondrial maintenance, and redox homeostasis pathways [11].

Anticancer activity has been reported across multiple tumor types: hepatocellular carcinoma (Wnt/beta-catenin pathway inactivation) [12], osteosarcoma (G2/M arrest, MMP-2/-9 suppression) [13], bladder cancer (cell cycle arrest and apoptosis induction) [14], leukemia (metabolic reprogramming and apoptosis) [15], triple-negative breast cancer (cytotoxicity and migration suppression) [16], and esophageal cancer [17]. Bone-protective effects were demonstrated in ovariectomy-induced osteoporosis through suppression of osteoclastogenesis via ERK/NF-kappaB pathway inhibition [18]. Spinal cord injury recovery was promoted through NLRP3 inflammasome inhibition and M1/M2 microglial polarization modulation [19].

No human clinical trials of exogenous urolithin B supplementation have been completed. The endogenous pharmacokinetic profile is characterized by extensive hepatic phase II conjugation to glucuronide and sulfate metabolites, with total circulating urolithin concentrations of 0.003 to 5.2 micromolar in UM-B individuals following dietary ellagitannin consumption [5]. The compound is available as a research-grade preparation from multiple suppliers and represents a candidate for translational investigation in sarcopenia, age-related cognitive decline, type 2 diabetes, and inflammatory conditions.

3. Discovery and Development History

3.1 Identification as a gut metabolite

The urolithin class was first identified as a product of ellagic acid metabolism by human colonic microflora in the early 2000s. Cerda et al. (2005) formally characterized urolithin A and urolithin B as the principal terminal metabolites of ellagic acid in human fecal incubations and in urine and plasma following pomegranate juice consumption, establishing the gut microbiota origin of the compound class [3]. Earlier work by Doyle and Griffiths (1955) had identified related dibenzopyranone structures in animal studies, but the systematic characterization of the urolithin metabolic pathway, including the intermediate urolithins C, D, M-5, and M-6, was completed by the Tomas-Barberan and Espin laboratories at the Spanish National Research Council (CEBAS-CSIC) through a series of publications from 2004 to 2013 [2, 3, 5].

3.2 Metabotype classification

The concept of urolithin metabolotypes was formalized by Tomas-Barberan et al. (2014), who classified individuals into three groups based on their urolithin production profile following ellagitannin consumption: UM-A (producers of urolithin A conjugates only), UM-B (producers of urolithin A, isourolithin A, and urolithin B conjugates), and UM-0 (non-producers) [5]. This classification was subsequently linked to specific gut bacterial taxa, with UM-A individuals enriched in *Gordonibacter* and *Paraeggerthella* species and UM-B individuals additionally harboring *Ellagibacter* and *Senegalimassilia* species capable of the final dehydroxylation step that produces urolithin B. The metabotype concept has implications for bioavailability, inter-individual variability in response to ellagitannin-rich diets, and for the design of clinical investigations.

3.3 Expansion of the pharmacological literature

Beginning approximately 2015, the research literature on urolithin B expanded beyond its characterization as a dietary metabolite into active pharmacological investigation. The Rodriguez et al. (2017) demonstration of skeletal muscle anabolic ac-

tivity represented a significant inflection point, as it established urolithin B as a distinct pharmacological entity with activity profiles not shared by the better-studied urolithin A [8]. This was followed by the Lee et al. (2019) characterization of anti-inflammatory mechanisms in microglia [10], the Chen et al. (2021) neuroprotection study in aging mice [9], the Savastano et al. (2022) IAPP proteotoxicity study [11], and a series of anticancer reports across multiple tumor types between 2017 and 2025 [12, 13, 14, 15, 16, 17]. The bone-protective activity was reported by Tan et al. (2022) [18], and the spinal cord injury application was characterized in 2025 [19].

3.4 Current development status

Urolithin B has not entered formal pharmaceutical development. Unlike urolithin A, which has been formulated as the proprietary preparation Mitopure (Timeline/Amazentis) and has completed multiple human clinical trials for mitochondrial and muscle health endpoints with FDA Generally Recognized as Safe (GRAS) status, urolithin B remains at the preclinical research stage. No investigational new drug applications, clinical trial registrations, or commercial development programs for urolithin B have been identified as of monograph preparation. The compound is positioned as a research tool and a candidate for translational investigation, with the skeletal muscle, neuroprotective, and anti-diabetic applications representing the most mature preclinical evidence bases.

4. Mechanism of Action

Urolithin B is a multi-target bioactive compound. Its principal molecular activities, characterized in cell-based systems and confirmed in rodent models, span skeletal muscle anabolism, neuroprotection, anti-inflammatory signaling, antioxidant defense, anti-amyloidogenic activity, and anticancer mechanisms. These activities operate through distinct but partially overlapping signaling cascades.

4.1 Skeletal muscle anabolism via androgen receptor and mTORC1

The skeletal muscle activity of urolithin B was characterized by Rodriguez et al. (2017) using differentiated C2C12 myotubes and confirmed in vivo in mice [8]. The molecular mechanism involves:

Androgen receptor activation: Urolithin B enhances muscle protein synthesis through a pathway that requires the androgen receptor (AR). siRNA knockdown of the AR in C2C12 myotubes completely abolished the protein synthesis enhancement. Pharmacological blockade with the AR antagonist bicalutamide similarly prevented the effect. The compound does not alter circulating testosterone levels in vivo, suggesting direct ligand or co-activator activity at the receptor rather than steroidogenic modulation.

mTORC1/rpS6 signaling: Downstream of AR activation, urolithin B increases phosphorylation of the mammalian target of rapamycin (mTOR) and its effector ribosomal protein S6 (rpS6). This activation promotes cap-dependent mRNA translation and ribosome biogenesis, the principal drivers of muscle protein synthesis.

AMPK dephosphorylation: Urolithin B reduces AMPK phosphorylation by 42.2 percent, suggesting that the compound relieves the AMPK-mediated inhibition of mTORC1 that normally suppresses anabolic signaling under energy stress conditions [8]. AMPK may therefore serve as an intermediate link between AR activation and mTORC1 disinhibition.

Ubiquitin-proteasome suppression: The compound reduces ubiquitinated protein levels by 22.1 percent and decreases mRNA expression of the muscle-specific E3 ubiquitin ligases MAFbx (atrogin-1) and MuRF1 [8]. Downregulation of FoxO1 and FoxO3a transcription factor expression contributes to the suppressed atrogene program. The net result is simultaneous promotion of protein synthesis and repression of protein degradation.

Akt independence: Unlike insulin and insulin-like growth factor 1 signaling, the urolithin B anabolic pathway does not require Akt phosphorylation, establishing a mechanistically distinct route to mTORC1 activation.

4.2 Neuroprotection via PI3K/Akt and anti-apoptotic signaling

The neuroprotective mechanism was characterized by Chen et al. (2021) in D-galactose-induced aging mice and involves multiple convergent pathways [9]:

PI3K/Akt activation: Urolithin B stimulates phosphoinositide 3-kinase (PI3K) activity and promotes Akt phosphorylation at both Thr308 and Ser473, the two regulatory phosphorylation sites that confer full kinase activity. The activated Akt promotes neuronal survival through phosphorylation and inactivation of the pro-apoptotic protein Bad at Ser112 and Ser136, sequestering Bad in the cytoplasm bound to 14-3-3 proteins and preventing its translocation to mitochondria.

Cytochrome c retention: By maintaining mitochondrial membrane integrity through Bad inactivation, urolithin B prevents cytochrome c release from the intermembrane space to the cytosol, blocking activation of the intrinsic (mitochondrial) apoptotic pathway and downstream caspase activation.

JNK/p38 suppression: Urolithin B suppresses phosphorylation of the stress-activated kinases JNK and p38 MAPK, which are chronically elevated in aging brain tissue and promote neuronal apoptosis through transcriptional activation of pro-apoptotic genes and direct phosphorylation of mitochondrial targets.

AGE reduction: The compound reduces mRNA expression of advanced glycation end products (AGEs), carboxymethyllysine (CML), and carboxyethyllysine (CEL) in aging brain tissue [9]. AGE accumulation is a hallmark of brain aging and contributes to neuroinflammation and neuronal dysfunction through receptor for advanced glycation end products (RAGE) signaling.

Synaptic restoration: Urolithin B treatment restores expression of the postsynaptic density protein PSD95 and the presynaptic vesicle protein synapsin I, and increases dendritic spine density as assessed by Golgi staining [9]. These structural and molecular markers of synaptic integrity are degraded in aging and in neurodegenerative disease.

4.3 Anti-inflammatory signaling via NF-kappaB and NLRP3

The anti-inflammatory mechanism has been characterized in multiple cell types and in vivo models:

NF-kappaB pathway inhibition: In LPS-stimulated BV2 microglial cells, urolithin B inhibits NF-kappaB activity by reducing the phosphorylation and proteasomal degradation of IkappaBalpha, the inhibitory subunit that sequesters NF-kappaB dimers in the cytoplasm [10]. The consequence is reduced nuclear translocation of NF-kappaB and decreased transcription of pro-inflammatory genes encoding TNF-alpha, IL-6, IL-1beta, iNOS, and COX-2.

MAPK suppression: Urolithin B suppresses phosphorylation of JNK, ERK, and p38, the three principal branches of the mitogen-activated protein kinase signaling cascade that converge on AP-1-driven inflammatory gene transcription [10].

AMPK activation: In contrast to the AMPK dephosphorylation observed in muscle cells, urolithin B enhances AMPK phosphorylation in microglial and macrophage contexts [10]. This difference likely reflects cell-type-specific signaling contexts, with AMPK activation in immune cells promoting anti-inflammatory and antioxidant gene programs through downstream effects on SIRT1 and PGC-1alpha.

NLRP3 inflammasome inhibition: In spinal cord injury models, urolithin B inhibited the NLRP3/Caspase-1/IL-1beta signaling axis and promoted M2 (anti-inflammatory) microglial polarization while suppressing M1 (pro-inflammatory) polarization [19]. The NLRP3 inflammasome is a multiprotein complex that senses cellular stress signals and drives pyroptotic cell death and IL-1beta/IL-18 maturation.

Nrf2/ARE antioxidant signaling: Urolithin B upregulates heme oxygenase-1 (HO-1) expression through activation of nuclear factor erythroid 2-related factor 2 (Nrf2) and its binding to the antioxidant response element (ARE) in the HO-1 promoter

[10]. The compound also reduces intracellular ROS production and NADPH oxidase subunit expression.

Cholestatic liver injury protection: In unilateral bile duct ligation models, urolithin B mitigated cholestatic liver injury through simultaneous activation of PPARalpha and Nrf2 antioxidant signaling and suppression of NF-kappaB pro-inflammatory signaling [20].

4.4 Anti-amyloidogenic activity against IAPP

The anti-IAPP activity was characterized by Savastano et al. (2022) and represents a pharmacological action unique to urolithin B within the urolithin family [11]:

Aggregation modulation: Urolithin B delays the formation of IAPP amyloid fibrils and alters the size and morphology of the resulting aggregates. The compound reshapes low-order oligomeric species (the most cytotoxic intermediates) and the pre-amyloid fibers, leading to formation of less toxic aggregate morphologies.

Autophagy activation: Genome-wide transcriptomic analysis and functional validation identified autophagy as a critical mediator of urolithin B protection against IAPP proteotoxicity. The compound activates protein clearance pathways that facilitate removal of toxic IAPP aggregates.

Mitochondrial and redox maintenance: Urolithin B maintains mitochondrial membrane potential and function in the face of IAPP-induced proteotoxic stress, and sustains cellular redox homeostasis. These effects rescue the mitochondrial dysfunction and oxidative damage that characterize IAPP-mediated beta-cell death in type 2 diabetes pathogenesis.

Isomer specificity: Urolithin A did not confer significant protection against IAPP proteotoxicity under the same experimental conditions, regardless of concentration or attempts to enhance cell permeability [11]. This established urolithin B as the active urolithin species for this target.

4.5 Anticancer mechanisms

Urolithin B exerts antiproliferative and pro-apoptotic effects across multiple cancer cell types through several pathways:

Wnt/beta-catenin inactivation: In hepatocellular carcinoma cells, urolithin B inhibits proliferation through cell cycle arrest and apoptosis driven by inactivation of the canonical Wnt/beta-catenin signaling pathway [12]. Beta-catenin nuclear translocation and transcription of Wnt target genes (cyclin D1, c-Myc) are suppressed.

G2/M cell cycle arrest: In osteosarcoma MG-63 cells, urolithin B induces G2/M arrest, promotes late apoptosis and necrosis, generates reactive oxygen species, and suppresses matrix metalloproteinase expression (MMP-2 and MMP-9), reducing migratory and invasive capacity [13].

Metabolic reprogramming: In leukemic K562 and Jurkat cells, urolithin B treatment altered cellular metabolism and induced metabolites associated with apoptosis, with 50 to 70 percent apoptosis induction at tested concentrations [15].

Regulation of tumor suppressors and oncogenes: Across multiple cancer cell types, urolithins regulate p21, p53, c-Myc, CDKN1A, RB1, and AKT expression, establishing a broadly applicable anticancer gene expression signature [14, 16, 17].

4.6 Bone-protective activity

Urolithin B suppressed osteoclast formation and activation in ovariectomy-induced osteoporosis models through downregulation of the ERK/NF-kappaB signaling pathway [18]. The effect reduced bone loss in ovariectomized mice, suggesting potential application in postmenopausal osteoporosis and other conditions of accelerated bone resorption.

5. Pharmacokinetics and Routes of Administration

5.1 Endogenous production and absorption

Urolithin B is generated in the colon from dietary ellagitannins through microbial catabolism. The production is confined to individuals with the UM-B gut microbiota phenotype and is dependent on the presence of bacterial taxa capable of the final dehydroxylation step from urolithin A to urolithin B [5]. Production begins approximately 24 to 48 hours after ellagitannin ingestion, reflecting the transit time to the colon and the sequential enzymatic processing.

Absorption of urolithin B from the colon occurs through passive transcellular diffusion, facilitated by the compound's moderate lipophilicity. The absorbed compound enters the portal circulation and is transported to the liver for phase II conjugation. Systemic bioavailability of the free aglycone is low owing to extensive first-pass metabolism.

5.2 Distribution

Following absorption, urolithin B distributes to multiple tissues. Detection in plasma, urine, feces, breastmilk, and in organ tissues including prostate, colon, breast, and heart has been reported for urolithins and their conjugated metabolites [5]. Animal studies have demonstrated preferential accumulation of urolithin B in cardiac tissue, consistent with the cardiovascular protective effects reported in pre-clinical models. The compound crosses the blood-brain barrier, as evidenced by the central nervous system effects observed in aging mouse models at oral doses [9].

Total circulating urolithin concentrations in UM-B individuals following ellagitannin consumption typically range from 0.003 to 5.2 micromolar, with considerable inter-individual variability dependent on metabotype, dietary dose, and the specific ellagitannin source [5]. Urinary excretion of total urolithins can reach up to 50 micromolar. Conjugated forms (glucuronides and sulfates) predominate in systemic circulation, with free (unconjugated) urolithin B present at trace levels.

5.3 Metabolism

Urolithin B undergoes extensive hepatic phase II metabolism. The principal metabolic transformations are:

Glucuronidation: Uridine diphosphate glucuronosyltransferases (UGTs) catalyze conjugation of the 3-hydroxyl group with glucuronic acid, producing urolithin B-3-O-glucuronide, the predominant circulating metabolite.

Sulfation: Sulfotransferases (SULTs) catalyze conjugation with sulfate at the 3-hydroxyl, producing urolithin B-3-O-sulfate.

The conjugated metabolites retain some biological activity but at reduced potency compared to the free aglycone. Incubation of urolithin B glucuronide with neonatal rat ventricular cardiomyocytes under hyperglycemic conditions produced significant reductions in inflammatory markers, indicating that conjugated forms are not biologically inert [1]. Enterohepatic recirculation through biliary excretion and bacterial deconjugation in the colon may regenerate the free aglycone and extend the effective exposure window.

5.4 Elimination

Urolithin B and its conjugated metabolites are excreted primarily through the kidneys. The plasma detection window extends approximately 3 to 4 days after a single dietary ellagitannin exposure, reflecting the combination of continued colonic production, enterohepatic recirculation, and renal clearance of conjugated metabolites [1]. Fecal excretion of unconjugated urolithins also occurs, representing unabsorbed colonic production.

5.5 Routes of administration in research

Oral gavage: The principal route in rodent studies. Doses of 50 to 150 mg/kg/day by oral gavage for 8 weeks produced neuroprotective effects in aging mice [9].

Subcutaneous osmotic pump: Rodriguez et al. (2017) delivered urolithin B at 10 micrograms per day via subcutaneous mini-osmotic pumps, achieving steady-state plasma concentrations of approximately 1.3 micromolar [8]. This route bypasses first-pass hepatic metabolism and provides sustained exposure.

In vitro concentrations: Cell-based studies typically employ 5 to 50 micromolar urolithin B, with 15 micromolar representing the optimal concentration for myotube anabolic effects [8] and 5 to 10 micromolar for anti-inflammatory effects in colonic fibroblasts [1].

Dietary exposure: Endogenous production from ellagitannin-rich foods (pomegranate juice, walnuts, raspberries) in UM-B individuals produces the physiological concentrations described in section 5.2.

5.6 Special populations

No formal pharmacokinetic studies in special populations have been conducted for exogenous urolithin B. The UM-0 population (non-producers of any urolithins) would receive no endogenous exposure from dietary sources and would require exogenous supplementation to achieve any urolithin B exposure. Pediatric and geriatric pharmacokinetics have not been characterized. Pregnancy and lactation data are limited to the observation that urolithins have been detected in human breastmilk.

6. Preclinical Pharmacology

6.1 Skeletal muscle anabolism

The Rodriguez et al. (2017) study is the foundational preclinical report on urolithin B muscle activity [8]. In differentiated C2C12 myotubes treated with 15 micromolar urolithin B for 24 hours, protein synthesis (measured by SUnSET puromycin incorporation) increased by 96.1 percent ($p < 0.001$), exceeding the 61.5 percent increase produced by insulin. Myotube mean diameter increased significantly, and the fusion index (proportion of multinucleated cells) increased by 16.3 percent, indicating enhanced differentiation. Protein degradation decreased by 16.7 percent ($p < 0.001$). Myogenin and desmin expression increased, consistent with differentiation marker upregulation.

In vivo, male mice receiving 10 micrograms per day of urolithin B via subcutaneous osmotic pump for 28 days showed 11.9 percent increases in tibialis anterior fiber cross-sectional area, significant weight increases in quadriceps, soleus, and tibialis anterior muscles, and a shift in fiber size distribution toward larger fibers. Puromycin incorporation was elevated in tibialis anterior ($p < 0.01$) and soleus ($p < 0.01$).

In female mice subjected to sciatic nerve transection (denervation atrophy model), urolithin B treatment preserved muscle weight ratios (denervated/innervated) in the tibialis anterior, extensor digitorum longus, soleus, and quadriceps. The soleus (a predominantly slow-twitch muscle) showed the largest atrophy reduction. At day 3 post-denervation, mRNA expression of FoxO1, FoxO3a, MAFbx, MuRF1, and myostatin was reduced by approximately 20 percent in treated animals [8].

Critically, urolithin A at identical concentrations and durations produced no measurable effect on myotube diameter, protein synthesis, or protein degradation, establishing the isomer-specific nature of the anabolic activity.

6.2 Neuroprotection in aging models

Chen et al. (2021) administered urolithin B at 50, 100, and 150 mg/kg/day by oral gavage for 8 weeks to D-galactose-treated aging-model mice [9]. Behavioral testing demonstrated dose-dependent rescue:

Morris water maze escape latency was significantly prolonged in D-galactose mice ($F(4,55) = 15.51$, $p < 0.01$) and improved with urolithin B treatment. Probe trial target quadrant time and platform crossings increased significantly (both $p < 0.01$). Y-maze spontaneous alternation and novel arm entries improved. Open field central zone exploration increased, suggesting reduced anxiety-like behavior.

Histological assessment revealed near-complete restoration of hippocampal structure by high-dose (150 mg/kg) urolithin B. Nissl body recovery was significant ($F(4,25) = 53.43$, $p < 0.01$). NeuN-positive neuron counts increased substantially ($F(4,25) = 68.17$, $p < 0.01$). Dendritic spine density recovered in Golgi-stained preparations. PSD95 ($F(4,10) = 120.76$, $p < 0.01$) and synapsin I ($F(4,10) = 171.45$, $p < 0.01$) expression was restored.

Molecular analysis confirmed PI3K/Akt activation (Akt phosphorylation at Thr308 and Ser473, both $p < 0.01$), JNK/p38 suppression (both $p < 0.01$), Bad phosphorylation at Ser112 and Ser136 (both $p < 0.01$), cytochrome c retention in mitochondria, and reduced AGE expression. Antioxidant enzymes Cu,Zn-SOD and catalase were elevated, while malondialdehyde (a lipid peroxidation marker) was reduced. Glial activation markers GFAP (astrocytes) and IBA1 (microglia) were significantly decreased [9].

6.3 Anti-inflammatory activity in microglia

Lee et al. (2019) characterized urolithin B in BV2 microglial cells stimulated with LPS, lipoteichoic acid (LTA), and polyinosinic-polycytidylic acid (poly(I:C)) [10]. Urolithin B inhibited NO, TNF- α , and IL-6 production across all three stimulation paradigms, indicating that the anti-inflammatory effect is not restricted to a single toll-like receptor pathway. IL-10 (anti-inflammatory) production was increased. The effect was mediated through NF- κ B (IkappaB α stabilization), MAPK (JNK, ERK, Akt phosphorylation suppression), AMPK (phosphorylation enhancement), and Nrf2/ARE (HO-1 upregulation) signaling. In vivo validation in LPS-injected mouse brain confirmed the microglial modulation.

6.4 IAPP proteotoxicity protection

Savastano et al. (2022) demonstrated that urolithin B, but not urolithin A, protected cells against IAPP aggregation-induced toxicity relevant to type 2 diabetes [11]. The compound delayed amyloid fibril formation, reshaped oligomeric intermediates into less toxic morphologies, and activated autophagy, mitochondrial maintenance, and redox homeostasis pathways. Genome-wide transcriptomic analysis identified autophagy as the principal protective mechanism, with functional validation confirming its requirement for urolithin B-mediated rescue of IAPP-induced cell dysfunction and death.

6.5 Anticancer activity

Hepatocellular carcinoma: Urolithin B suppressed proliferation of HCC cells through cell cycle arrest and apoptosis, mediated by inactivation of Wnt/beta-catenin signaling [12]. Beta-catenin nuclear accumulation was reduced, and downstream target genes cyclin D1 and c-Myc were downregulated.

Osteosarcoma: In MG-63 cells, urolithin B induced G2/M arrest, promoted late apoptosis and necrosis, elevated ROS generation, and suppressed MMP-2 and MMP-9 expression, inhibiting both proliferation and migration [13].

Bladder cancer: In UMUC3 cells, urolithins impaired proliferation, arrested the cell cycle, and induced apoptosis [14].

Leukemia: In K562 and Jurkat cells, urolithin B altered cellular metabolism and induced metabolites associated with apoptosis, with 50 to 70 percent apoptosis induction [15].

Triple-negative breast cancer: Urolithin B was cytotoxic to MDA-MB-231 cells and suppressed cell migration in scratch assays [16].

Esophageal cancer: Both urolithins A and B induced apoptosis and caused G2/M cell cycle arrest in KYSE-30 and YM-1 cells, with urolithin A showing greater potency [17].

Lung adenocarcinoma: Urolithin B liposome formulations demonstrated anti-tumor effects, suggesting that nanoparticle delivery may enhance the anticancer efficacy of the compound [21].

6.6 Bone protection

Tan et al. (2022) reported that urolithin B suppressed osteoclast formation and activation in ovariectomy-induced osteoporosis through downregulation of ERK and NF-kappaB signaling [18]. In ovariectomized mice, urolithin B treatment attenuated bone loss, with reduced osteoclast numbers on bone surfaces and preserved trabecular bone architecture.

6.7 Spinal cord injury

In 2025, urolithin B was reported to promote functional recovery from spinal cord injury by alleviating neuroinflammation through inhibition of the NLRP3/Caspase-1/IL-1beta signaling pathway [19]. The compound promoted nerve regeneration, regulated M1/M2 microglial polarization toward the anti-inflammatory M2 phenotype, and reduced glial scar formation.

6.8 Cardiovascular protection

Urolithin B decreased fractalkine levels (a pro-inflammatory chemokine affecting myocardial function) in streptozotocin-induced diabetic cardiomyopathy rat models. Fourteen-day continuous administration improved CD68-positive macrophage infiltration after myocardial infarction and reduced CD68 mRNA expression in post-infarction hearts [1]. Urolithin B glucuronide, the principal circulating conjugate, retained anti-inflammatory activity in neonatal rat ventricular cardiomyocytes under hyperglycemic conditions.

7. Clinical Evidence Base

7.1 Absence of direct clinical trials

No human clinical trials of exogenous urolithin B supplementation have been completed or registered as of monograph preparation. The clinical evidence for urolithin B is therefore indirect, deriving from observational studies of urolithin metabolotypes and from the clinical trial literature on the closely related urolithin A.

7.2 Metabotype-based observational evidence

Epidemiological and dietary intervention studies have characterized the urolithin metabolotype distribution in human populations and correlated metabolotype with health outcomes. The UM-B phenotype (producers of urolithin B in addition to urolithin A) has been associated with specific gut microbiota compositions enriched in Eggerthellaceae family members [5]. Associations between UM-B status and cardiometabolic risk markers have been reported, though the direction and magnitude of these associations are not consistent across studies and are confounded by the broader dietary and microbiome differences between metabolotype groups.

7.3 Urolithin A clinical data as translational context

The clinical trial literature for urolithin A provides relevant context for urolithin B translational expectations:

Urolithin A (as Mitopure, Timeline/Amazentis) has completed multiple human clinical trials at doses of 250 to 1000 mg/day for 28 days to 4 months in healthy middle-aged and older adults [22]. These studies demonstrated dose-dependent anti-inflammatory effects, upregulation of mitochondrial genes, markers of autophagy and fatty acid oxidation, and improvements in muscle endurance biomarkers. Urolithin A received FDA GRAS status.

The clinical safety profile of urolithin A provides a partial basis for predicting urolithin B tolerability, given the structural similarity (differing by one hydroxyl group). However, the distinct pharmacological profiles of the two isomers

(urolithin A: mitophagy-centric; urolithin B: anabolic/AR-centric) indicate that safety and efficacy translation between the two compounds should not be assumed without direct clinical investigation.

7.4 Rationale for clinical investigation

The preclinical evidence base supports investigation of urolithin B in several clinical contexts:

Sarcopenia and muscle wasting: The anabolic activity via androgen receptor/mTORC1, the anti-atrophy effects in denervation models, and the absence of circulating testosterone elevation suggest a potential application in age-related sarcopenia, disuse atrophy, and disease-related cachexia without the androgenic side effects of conventional anabolic agents.

Age-related cognitive decline: The neuroprotective effects in aging mice, including restoration of hippocampal synaptic markers and behavioral performance, support investigation in mild cognitive impairment and early-stage neurodegenerative conditions.

Type 2 diabetes: The IAPP proteotoxicity protection and the anti-inflammatory/antioxidant profile suggest potential application in preserving beta-cell function in type 2 diabetes.

8. Sourcing and Quality Verification

Research-grade urolithin B is available from multiple chemical and biochemical research suppliers at greater than 95 percent purity. Principal sources include:

Sigma-Aldrich (catalog SML1649; greater than or equal to 95 percent purity by HPLC). Cayman Chemical (catalog 33757). Santa Cruz Biotechnology (CAS 1139-83-9). Selleck Chemicals (marketed as an NF-kappaB inhibitor). MedChemExpress (marketed as an NF-kappaB inhibitor). BOC Sciences (CAS 1139-83-9).

Supply is available in milligram to gram quantities as the free phenol. Pricing is moderate, typically in the range of \$30 to \$150 per 50 to 100 milligrams of greater than 95 percent material at the time of monograph preparation. Larger quantities (gram scale) are available from bulk suppliers at reduced per-unit cost.

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

- High-performance liquid chromatography (HPLC) area-percent purity, targeting greater than 95 percent (greater than 98 percent preferred for dose-response studies)
- Mass spectrometry confirmation of molecular weight (213.0552 for [M+H]⁺ or 211.0395 for [M-H]⁻)
- UV-visible spectrophotometry confirming absorption maxima at 231, 279, and 304 nm
- Nuclear magnetic resonance spectroscopy (¹H and ¹³C) for structural confirmation
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography

Third-party analytical confirmation of vendor certificates of analysis is recommended for investigations where dose-response precision is critical. The urolithin B research-grade market is moderately established; lot-to-lot variability in purity and residual solvent content has been observed across suppliers, and independent analytical verification is appropriate.

9. Reconstitution and Handling

Urolithin B is supplied as a crystalline or lyophilized powder with limited aqueous solubility. Stock solutions should be prepared in organic solvents:

DMSO stock solutions: The compound dissolves at 30 mg/mL (approximately 141 mM) in dimethyl sulfoxide. DMSO stocks should be aliquoted for single use and stored at -20 degrees Celsius. Stability in DMSO at -20 degrees Celsius is maintained for at least 6 months. Final DMSO concentration in cell culture experiments should not exceed 0.1 to 0.5 percent (v/v) to avoid solvent cytotoxicity.

DMF stock solutions: Solubility of 30 mg/mL in dimethylformamide provides an alternative for applications where DMSO interference is a concern.

Ethanol stock solutions: Solubility of 30 mg/mL in ethanol is suitable for in vivo formulations and for cell culture applications where ethanol vehicle is preferred. Ethanol stocks should be prepared fresh or stored at -20 degrees Celsius with protection from evaporation.

Aqueous formulations: For in vivo oral gavage, urolithin B can be suspended in aqueous vehicles containing small percentages of DMSO, ethanol, or cyclodextrin complexation agents to achieve the target dose concentrations. The Chen et al. (2021) neuroprotection study administered the compound by oral gavage, though the specific vehicle composition was not detailed [9].

Storage of solid: The crystalline powder should be stored desiccated at -20 degrees Celsius, protected from light and moisture. Stability under these conditions exceeds 2 years.

Light sensitivity: While formal photostability data are limited, the aromatic chromophore system suggests reasonable stability under ambient laboratory lighting. Extended exposure to direct ultraviolet light should be avoided during stock preparation.

Freeze-thaw cycles: DMSO stock solutions should be limited to fewer than 5 freeze-thaw cycles. Single-use aliquoting is recommended for quantitative work.

10. Stack Interactions and Combinations

Urolithin B interacts with several biological systems through its multi-target pharmacology. Investigators conducting research with urolithin B, especially in combination protocols, should consider:

Androgen receptor modulators: The AR-dependent muscle anabolic mechanism predicts pharmacodynamic interactions with AR agonists (testosterone, nandrolone, selective androgen receptor modulators) and AR antagonists (bicalutamide, enzalutamide, flutamide). Concurrent AR agonists may produce additive or synergistic anabolic effects; concurrent AR antagonists will attenuate or abolish the muscle activity.

mTOR inhibitors: Rapamycin and everolimus suppress mTORC1 signaling, the downstream effector of the urolithin B anabolic pathway. Concurrent administration is predicted to abolish the anabolic effect and is a useful mechanistic probe but is counterproductive for muscle-building applications.

AMPK activators: Metformin, AICAR, and other AMPK activators may counteract the AMPK dephosphorylation that contributes to urolithin B anabolic signaling in muscle. In inflammatory contexts, where urolithin B enhances AMPK phosphorylation, the interaction may be additive.

NF-kappaB inhibitors: Concurrent administration with other NF-kappaB pathway inhibitors (curcumin, sulforaphane, BAY 11-7082) may produce additive anti-inflammatory effects. The combination has not been studied in preclinical models but represents a plausible research direction.

Urolithin A: The two urolithins have distinct pharmacological profiles. Urolithin A acts primarily through mitophagy induction (PINK1/Parkin pathway) while urolithin B acts through AR/mTORC1 anabolism and IAPP inhibition. The combination may produce complementary effects on muscle health (mitochondrial quality control from urolithin A, protein synthesis from urolithin B) and is a rational research combination. No formal interaction studies have been conducted.

Ellagitannin-rich dietary sources: Consumption of pomegranate juice, walnuts, raspberries, or other ellagitannin-rich foods will produce endogenous urolithins in UM-A and UM-B individuals. Investigators studying exogenous urolithin B should consider dietary standardization or restriction of ellagitannin sources to control for background urolithin production.

Cholinesterase inhibitors: Urolithin B derivatives have shown cholinesterase inhibitory activity comparable to galantamine and superior to rivastigmine [6]. Concurrent administration with clinical cholinesterase inhibitors (donepezil, rivastigmine, galantamine) in cognitive research protocols should anticipate additive cholinergic effects.

Chemotherapy agents: Urolithins have been reported to increase the anticancer effects of chemical drugs, ionizing radiation, and hyperthermia in esophageal carcinoma cells in vitro [17]. Combination protocols with conventional chemotherapy may produce additive or synergistic cytotoxicity, but clinical translation has not been investigated.

11. Adverse Events and Safety Signal

11.1 Preclinical safety

Formal toxicology studies specific to urolithin B are limited. The available preclinical evidence suggests a favorable safety profile:

The Rodriguez et al. (2017) 28-day subcutaneous pump study in mice reported no adverse events at the 10 microgram/day dose that produced significant muscle hypertrophy [8]. Body weight gain was observed during the first 3 weeks but plateaued by week 4.

The Chen et al. (2021) 8-week oral gavage study in mice at doses up to 150 mg/kg/day reported no apparent toxicity [9].

No target-organ toxicity has been identified in published preclinical studies across the anti-inflammatory, anticancer, bone-protective, or spinal cord injury applications.

11.2 Safety inference from urolithin A

The urolithin A safety database provides a structural analog reference. Urolithin A has received FDA GRAS status and has demonstrated safety in clinical trials at doses up to 1000 mg/day for 4 months, with adverse events generally mild and without clear patterns [22]. Given the structural similarity (one fewer hydroxyl group in urolithin B), the safety profile is expected to be broadly comparable, though this inference requires direct confirmation in urolithin B clinical studies.

11.3 Theoretical safety considerations

Androgen receptor activation: The AR-mediated anabolic mechanism raises theoretical concerns about androgenic side effects (virilization, prostate effects, hepatic effects) at high chronic doses. The Rodriguez et al. data showing no change in circulating testosterone levels are reassuring, but the possibility of direct AR activation without steroidogenic modulation may still carry tissue-specific risks at supratherapeutic exposures.

Estrogenic activity: Urolithins have been reported to exhibit estrogenic and antiestrogenic activities in cell-based assays [23]. The clinical significance of this activity at physiological urolithin concentrations is unclear, but it represents a theoretical consideration for chronic high-dose supplementation in hormone-sensitive populations.

Pro-oxidant activity: Urolithin B has been reported to exhibit both antioxidant and pro-oxidant activities depending on the assay system and conditions [4]. At high concentrations or in specific cellular contexts (particularly in the presence of transition metals), pro-oxidant effects may emerge.

11.4 Pregnancy and lactation

No reproductive or developmental toxicity data are available for urolithin B. Urolithins have been detected in human breastmilk, indicating transfer to nursing infants during dietary exposure. Use of exogenous urolithin B in pregnancy or lactation should be considered experimental and approached with appropriate caution.

11.5 Inter-individual variability

The dependence of endogenous urolithin B production on gut microbiota composition introduces substantial inter-individual variability in exposure. UM-0 individuals produce no urolithins; UM-A individuals produce urolithin A without urolithin B; only UM-B individuals produce both. This variability should be considered in the design of clinical investigations and in the interpretation of dietary intervention studies involving ellagitannin-rich foods.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five compounds against urolithin B, evaluated on five competency standards: novelty, effect size, promising potential (current state and trajectory), side-effect profile, and overall validation. The five comparators were selected to represent the principal structural analogs, functional comparators, and alternative approaches to the pharmacological targets of urolithin B.

12.1 Urolithin A (3,8-dihydroxy-6H-dibenzo[b,d]pyran-6-one)

Mechanism: Mitophagy inducer through PINK1/Parkin pathway activation; mitochondrial quality control enhancer; anti-inflammatory through mitophagy-dependent NLRP3 suppression. Does not share the AR/mTORC1 muscle anabolic mechanism or the IAPP anti-amyloidogenic activity of urolithin B.

Novelty: Low relative to urolithin B for muscle anabolism (inactive at this target) but high for mitophagy induction, where urolithin A is the index compound for the class.

Effect size: Strong in mitophagy and mitochondrial biomarker endpoints in human clinical trials (dose-dependent anti-inflammatory effects, mitochondrial gene upregulation at 250 to 1000 mg/day) [22]. Absent for muscle protein synthesis, myotube diameter, and IAPP proteotoxicity protection, where urolithin B is active and urolithin A is not [8, 11].

Promising potential: High. FDA GRAS status achieved. Multiple completed human clinical trials. Commercial product (Mitopure) available. Active clinical development for muscle health, aging, and metabolic endpoints. The most clinically advanced urolithin.

Side-effect profile: Favorable. Clinical trials reported mild adverse events without clear patterns. No serious adverse events attributed to the compound at doses up to 1000 mg/day for 4 months [22].

Overall validation: High. Urolithin A is the most extensively validated urolithin in humans, with Phase 2-equivalent clinical evidence and commercial availability. However, its pharmacological profile does not overlap with urolithin B at the muscle anabolic or IAPP targets.

Comparison to urolithin B: The two compounds are structurally related (differing by one hydroxyl group) but pharmacologically complementary rather than interchangeable. Urolithin A leads in clinical development and mitophagy applications; urolithin B leads in muscle anabolism, IAPP protection, and AR-mediated signaling. The combination represents a rational research strategy for comprehensive muscle health (mitochondrial quality from urolithin A, protein synthesis from urolithin B).

12.2 Ellagic acid (2,3,7,8-tetrahydroxy[1]benzofuro[3,2-b][1]benzofuran-6,11-dione)

Mechanism: Antioxidant through direct radical scavenging and metal chelation; anti-inflammatory through NF-kappaB suppression; anticancer through cell cycle arrest and apoptosis induction; anti-angiogenic. The parent polyphenol from which all urolithins are derived.

Novelty: Low. Ellagic acid has been studied for decades and is a well-established dietary polyphenol. No novel mechanism of action distinguishes it from other polyphenolic antioxidants.

Effect size: Modest in preclinical models across antioxidant, anti-inflammatory, and anticancer endpoints. Limited clinical evidence. Bioavailability is poor owing to extensive hepatic metabolism and low aqueous solubility, which substantially limits achievable plasma concentrations.

Promising potential: Low to moderate. The compound is widely available as a dietary supplement but has not achieved significant clinical development. The poor bioavailability is a persistent limitation that favors the urolithin metabolites as the biologically relevant effectors of ellagitannin-rich dietary intake.

Side-effect profile: Favorable. Generally recognized as safe at dietary intake levels. No significant adverse events reported in supplementation studies.

Overall validation: Moderate. Extensive preclinical literature but limited clinical translation. The recognition that urolithins, rather than ellagic acid itself, are the biologically active metabolites in vivo has shifted research attention toward the urolithin metabolites.

Comparison to urolithin B: Ellagic acid is the metabolic precursor of urolithin B but has inferior bioavailability and lacks the specific AR/mTORC1 anabolic mechanism, the IAPP anti-amyloidogenic activity, and the PI3K/Akt neuroprotective signaling that distinguish urolithin B. The gut microbiota conversion of ellagic acid to urolithins is now understood as the principal mechanism through which ellagitannin-rich diets exert their health effects.

12.3 HMB (beta-hydroxy-beta-methylbutyrate)

Mechanism: Leucine metabolite that stimulates muscle protein synthesis through mTOR activation and inhibits protein degradation through ubiquitin-proteasome suppression. Functionally analogous to urolithin B at the endpoint level (anabolism plus anti-catabolism) but operating through different proximal signaling (leucine metabolism rather than androgen receptor).

Novelty: Low. HMB has been studied for over 25 years in muscle health applications and is a well-established nutritional supplement.

Effect size: Modest in clinical trials. Meta-analyses of HMB supplementation (typically 3 g/day) in older adults show small but statistically significant improvements in lean body mass and muscle strength, with effect sizes (Cohen's d) of approximately 0.15 to 0.30 [24]. Effect is more pronounced in untrained individuals and in catabolic states (bed rest, critical illness).

Promising potential: Moderate. Commercially available as a dietary supplement. Multiple clinical trials completed. The compound is established but has not produced large effect sizes that would drive widespread clinical adoption.

Side-effect profile: Favorable. No significant adverse events reported in clinical trials at standard doses. The compound has GRAS status and is available as a dietary supplement.

Overall validation: Moderate to high. Extensive human clinical data but modest effect sizes. The compound serves as a useful benchmark for urolithin B anabolic efficacy comparisons.

Comparison to urolithin B: Both compounds promote muscle protein synthesis and suppress protein degradation, but through different mechanisms (HMB through leucine-mTOR signaling, urolithin B through AR-mTORC1 signaling). Urolithin B produced a larger protein synthesis increase in C2C12 myotubes (96.1 percent) than typically reported for HMB in comparable assays. HMB has the advantage of extensive clinical validation; urolithin B has the advantage of a more diverse pharmacological profile (neuroprotection, anti-inflammatory, IAPP inhibition) and a distinct mechanism. The combination of HMB and urolithin B represents a rational dual-mechanism approach to muscle health that has not been investigated.

12.4 Epicatechin ((-)-epicatechin)

Mechanism: Flavanol that stimulates muscle growth through nitric oxide/cGMP signaling and follistatin/myostatin ratio modulation; mitochondrial biogenesis enhancer through PGC-1alpha activation; vascular endothelial function enhancer.

Novelty: Moderate. The muscle application of epicatechin is relatively recent (post-2010) and represents a non-obvious extension of the cardiovascular flavanol literature.

Effect size: Moderate in preclinical models. In human studies, dark chocolate or epicatechin supplementation (approximately 1 mg/kg/day) has produced small improvements in grip strength and follistatin/myostatin ratio in elderly subjects and in heart failure patients [25]. Effect sizes are modest and not consistently replicated across studies.

Promising potential: Low to moderate. The compound is available as a dietary supplement and in dark chocolate but has not achieved significant clinical development as a muscle therapeutic. Bioavailability is moderate after oral administration, with extensive hepatic metabolism to glucuronide and sulfate conjugates.

Side-effect profile: Favorable. No significant adverse events at studied doses. The compound is a natural component of cocoa and tea with established dietary safety.

Overall validation: Low to moderate. Limited clinical evidence for the muscle application. The vascular and cardiovascular applications are better validated but are not directly comparable to the urolithin B muscle anabolic profile.

Comparison to urolithin B: Both compounds enhance muscle mass through distinct mechanisms (epicatechin through NO/follistatin/myostatin, urolithin B through AR/mTORC1). Urolithin B produced larger in vitro anabolic effects and has a broader pharmacological profile. Epicatechin has the advantage of established dietary safety and moderate clinical data; urolithin B has the advantage of greater potency and mechanistic diversity.

12.5 Sulforaphane (1-isothiocyanato-4-methylsulfinylbutane)

Mechanism: Isothiocyanate that activates Nrf2/ARE-dependent antioxidant gene transcription, inhibits NF-kappaB-driven inflammation, and induces phase II detoxification enzymes. Functionally analogous to urolithin B at the Nrf2/NF-kappaB signaling level but without the muscle anabolic or IAPP anti-amyloidogenic activities.

Novelty: Low to moderate. Sulforaphane has been studied for over 30 years as the principal bioactive isothiocyanate from cruciferous vegetables. The Nrf2 activation mechanism is well characterized.

Effect size: Moderate in preclinical models across anticancer, anti-inflammatory, neuroprotective, and detoxification endpoints. Clinical trials have shown modest anti-inflammatory and metabolic benefits at doses of 30 to 90 mg/day of sulforaphane or glucoraphanin equivalents. Anticancer clinical trials (broccoli sprout extracts) have produced mixed results.

Promising potential: Moderate. Multiple clinical trials completed. Commercial products available (broccoli seed extract, stabilized sulforaphane). The compound is a legitimate nutraceutical candidate with modest clinical traction.

Side-effect profile: Generally favorable. Mild gastrointestinal effects (bloating, gas) at higher doses. No serious adverse events in clinical trials.

Overall validation: Moderate. Extensive preclinical literature, moderate clinical evidence, established dietary safety. The most clinically advanced Nrf2 activator of dietary origin.

Comparison to urolithin B: Both compounds activate Nrf2/ARE signaling and suppress NF-kappaB. Sulforaphane is more extensively validated as an Nrf2 activator but lacks the AR/mTORC1 muscle anabolic activity, the IAPP anti-amyloidogenic

effect, the PI3K/Akt neuroprotective signaling, and the bone-protective activity that distinguish urolithin B. For anti-inflammatory and antioxidant applications, the two compounds represent mechanistically overlapping but not identical strategies.

12.6 Comparator summary

The five comparators occupy distinct positions relative to urolithin B:

Urolithin A is the structurally closest analog and the most clinically advanced, but operates through a fundamentally different mechanism (mitophagy vs. AR/mTORC1 anabolism) and lacks activity at the IAPP and muscle protein synthesis targets where urolithin B is uniquely active. **Ellagic acid** is the metabolic precursor with inferior bioavailability and a less specific pharmacological profile. **HMB** is the most clinically validated muscle anabolic comparator, with established but modest effect sizes; urolithin B produced larger in vitro effects through a distinct mechanism. **Epicatechin** represents an alternative natural product approach to muscle health with moderate but inconsistent clinical data. **Sulforaphane** is the most validated dietary Nrf2 activator but lacks the anabolic and anti-amyloidogenic activities unique to urolithin B.

Urolithin B occupies a distinctive position in this comparator landscape: it is the only compound with demonstrated AR/mTORC1-mediated muscle anabolism among dietary metabolites, the only compound with specific IAPP anti-amyloidogenic activity, and the only compound that combines muscle anabolic, neuroprotective (PI3K/Akt), anti-inflammatory (NF-kappaB/NLRP3), antioxidant (Nrf2/ARE), anticancer, and bone-protective activities in a single molecular entity. Its principal limitation is the absence of human clinical trial data, which places it behind urolithin A, HMB, and sulforaphane in translational validation. The preclinical evidence base, particularly the Rodriguez et al. (2017) muscle study and the Chen et al. (2021) neuroprotection study, is robust and supports progression to clinical investigation.

The principal practical question for the research-clinical positioning of urolithin B is whether its multi-target profile represents a strength (diverse pharmacological coverage from a single agent) or a weakness (lack of selectivity that complicates mechanism-based clinical development). The specificity of the AR/mTORC1 muscle anabolic effect (abolished by AR knockdown, absent in urolithin A) and the specificity of the IAPP protection (absent in urolithin A) argue for genuine target selectivity within the multi-target profile rather than nonspecific pleiotropism.

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. No human clinical trials of exogenous urolithin B have been completed; all pharmacological and efficacy data are preclinical. Endogenous urolithin B production depends on individual gut microbiota composition (UM-B metabotype). Investigators should obtain analytical confirmation of identity and purity on every research-grade lot. The compound has not been approved by any regulatory authority for therapeutic use.