

RESEARCH MONOGRAPH . COMPOUND PROFILE

Sulforaphane

A dietary isothiocyanate first isolated from broccoli at Johns Hopkins University as the most potent naturally occurring inducer of mammalian phase 2 cytoprotective enzymes, now established as a multimechanistic agent acting through Keap1-Nrf2 electrophilic signaling, NF-kappaB suppression, and histone deacetylase inhibition across chemopreventive, metabolic, neurobehavioral, and anti-inflammatory research applications.

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ABSTRACT

Sulforaphane (1-isothiocyanato-4-methylsulfinylbutane) is a low-molecular-weight isothiocyanate generated by myrosinase-catalyzed hydrolysis of the glucosinolate glucoraphanin, found at highest concentration in broccoli sprouts and at progressively lower concentration in mature broccoli, Brussels sprouts, cauliflower, and other cruciferous vegetables. First identified in 1992 by Paul Talalay and colleagues at the Johns Hopkins University School of Medicine as the most potent naturally occurring inducer of mammalian phase 2 detoxification enzymes, sulforaphane has become the most extensively studied dietary isothiocyanate in human pharmacology and the reference compound for nutrigenomic Nrf2 activation. The primary molecular mechanism is electrophilic modification of reactive cysteine residues on the Kelch-like ECH-associated protein 1 (Keap1) sensor, leading to stabilization and nuclear translocation of the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) and subsequent transcriptional upregulation of a battery of cytoprotective genes including NAD(P)H:quinone oxidoreductase 1 (NQO1), heme oxygenase-1 (HO-1), glutathione S-transferases (GSTs), and thioredoxin reductase. Sulforaphane activates Nrf2 with a potency approximately 13-fold greater than curcumin, 18-fold greater than silymarin, and over 100-fold greater than resveratrol in standardized NQO1 inducer assays. A second established mechanism is the suppression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) signaling through inhibition of IkappaB-alpha phosphorylation and degradation, producing broad anti-inflammatory activity. A third mechanism, characterized by

Myzak et al. in 2004, is inhibition of histone deacetylase (HDAC) enzymes by the mercapturic acid pathway metabolites sulforaphane-cysteine and sulforaphane-N-acetylcysteine, producing epigenetic reactivation of tumor suppressor genes including p21 and Bax. Pharmacokinetics in humans are characterized by rapid oral absorption (peak plasma concentration within 1 to 3 hours), a short elimination half-life of approximately 1.8 to 2.2 hours, extensive metabolism through the mercapturic acid (glutathione conjugation) pathway, and urinary excretion of 60 to 80 percent of administered sulforaphane equivalents within 24 hours. Oral bioavailability of free sulforaphane is approximately 70 to 80 percent, while bioavailability from the glucoraphanin precursor is approximately 10 to 40 percent depending on myrosinase activity and interindividual variation in gut microbial glucosinolate hydrolysis. Over 80 interventional clinical trials have examined sulforaphane or sulforaphane-yielding preparations in human subjects across indications including cancer chemoprevention (prostate, breast, lung, colorectal, bladder), autism spectrum disorder, type 2 diabetes, schizophrenia, chronic obstructive pulmonary disease, *Helicobacter pylori* infection, and air pollution detoxification. The Singh et al. (2014) randomized placebo-controlled trial in young men with moderate to severe autism spectrum disorder demonstrated substantial and reversible behavioral improvement on the Aberrant Behavior Checklist and Social Responsiveness Scale after 18 weeks of daily sulforaphane administration. The Axelsson et al. (2017) trial in obese patients with dysregulated type 2 diabetes demonstrated reduced fasting blood glucose and improved glycated hemoglobin with concentrated broccoli sprout extract. The compound is generally well tolerated; the principal adverse events are mild gastrointestinal disturbance (flatulence,

bloating, loose stools). Goitrogenic potential at high doses is a theoretical concern for individuals with pre-existing thyroid dysfunction. This monograph reviews the chemistry, biosynthesis, and stereochemistry of sulforaphane; the tripartite molecular pharmacology (Keap1-Nrf2, NF-kappaB, HDAC); comprehensive human pharmacokinetics; the preclinical and clinical evidence base across chemopreventive, metabolic, neurobehavioral, and anti-inflammatory indications; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event and safety signal; and a comparative assessment of five alternative Nrf2-activating or cruciferous-derived cytoprotective compounds against sulforaphane on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Preferred name: Sulforaphane.

Systematic names: 1-Isothiocyanato-4-methylsulfinylbutane; 4-methylsulfinylbutyl isothiocyanate.

Common synonyms: SFN, sulphoraphane (British spelling), L-sulforaphane (for the naturally occurring R-enantiomer).

Development and research codes: The compound does not carry a single canonical development code. In the literature it is identified by its trivial name sulforaphane, established in the Talalay laboratory publications from 1992 onward [1].

Chemical Abstracts Service registry numbers: 4478-93-7 (racemic DL-sulforaphane), 142825-10-3 (R-sulforaphane, the naturally occurring enantiomer; also designated L-sulforaphane in some nomenclature systems). The racemic CAS number is the most commonly cited in commercial and research contexts. The naturally occurring form in cruciferous vegetables is the R-enantiomer.

International Union of Pure and Applied Chemistry name: 1-isothiocyanato-4-(methylsulfinyl)butane.

PubChem CID: 5350.

Precursor compound: Glucoraphanin (4-methylsulfinylbutyl glucosinolate; CAS 21414-41-5) is the stable, water-soluble glucosinolate precursor stored in intact plant tissue. Hydrolysis by the endogenous plant enzyme myrosinase (thioglucoside glucohydrolase, EC 3.2.1.147) or by gut microbial thioglucosidases yields sulforaphane upon tissue disruption.

1.2 Structural class and chemistry

Sulforaphane is an aliphatic isothiocyanate. It belongs to the larger chemical family of organosulfur compounds and is classified within the isothiocyanate ($-N=C=S$) functional group series derived from glucosinolate hydrolysis in cruciferous plants.

The structural class is distinct from the aromatic isothiocyanates (phenethyl isothiocyanate, benzyl isothiocyanate) and from the indole glucosinolate derivatives (indole-3-carbinol, 3,3'-diindolylmethane) that co-occur in cruciferous vegetables.

Molecular formula: C₆H₁₁NOS₂.

Exact mass: 177.0282 g/mol (monoisotopic).

Molecular weight: 177.29 g/mol.

Physical properties: Sulforaphane in pure form is a slightly yellow, viscous liquid at room temperature. It is soluble in water, dimethyl sulfoxide (DMSO), methanol, ethanol, and other polar solvents. The compound is lipophilic relative to its molecular weight, contributing to favorable membrane permeability and oral absorption. Melting point is below room temperature (the compound is a liquid under standard conditions). Boiling point is approximately 153 to 157 degrees Celsius at reduced pressure (0.1 mmHg); the compound decomposes before boiling at atmospheric pressure.

Stereochemistry: Sulforaphane contains a chiral sulfoxide center. The naturally occurring form in cruciferous vegetables is the R-enantiomer at the sulfoxide sulfur. Commercial research-grade material is commonly supplied as the racemic mixture (DL-sulforaphane, CAS 4478-93-7); enantiopure R-sulforaphane (CAS 142825-10-3) is available from specialized suppliers at higher cost. Both enantiomers are biologically active as Nrf2 inducers; the R-enantiomer is generally reported as modestly more potent in cell-based NQO1 induction assays, though the difference is small and both forms are used in research.

Key functional group: The isothiocyanate group (-N=C=S) is the electrophilic center responsible for the primary biological activity. The central carbon of the isothiocyanate is highly electrophilic and reacts readily with thiol groups (cysteine residues) in proteins and with glutathione, forming dithiocarbamate adducts. This electrophilic reactivity is the molecular basis for both the Keap1-Nrf2 signaling mechanism and the mercapturic acid pathway metabolism.

1.3 Biosynthesis and preparation

Sulforaphane is not directly present in intact plant tissue. It is generated from the glucosinolate precursor glucoraphanin by myrosinase-catalyzed hydrolysis when plant tissue is damaged (by chewing, cutting, crushing, or processing). The hydroly-

ysis reaction cleaves the thioglucose bond in glucoraphanin, releasing glucose and an unstable thiohydroximate-O-sulfonate intermediate that spontaneously rearranges to yield sulforaphane (the isothiocyanate) as the major product under mildly acidic to neutral conditions. Under conditions of elevated pH, in the presence of ferrous ion, or in the presence of the specifier protein epithiospecifier protein (ESP), the rearrangement favors production of the nitrile sulforaphane nitrile rather than the isothiocyanate; the nitrile is biologically inactive as an Nrf2 inducer. Heat inactivation of myrosinase during cooking (blanching, boiling, microwaving) substantially reduces sulforaphane yield from whole vegetables, though gut microbial thioglucosidases provide a secondary conversion pathway for ingested intact glucoraphanin [2, 3].

For research and supplement applications, sulforaphane is obtained by three principal routes: (a) extraction from broccoli sprouts (which contain 20- to 50-fold higher glucoraphanin concentrations than mature broccoli florets), with myrosinase-mediated conversion either in situ during aqueous extraction or by exogenous myrosinase addition; (b) chemical synthesis from 4-methylsulfinylbutylamine and thiophosgene or carbon disulfide (standard isothiocyanate synthesis), followed by purification and, if enantiopure material is required, chiral resolution or asymmetric sulfoxidation; and (c) stabilized glucoraphanin preparations co-formulated with exogenous myrosinase (from mustard seed or daikon radish) to enable in vivo conversion after oral administration [4].

2. Abstract

Sulforaphane (1-isothiocyanato-4-methylsulfinylbutane; CAS 4478-93-7) is the most potent naturally occurring small-molecule inducer of the Keap1-Nrf2-ARE (antioxidant response element) cytoprotective signaling axis and the most extensively investigated dietary isothiocyanate in human pharmacology. The compound was identified in 1992 by Paul Talalay and Yuesheng Zhang at the Johns Hopkins University School of Medicine through a bioassay-guided fractionation of broccoli extracts for inducers of the phase 2 enzyme NAD(P)H:quinone oxidoreductase 1 (NQO1) in murine hepatoma cells [1]. The subsequent 1994 discovery by Jed Fahey that 3-day-old broccoli sprouts contain 20 to 50 times the glucoraphanin concentration of mature broccoli provided a concentrated dietary source and catalyzed translation into human intervention studies [5].

The molecular pharmacology of sulforaphane is tripartite. The primary mechanism is electrophilic modification of critical cysteine residues (principally Cys151, Cys273, and Cys288) on Keap1, the cytoplasmic repressor of Nrf2, leading to Nrf2 nuclear translocation and transcriptional activation of over 200 cytoprotective genes through the antioxidant response element [6]. The second mechanism is suppression of NF-kappaB-dependent proinflammatory transcription through inhibition of IkappaB kinase activity and direct dithiocarbamate formation with NF-kappaB subunits, reducing expression of tumor necrosis factor alpha, interleukin-1 beta, interleukin-6, cyclooxygenase-2, and inducible nitric oxide synthase [7]. The third mechanism is inhibition of histone deacetylase (HDAC) enzymes by the mercapturic acid pathway metabolites sulforaphane-cysteine and sulforaphane-N-acetylcysteine, producing epigenetic derepression of tumor suppressor genes including p21(WAF1/CIP1) and Bax in cancer cells [8].

Over 80 interventional clinical trials have been registered or completed for sulforaphane or sulforaphane-yielding broccoli preparations across indications including cancer chemoprevention, autism spectrum disorder, type 2 diabetes, schizophrenia, chronic obstructive pulmonary disease, and environmental toxicant detoxification. The Singh et al. (2014) randomized double-blind placebo-controlled trial in 44 young men with moderate to severe autism spectrum disorder demonstrated substantial behavioral improvement on the Aberrant Behavior Checklist (decrease from 62.4 to 45.0, $p < 0.001$) and the Social Responsiveness Scale after 18

weeks of daily sulforaphane at 50 to 150 micromoles, with reversal upon discontinuation [9]. The Axelsson et al. (2017) randomized trial in obese patients with dysregulated type 2 diabetes demonstrated that concentrated broccoli sprout extract (providing approximately 150 micromoles sulforaphane daily for 12 weeks) significantly reduced fasting blood glucose and glycated hemoglobin relative to placebo [10]. The Egner et al. (2014) crossover trial in Qidong, China, demonstrated that a broccoli sprout beverage producing approximately 600 micromoles sulforaphane equivalents daily for 12 weeks significantly enhanced urinary excretion of the air pollutant metabolites benzene-mercapturic acid and acrolein-mercapturic acid, providing direct evidence for sulforaphane-mediated upregulation of phase 2 detoxification in a human environmental exposure context [11].

Sulforaphane is not approved as a drug by any regulatory authority. It is commercially available as a dietary supplement in multiple formulations (free sulforaphane, stabilized glucoraphanin with myrosinase, and broccoli sprout extracts standardized to sulforaphane or glucoraphanin content). The compound is generally well tolerated at studied doses (equivalent to 20 to 200 micromoles daily); the principal adverse events are mild gastrointestinal disturbance. This monograph documents chemistry, biosynthesis, tripartite molecular pharmacology, comprehensive pharmacokinetics, the preclinical and clinical evidence base, sourcing and quality verification, reconstitution and handling, stack interactions, adverse-event and safety signal, and a structured comparative assessment of five alternative cytoprotective compounds against sulforaphane on five competency standards.

3. Discovery and Development History

3.1 Origin

The discovery of sulforaphane as a chemoprotective agent emerged from a systematic research program at the Johns Hopkins University School of Medicine directed by Paul Talalay, beginning in the late 1980s. Talalay and colleagues hypothesized that dietary inducers of phase 2 detoxification enzymes could provide a practical strategy for cancer chemoprevention by amplifying cellular capacity to neutralize reactive carcinogenic intermediates before they damaged DNA. The research group developed a rapid bioassay for phase 2 enzyme induction using NQO1 activity in murine hepatoma (Hepa 1c1c7) cells and applied this bioassay to screen fractions from edible plants, with a focus on cruciferous vegetables [1].

3.2 Identification and characterization (1992)

In 1992, Yuesheng Zhang, working in the Talalay laboratory, reported the isolation of sulforaphane from broccoli as the principal inducer of phase 2 enzymes in the Hepa 1c1c7 bioassay. The compound was identified by bioassay-guided fractionation of a broccoli extract, with structure elucidation by mass spectrometry and nuclear magnetic resonance spectroscopy. The publication in the Proceedings of the National Academy of Sciences reported that sulforaphane was the most potent phase 2 enzyme inducer identified from a natural dietary source, with a concentration for doubling NQO1 activity (CD value) of approximately 0.2 micromolar in the Hepa 1c1c7 assay [1]. The finding was widely reported in the popular press, including the front page of The New York Times, and was subsequently listed among the notable scientific discoveries of the decade.

3.3 Broccoli sprout discovery (1994 to 1997)

Jed Fahey, a botanist and nutritional biochemist in the Talalay laboratory, hypothesized that 3-day-old broccoli sprouts, being in an early stage of seedling development, might contain substantially higher concentrations of glucoraphanin than mature broccoli. This hypothesis was confirmed: broccoli sprouts were found to contain 20 to 50 times the glucoraphanin concentration of commercially available

mature broccoli on a weight basis [5]. The finding, published in 1997 in the Proceedings of the National Academy of Sciences, provided a practical concentrated dietary source for human intervention studies and stimulated the development of commercial broccoli sprout products and broccoli seed extracts.

3.4 Expansion of the mechanistic and clinical literature

Between 1997 and the present, the sulforaphane research literature has expanded to encompass over 4,000 publications. Key milestones include: the molecular characterization of the Keap1-Nrf2 interaction and the identification of the specific Keap1 cysteine residues modified by sulforaphane (Dinkova-Kostova et al., 2002) [6]; the discovery of HDAC inhibitory activity by the sulforaphane metabolites (Myzak et al., 2004) [8]; the first human pharmacokinetic studies with pure sulforaphane and with broccoli sprout preparations (Shapiro et al., 2006; Egner et al., 2011) [12, 13]; the autism spectrum disorder clinical trial (Singh et al., 2014) [9]; the type 2 diabetes clinical trial (Axelsson et al., 2017) [10]; and the air pollutant detoxification crossover trial in Qidong, China (Egner et al., 2014) [11]. The compound is now the subject of over 80 registered interventional clinical trials and is the most extensively human-studied member of the isothiocyanate class.

3.5 Current status

Sulforaphane has not been submitted for regulatory approval as a drug by any sponsor in any jurisdiction. It is sold as a dietary supplement in the United States, the European Union, Australia, Japan, and other markets, under the regulatory frameworks applicable to dietary supplements and food-derived preparations. The Johns Hopkins University holds patents on broccoli sprout preparations and has licensed these to commercial entities (Brassica Protection Products LLC, which markets the TrueBroc and Avmacol brands). Research-grade sulforaphane is available from multiple chemical suppliers. Clinical development of sulforaphane as a pharmaceutical agent would require an Investigational New Drug application and Phase 1 through Phase 3 registration trials; no sponsor has initiated this pathway as of the current monograph revision.

4. Mechanism of Action

Sulforaphane is a multimechanistic compound. Its principal molecular activities, characterized in cell-free, cell-based, and in vivo systems, are activation of the Keap1-Nrf2-ARE cytoprotective signaling axis; suppression of NF-kappaB-dependent proinflammatory transcription; and inhibition of histone deacetylase enzymes by mercapturic acid pathway metabolites. These activities operate at concentrations achieved by dietary and supplemental doses and contribute differentially to the observed chemopreventive, anti-inflammatory, metabolic, and neurobehavioral effects.

4.1 Keap1-Nrf2-ARE pathway activation

The Keap1-Nrf2-ARE axis is the primary sensor and effector system for electrophilic and oxidative cellular stress in mammalian cells. Under basal (unstressed) conditions, the transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2) is sequestered in the cytoplasm by the adapter protein Keap1 (Kelch-like ECH-associated protein 1), which targets Nrf2 for ubiquitination by the Cullin 3 E3 ubiquitin ligase complex and subsequent proteasomal degradation. The half-life of Nrf2 under basal conditions is approximately 15 to 20 minutes, maintaining low constitutive expression of Nrf2 target genes.

Sulforaphane, by virtue of the electrophilic isothiocyanate carbon, reacts with specific reactive cysteine residues on Keap1, principally Cys151 in the BTB domain and Cys273 and Cys288 in the intervening region. These thiol modifications produce a conformational change in Keap1 that disrupts the Keap1-Nrf2 interaction, preventing Nrf2 ubiquitination and proteasomal degradation. Stabilized Nrf2 accumulates in the cytoplasm and translocates to the nucleus, where it heterodimerizes with small Maf proteins and binds the antioxidant response element (ARE; also termed the electrophile response element, EpRE) in the promoter regions of target genes [6].

The resulting transcriptional program upregulates a battery of over 200 cytoprotective genes, including: NQO1, the quinone reductase used as the standard bioassay for Nrf2 induction; HO-1 (heme oxygenase-1), catalyzing the rate-limiting step in heme catabolism to biliverdin, carbon monoxide, and free iron; the glutathione

S-transferase (GST) family, catalyzing conjugation of electrophilic xenobiotics with glutathione; glutamate-cysteine ligase (GCL) catalytic and modifier subunits, the rate-limiting enzymes in de novo glutathione biosynthesis; thioredoxin reductase (TXNRD1); and UDP-glucuronosyltransferases [14].

Sulforaphane is the most potent naturally occurring Nrf2 activator in standardized NQO1 induction assays, with a CD value (concentration required to double NQO1 specific activity in Hepa 1c1c7 cells) of approximately 0.2 micromolar. Comparative NQO1 inducer potency studies have established that sulforaphane is approximately 13-fold more potent than curcumin, approximately 18-fold more potent than silymarin (milk thistle extract), and over 100-fold more potent than resveratrol [15].

4.2 NF-kappaB pathway suppression

The NF-kappaB transcription factor family (p65/RelA, p50, RelB, c-Rel, p52) is the principal regulator of proinflammatory gene expression in mammalian cells. In the canonical activation pathway, inflammatory stimuli (tumor necrosis factor alpha, interleukin-1 beta, lipopolysaccharide, reactive oxygen species) activate the IkappaB kinase (IKK) complex, which phosphorylates the inhibitory protein IkappaB-alpha, targeting it for ubiquitination and proteasomal degradation. Freed NF-kappaB dimers translocate to the nucleus and activate transcription of proinflammatory genes including TNF-alpha, IL-1beta, IL-6, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and matrix metalloproteinases.

Sulforaphane suppresses NF-kappaB signaling through multiple converging mechanisms. Direct electrophilic modification of cysteine residues on the IKK-beta subunit and on the p65 subunit inhibits IKK enzymatic activity and p65 DNA-binding capacity, respectively. The dithiocarbamate adduct formed by reaction of the isothiocyanate with thiol groups on NF-kappaB subunits directly impairs transactivation. Additionally, Nrf2-mediated upregulation of HO-1 and other antioxidant enzymes reduces intracellular reactive oxygen species, which are required as signaling intermediates for sustained NF-kappaB activation [7].

The net anti-inflammatory consequence is reduced expression of proinflammatory cytokines, reduced prostaglandin synthesis through COX-2 suppression, and reduced nitric oxide production through iNOS suppression. This anti-inflammatory

activity is the molecular basis for the reported efficacy in preclinical models of inflammatory bowel disease, neuroinflammation, airway inflammation, arthritis, and diabetic complications.

4.3 Histone deacetylase inhibition

The Myzak et al. (2004) report from the Dashwood laboratory at Oregon State University identified a novel mechanism of sulforaphane chemoprotection: inhibition of histone deacetylase (HDAC) enzymes by the mercapturic acid pathway metabolites of sulforaphane, specifically the cysteine conjugate (SFN-Cys) and the N-acetylcysteine conjugate (SFN-NAC) [8].

The parent sulforaphane compound was not an effective HDAC inhibitor in cell-free assays. However, SFN-Cys and SFN-NAC, generated by cellular metabolism through the mercapturic acid pathway, fitted within the HDAC active site through a dithiocarbamate interaction with the catalytic zinc ion, producing competitive inhibition. In HCT116 human colorectal cancer cells, sulforaphane treatment dose-dependently increased global histone H3 and H4 acetylation, increased acetylated histone association with the p21(WAF1/CIP1) promoter (demonstrated by chromatin immunoprecipitation), and induced p21 protein expression, leading to cell cycle arrest at G2/M [8].

Subsequent studies extended the HDAC inhibition to additional cancer cell lines and to in vivo rodent models. The HDAC inhibitory activity produces epigenetic derepression of silenced tumor suppressor genes and contributes to the cell cycle arrest, differentiation, and apoptosis observed in cancer cells treated with sulforaphane at concentrations achievable by dietary or supplemental intake (1 to 15 micromolar). The mechanism is complementary to the Nrf2-mediated cytoprotection and operates through a metabolite-dependent pathway, distinguishing sulforaphane from direct HDAC inhibitors such as vorinostat and trichostatin A [16].

4.4 Additional molecular targets

Sulforaphane has been reported to modulate additional signaling pathways at pharmacologically relevant concentrations, including: inhibition of phase 1 cytochrome P450 enzymes (CYP1A1, CYP1A2, CYP3A4) involved in carcinogen bioactivation, providing a bifunctional (phase 1 inhibition plus phase 2 induction) chemoprotective mechanism [17]; activation of the mitogen-activated protein kinase (MAPK)

cascade (ERK1/2, JNK, p38) which intersects with Nrf2 phosphorylation and stabilization; modulation of the SIRT1 deacetylase pathway; and interaction with the TrkB neurotrophin receptor signaling pathway, which has been proposed as a contributing mechanism for the neurobehavioral effects observed in autism spectrum disorder studies [18].

4.5 Composite pharmacology

The composite molecular pharmacology of sulforaphane at dietary and supplemental doses (producing approximate peak plasma concentrations of 0.5 to 2 micromolar in humans after administration of 100 to 200 micromoles) provides simultaneous engagement of the Keap1-Nrf2 cytoprotective axis (CD approximately 0.2 micromolar, well within achieved plasma concentrations), NF-kappaB suppression (effective concentrations 1 to 10 micromolar, achievable in tissue at upper supplemental doses), and HDAC inhibition (effective concentrations of metabolites approximately 3 to 15 micromolar, achievable in colorectal tissue after oral dosing). The relative contribution of each mechanism varies by tissue, by dose, and by the specific endpoint under investigation. The Nrf2-mediated cytoprotective mechanism is the most robustly characterized, the most potently engaged at dietary doses, and the principal basis for the chemopreventive and detoxification applications.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Sulforaphane is rapidly absorbed from the gastrointestinal tract after oral administration. The compound is a small, lipophilic molecule (molecular weight 177 g/mol) with favorable membrane permeability. Absorption occurs predominantly in the proximal small intestine. Peak plasma concentration is reached within 1 to 3 hours after ingestion of free sulforaphane; when glucoraphanin is administered as the precursor (requiring myrosinase or microbial conversion), peak plasma concentration is delayed and more variable, with time to peak of 3 to 6 hours depending on the formulation and the myrosinase source [12, 13].

Oral bioavailability of free sulforaphane (as from broccoli sprout homogenates with intact myrosinase or from purified sulforaphane) is approximately 70 to 80 percent. Bioavailability of sulforaphane from glucoraphanin-only preparations (without exogenous myrosinase) is substantially lower, approximately 10 to 40 percent, with high interindividual variability attributable to differences in gut microbial thioglucosidase activity. Co-administration of exogenous myrosinase (from mustard seed or daikon radish) with glucoraphanin preparations increases bioavailability approximately 2- to 4-fold in most subjects [4, 12].

The Shapiro et al. (2006) crossover study in healthy volunteers demonstrated that bioavailability of sulforaphane from a broccoli sprout preparation with active myrosinase was approximately 7-fold greater than bioavailability from a glucoraphanin-rich preparation in which myrosinase had been heat-inactivated [12]. The Egner et al. (2011) study confirmed these findings in a larger cohort and established the sulforaphane-rich preparation as the preferred pharmacokinetic form for clinical research [13].

5.2 Distribution

Sulforaphane has a large apparent volume of distribution (approximately 60 liters, or approximately 0.8 L/kg for a 75 kg individual), consistent with extensive tissue distribution beyond the vascular compartment. The compound is not extensively protein-bound in plasma. Tissue distribution studies in rodents demonstrate rapid accumulation in liver, kidney, intestinal mucosa, lung, and other organs; central nervous system penetration has been demonstrated by measurement of sulforaphane and its metabolites in brain tissue of rodents after oral dosing [19].

Peak plasma concentrations after oral administration of 200 micromoles of sulforaphane (approximately 35 mg) in healthy volunteers are in the range of 0.9 to 2.3 micromolar, typically achieved within 1 to 3 hours of dosing. The intracellular concentration in target tissues (gut epithelium, hepatocytes) may exceed plasma concentration owing to active glutathione conjugation and intracellular trapping of dithiocarbamate metabolites.

5.3 Metabolism

Sulforaphane is metabolized extensively through the mercapturic acid pathway, the principal biotransformation route for electrophilic isothiocyanates in mammals. The pathway proceeds as follows: (a) conjugation with glutathione (GSH), catalyzed by glutathione S-transferases, to form the sulforaphane-glutathione conjugate (SFN-GSH); (b) sequential enzymatic cleavage of the glutathione tripeptide by gamma-glutamyltranspeptidase to yield the sulforaphane-cysteinylglycine conjugate (SFN-CysGly); (c) cleavage by dipeptidases to yield the sulforaphane-cysteine conjugate (SFN-Cys); and (d) N-acetylation by N-acetyltransferases to yield the sulforaphane-N-acetylcysteine conjugate (SFN-NAC, the terminal mercapturic acid) [20].

All four conjugates (SFN-GSH, SFN-CysGly, SFN-Cys, SFN-NAC) are detectable in human plasma and urine after oral sulforaphane administration. The SFN-Cys and SFN-NAC conjugates are the predominant urinary metabolites and together account for the majority of recovered sulforaphane equivalents. As noted in Section 4.3, the SFN-Cys and SFN-NAC metabolites are themselves biologically active as HDAC inhibitors.

Importantly, sulforaphane is not a significant substrate of the cytochrome P450 system for its own metabolism. It does, however, modulate CYP expression: sulforaphane inhibits CYP1A1, CYP1A2, CYP1B1, and CYP3A4 at micromolar concentrations, an activity that contributes to its bifunctional (phase 1 inhibition plus phase 2 induction) chemopreventive mechanism [17].

5.4 Elimination

The plasma elimination half-life of sulforaphane in humans is approximately 1.8 to 2.2 hours, making it a short-lived compound requiring repeated daily dosing to maintain sustained pharmacodynamic effect [12, 13]. Total body clearance is rapid, with urinary excretion of 60 to 80 percent of administered sulforaphane equivalents (as mercapturic acid pathway conjugates) within 24 hours of dosing. Fecal excretion accounts for a minor fraction. The pharmacodynamic effects (Nrf2 target gene induction, HDAC inhibition) outlast the plasma residence of the parent compound, with NQO1 and HO-1 mRNA elevations persisting for 24 to 48 hours after a single dose, consistent with the transcriptional rather than receptor-occupancy nature of the mechanism.

5.5 Routes of administration

Oral administration is the standard route for all clinical and research applications. Sulforaphane has been administered as: (a) broccoli sprout homogenates or juices with active myrosinase (highest bioavailability, but variable dose); (b) broccoli sprout extracts standardized to glucoraphanin content, with or without co-administered myrosinase; (c) purified sulforaphane in capsule or liquid formulation; and (d) broccoli sprout beverages prepared from hot water infusion of sprout powder (used in the Qidong environmental detoxification trials) [11].

Topical administration has been studied for skin cancer chemoprevention. Talalay et al. (2007) demonstrated that topical application of broccoli sprout extract to human skin induced NQO1 in the treated area and protected against ultraviolet radiation-induced erythema [21]. Topical sulforaphane is not in widespread clinical use.

Intravenous and parenteral administration have not been studied in humans. The compound is suitable for oral administration given its favorable oral bioavailability, and the clinical research base is entirely oral.

5.6 Special populations

Pharmacokinetic data in pediatric populations are limited but have been generated in the autism spectrum disorder trials [9]. The GSTM1 genotype (glutathione S-transferase mu 1, present in approximately 50 percent of the population) affects the rate of glutathione conjugation and may modulate both pharmacokinetics and pharmacodynamic response; GSTM1-null individuals show altered urinary metabolite profiles and, in some cancer chemoprevention studies, differential response to sulforaphane-containing interventions [22]. Elderly pharmacokinetics have not been separately characterized. Pregnancy and lactation data are absent; the safety of supplemental doses during pregnancy has not been established.

6. Preclinical Pharmacology

6.1 Cancer chemoprevention models

Sulforaphane has demonstrated chemopreventive and antitumor activity in a broad range of preclinical models. In chemically induced carcinogenesis models, sulforaphane administered orally or by gavage reduced tumor incidence in the DMBA-induced mammary tumor model in rats, the azoxymethane-induced colon tumor model in mice, the benzo[a]pyrene-induced forestomach tumor model in mice, and the DMBA/TPA-initiated skin tumor model in mice [23]. In xenograft models, sulforaphane inhibited growth of human prostate cancer (PC-3, LNCaP, DU145), breast cancer (MDA-MB-231, MCF-7), colon cancer (HCT116, HT-29), lung cancer (A549), bladder cancer (UM-UC-3), and pancreatic cancer cell lines at concentrations of 1 to 30 micromolar [24].

The antitumor mechanisms in these models include: Nrf2-mediated induction of phase 2 detoxification enzymes (protecting against carcinogen-DNA adduct formation); HDAC inhibition with epigenetic reactivation of p21, Bax, and other tumor suppressors; cell cycle arrest at G2/M through CDC2 and cyclin B1 modulation; induction of apoptosis through mitochondrial and death receptor pathways; inhibition of angiogenesis through HIF-1alpha and VEGF suppression; and inhibition of cancer stem cell self-renewal through Wnt/beta-catenin and Hedgehog pathway modulation [24, 25].

6.2 Neurological and neurobehavioral models

Preclinical models supporting the neurobehavioral applications include: rescue of social interaction deficits and repetitive behaviors in BTBR T+Itpr3tf/J mice (a model of autism-like behavior) by sulforaphane treatment at 1 to 5 mg/kg; improvement of cognitive function in rodent models of traumatic brain injury, ischemic stroke, and Alzheimer's disease through Nrf2-mediated neuroprotection and NF-kappaB-mediated neuroinflammation suppression; and improvement in the methionine-induced hyperhomocysteinemia model of cognitive impairment [18, 26].

6.3 Metabolic models

In rodent models of type 2 diabetes, sulforaphane reduced hepatic glucose production through suppression of gluconeogenic gene expression (G6Pase, PEPCK), improved insulin sensitivity, reduced hepatic steatosis, and normalized plasma glucose in high-fat diet and streptozotocin models. The Axelsson et al. (2017) study used a computational gene signature approach to identify sulforaphane as the compound whose transcriptional signature most strongly opposed the gene expression pattern of type 2 diabetes liver, and confirmed the mechanism in db/db mice and in diet-induced obese mice before the human trial [10].

6.4 Anti-inflammatory and anti-infective models

Sulforaphane suppressed *Helicobacter pylori* colonization and gastric inflammation in a murine infection model, with the mechanism attributed to Nrf2-mediated upregulation of gastric mucosal defense and direct bacteriostatic activity at high concentrations [27]. The compound also reduced airway inflammation in mouse models of asthma and chronic obstructive pulmonary disease, reduced retinal inflammation in models of diabetic retinopathy, and protected against renal ischemia-reperfusion injury through Nrf2 activation.

7. Clinical Evidence Base

7.1 Cancer chemoprevention

Multiple clinical trials have evaluated sulforaphane-containing preparations for cancer chemoprevention biomarkers and clinical endpoints.

Prostate cancer: A double-blind randomized placebo-controlled trial by Cipolla et al. (2015) in 78 men with rising prostate-specific antigen (PSA) after radical prostatectomy for prostate cancer reported that daily sulforaphane (60 mg, equivalent to approximately 340 micromoles) for 6 months produced a significantly longer PSA doubling time compared to placebo (28.9 versus 15.5 months, $p = 0.033$) [28]. The effect was not maintained after discontinuation, suggesting a cytostatic rather than curative mechanism. A Phase 2 trial by Alumkal et al. (2015) in men with recurrent prostate cancer found that 200 micromoles of sulforaphane-rich broccoli sprout extract daily for up to 20 weeks did not achieve the primary endpoint of a 50 percent PSA decline in the majority of subjects, though a subgroup showed PSA stabilization [29].

Breast cancer: The Cornblatt et al. (2007) study demonstrated that a single oral dose of broccoli sprout preparation induced NQO1 and HO-1 mRNA in breast ductal cells obtained by random periareolar fine needle aspiration, providing pharmacodynamic evidence that oral sulforaphane reaches the mammary epithelium at Nrf2-activating concentrations [30]. Subsequent trials have examined sulforaphane for breast cancer biomarker modulation, with positive signals for HDAC inhibition in peripheral blood mononuclear cells.

Bladder cancer: The Alumkal laboratory and others have examined sulforaphane in bladder cancer prevention, based on the observation that mercapturic acid pathway metabolites of sulforaphane are concentrated in urine, producing high urinary tract epithelial exposure. Clinical data are limited to biomarker and pharmacokinetic studies.

Environmental carcinogen detoxification: The Egner et al. (2014) crossover trial in 291 participants in Qidong, China (a region with high aflatoxin and air pollution exposure) demonstrated that a broccoli sprout beverage providing approximately 600 micromoles of sulforaphane equivalents daily for 12 weeks produced rapid and

sustained increases in urinary excretion of benzene-mercapturic acid (61 percent increase) and acrolein-mercapturic acid (23 percent increase), providing direct evidence for enhanced detoxification of environmental carcinogens [11].

7.2 Autism spectrum disorder

The Singh et al. (2014) randomized double-blind placebo-controlled trial enrolled 44 young men (aged 13 to 27 years) with moderate to severe autism spectrum disorder and randomized them to sulforaphane derived from broccoli sprout extract (50 to 150 micromoles daily based on body weight) or placebo for 18 weeks, followed by a 4-week washout period [9]. The primary endpoints were the Aberrant Behavior Checklist (ABC), the Social Responsiveness Scale (SRS), and the Clinical Global Impressions-Improvement (CGI-I) scale. At 18 weeks, the sulforaphane group showed significant improvement on the ABC (mean decrease from 62.4 to 45.0, $p < 0.001$), the SRS (mean decrease from 121.5 to 105.2, $p < 0.001$), and the CGI-I scale (46 percent much improved or very much improved versus 0 percent on placebo). Improvements were observed in social interaction, aberrant behavior, verbal communication, irritability, lethargy, stereotypy, and hyperactivity subscales. The improvements reversed upon discontinuation during the 4-week washout period, consistent with a pharmacological rather than developmental mechanism.

A subsequent randomized controlled trial by Zimmerman et al. (2021) in 45 children (aged 3 to 12 years) with autism spectrum disorder administered sulforaphane (approximately 2.5 micromoles/kg/day) for 15 weeks and reported improvements on the Ohio Autism Clinical Impressions Scale and on urinary metabolomic markers of oxidative stress [31]. A prospective randomized double-blind study by Bent et al. (2018) in children with autism reported more modest results, with improvement in some but not all behavioral measures [32]. The rationale for sulforaphane in autism centers on the observations that fever transiently improves autistic behavior (possibly through heat shock protein-mediated mechanisms), that oxidative stress and glutathione depletion are documented in autism, and that Nrf2 activation by sulforaphane addresses both the oxidative stress and the inflammatory pathways implicated in autism pathophysiology.

7.3 Type 2 diabetes and metabolic syndrome

The Axelsson et al. (2017) study, published in *Science Translational Medicine*, used a computational gene signature matching approach (Connectivity Map analysis of type 2 diabetes liver gene expression) to identify sulforaphane as the compound whose transcriptional profile most potently opposed the disease signature [10]. The authors confirmed the mechanism in hepatocytes and in diabetic mouse models, demonstrating that sulforaphane reduced hepatic glucose output by suppressing the nuclear translocation of HNF4- α and by downregulating key gluconeogenic enzymes. In the randomized placebo-controlled human trial (97 obese patients with dysregulated type 2 diabetes, 12 weeks of concentrated broccoli sprout extract providing approximately 150 micromoles of sulforaphane daily), the sulforaphane group showed a significant reduction in fasting blood glucose (mean difference -0.72 mmol/L, $p = 0.023$) and glycated hemoglobin (HbA1c) compared to placebo, with effect most pronounced in obese patients with baseline HbA1c above 7.5 percent [10].

7.4 *Helicobacter pylori* infection and gastric health

A randomized placebo-controlled trial by Yanaka et al. (2009) in 50 *Helicobacter pylori*-positive subjects in Japan demonstrated that consumption of 70 g/day of broccoli sprouts (providing approximately 420 micromoles of glucoraphanin) for 8 weeks significantly reduced urease activity (a biomarker of *H. pylori* burden), serum pepsinogens I and II, and gastric mucosal inflammation compared to alfalfa sprout placebo [27]. The anti-*Helicobacter* effect reversed after discontinuation. The mechanism is attributed to combined Nrf2-mediated enhancement of gastric mucosal defense and direct antibacterial isothiocyanate activity.

7.5 Respiratory and pulmonary health

Clinical trials in chronic obstructive pulmonary disease, asthma, and air pollution exposure have examined sulforaphane for enhancement of pulmonary Nrf2-mediated antioxidant defenses. Results have been mixed. A Phase 2 study by Wise et al. (2016) in COPD patients found no significant improvement in Nrf2 target gene expression in alveolar macrophages or in clinical spirometric endpoints after 4 weeks of broccoli sprout extract [33]. The Egner et al. (2014) air pollutant detoxification

trial in Qidong demonstrated enhanced urinary excretion of benzene and acrolein conjugates, supporting the detoxification mechanism but in a non-pulmonary endpoint context [11].

7.6 Schizophrenia

Pilot clinical studies have examined sulforaphane for cognitive symptoms and biomarkers of oxidative stress in schizophrenia. Shiina et al. (2015) reported a randomized double-blind study in which broccoli sprout extract (containing 30 mg of sulforaphane) administered daily for 8 weeks to schizophrenia patients produced trends toward improvement on cognitive testing and reduction in plasma levels of oxidative stress biomarkers [34]. The evidence base in schizophrenia is preliminary and smaller than that in autism spectrum disorder.

8. Sourcing and Quality Verification

8.1 Source categories

Sulforaphane is commercially available in three principal formulation categories:

Free sulforaphane preparations: Stabilized sulforaphane (the active isothiocyanate) encapsulated in dry or oil-based matrices. These provide the highest bioavailability and the most consistent dosing. Stability is the principal challenge, as free sulforaphane is reactive and can degrade at ambient temperature over weeks to months. Reputable products use proprietary stabilization technologies (e.g., microencapsulation, cyclodextrin complexation, or cold-chain storage).

Glucoraphanin preparations with myrosinase: Dried broccoli seed or broccoli sprout extracts standardized to glucoraphanin content and co-formulated with exogenous myrosinase (typically from mustard seed). These rely on in vivo enzymatic conversion and provide intermediate bioavailability (approximately 35 to 70 percent of free sulforaphane bioavailability when myrosinase is active). The Johns Hopkins-licensed TrueBroc glucoraphanin ingredient and the Avmacol product use this approach.

Glucoraphanin-only preparations: Dried broccoli sprout or seed extracts standardized to glucoraphanin content but without exogenous myrosinase. Conversion depends entirely on gut microbial thioglucosidases and is highly variable (10 to 40 percent bioavailability). These are the most shelf-stable but the least pharmacokinetically predictable formulations.

8.2 Research-grade material

Research-grade sulforaphane (racemic DL-sulforaphane or enantiopure R-sulforaphane) is available from multiple chemical suppliers (Sigma-Aldrich, Cayman Chemical, Toronto Research Chemicals, LKT Laboratories, MedChemExpress, others) at greater than 95 percent purity by HPLC. Supply is in milligram to gram quantities. Pricing ranges from approximately \$30 to \$300 per gram depending on purity and enantiomeric specification.

8.3 Quality verification

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

- High-performance liquid chromatography (HPLC) quantification of sulforaphane content (for free sulforaphane products) or glucoraphanin content (for precursor products), with comparison to authenticated reference standards
- Mass spectrometry confirmation of molecular weight (177.03 for sulforaphane $[M+H]^+$, or 436.04 for glucoraphanin $[M-H]^-$)
- For chiral-specific applications, chiral HPLC or optical rotation measurement to confirm enantiomeric composition
- Myrosinase activity assay (sinigrin hydrolysis assay or glucose release assay) for products containing myrosinase
- Heavy metals analysis (arsenic, cadmium, lead, mercury) by inductively coupled plasma mass spectrometry, appropriate for plant-derived materials
- Microbial contamination testing (total aerobic count, yeast, mold, coliforms, *Salmonella*, *E. coli*) for sprout-derived products

Third-party analytical laboratories (Eurofins, NSF International, ConsumerLab, others) provide independent verification of supplement label claims. Substantial variability has been documented between label claims and actual sulforaphane or glucoraphanin content in commercial supplements, with some products delivering less than 50 percent of the stated dose [35].

9. Reconstitution and Handling

9.1 Stability

Free sulforaphane is chemically reactive and temperature-sensitive. The pure compound should be stored at -20 degrees Celsius in sealed amber glass vials under inert atmosphere (nitrogen or argon) for long-term storage. Under these conditions, purity is maintained for at least 12 months. At room temperature, gradual degradation occurs over weeks; at 37 degrees Celsius, significant degradation (greater than 10 percent) can occur within 72 hours.

Glucoraphanin (the precursor) is substantially more stable than sulforaphane. Dried glucoraphanin preparations are stable at room temperature for 24 months or longer when stored in sealed containers protected from moisture.

9.2 Solution preparation

For in vitro research, sulforaphane stock solutions are typically prepared at 10 to 100 millimolar in DMSO (dimethyl sulfoxide) and stored at -20 degrees Celsius in single-use aliquots. Working dilutions are made in cell culture medium; final DMSO concentration should be kept below 0.1 percent (v/v) to avoid solvent cytotoxicity. Aqueous stock solutions (in phosphate-buffered saline or water) are less stable and should be prepared fresh and used within 24 hours.

For oral research administration in humans, sulforaphane is administered in capsule form or dissolved in a beverage. Broccoli sprout preparations are typically administered as a juice, a beverage (reconstituted from powder), or as capsules. No reconstitution in bacteriostatic water or parenteral formulation is required for the standard oral route.

9.3 Light and pH sensitivity

Sulforaphane is moderately light-sensitive; amber glass or foil-wrapped containers are appropriate. The compound is most stable at mildly acidic to neutral pH (pH 4 to 7). At alkaline pH (above 8), rearrangement to the inactive nitrile can be favored.

Acidic conditions (below pH 3) can promote hydrolysis. Standard formulation pH ranges are adequate for stability.

10. Stack Interactions and Combinations

Sulforaphane interacts with several drug and supplement classes through its Nrf2-activating, CYP-modulating, and glutathione-conjugating activities. Investigators conducting research with sulforaphane, especially in chronic dosing regimens or in combination with other compounds, should consider the following:

CYP enzyme modulation: Sulforaphane inhibits CYP1A1, CYP1A2, CYP1B1, and CYP3A4 at micromolar concentrations. Concurrent administration with drugs metabolized by these enzymes (warfarin, theophylline, caffeine via CYP1A2; midazolam, cyclosporine, many statins via CYP3A4) may increase plasma concentrations of the co-administered drug. Clinical significance at dietary doses is uncertain; at high supplemental doses (greater than 200 micromoles daily), the interaction may become pharmacokinetically meaningful. Investigators should exercise caution with narrow therapeutic index drugs [17].

Glutathione-depleting agents: Sulforaphane metabolism depends on glutathione conjugation. Concurrent administration with other glutathione-depleting compounds (acetaminophen at high doses, other electrophilic supplements, alcohol) could theoretically reduce sulforaphane bioavailability and could potentiate the glutathione-depleting effect of the co-administered agent.

Other Nrf2 activators: Concurrent administration with other Nrf2 pathway activators (curcumin, resveratrol, bardoxolone methyl, dimethyl fumarate, EGCG) may produce additive or synergistic Nrf2 target gene induction. The combination of sulforaphane with curcumin has been studied in preclinical cancer models and has shown synergistic antiproliferative effects. However, excessive Nrf2 activation in established tumors has been proposed as a potential pro-tumorigenic mechanism (the "dark side of Nrf2"), and combination Nrf2 activation in cancer patients should be approached with mechanistic caution [36].

Thyroid medications: Sulforaphane, like other isothiocyanates and glucosinolate-derived compounds, has potential goitrogenic activity through competition with iodide uptake by the sodium-iodide symporter and through interference with

thyroid peroxidase activity. Individuals on thyroid hormone replacement (levothyroxine) or antithyroid medications (methimazole, propylthiouracil) should be monitored if consuming high-dose sulforaphane supplementation.

Anticoagulants and antiplatelet agents: Sulforaphane has been reported to potentiate the anticoagulant effect of warfarin in animal models, possibly through CYP-mediated interaction and through NF-kappaB-mediated modulation of coagulation factor expression. Clinical significance is not established, but concurrent use with warfarin warrants monitoring of the international normalized ratio (INR).

Chemotherapy agents: Preclinical studies have examined sulforaphane in combination with cisplatin, doxorubicin, 5-fluorouracil, gemcitabine, and other cytotoxic agents. In most cancer cell line studies, sulforaphane enhanced cytotoxic efficacy (through HDAC inhibition, NF-kappaB suppression, and cancer stem cell targeting). However, the Nrf2-mediated cytoprotective mechanism can theoretically protect cancer cells from oxidative damage induced by certain chemotherapy agents, creating a potential for antagonism. The interaction is context-dependent and cancer-type-specific.

Dietary interactions: Cooking (boiling, microwaving, steaming for extended periods) inactivates myrosinase in cruciferous vegetables and substantially reduces sulforaphane yield. Brief steaming (1 to 3 minutes) preserves myrosinase activity while making glucoraphanin more bioavailable. Co-consumption of raw mustard, radish, or wasabi (which contain active myrosinase) with cooked cruciferous vegetables can restore sulforaphane conversion from residual glucoraphanin.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events reported in clinical trials at doses of 25 to 200 micromoles of sulforaphane daily (approximately 4 to 35 mg) or equivalent glucoraphanin preparations are:

- Gastrointestinal disturbance (flatulence, bloating, abdominal discomfort): reported in 5 to 20 percent of subjects, dose-dependent, generally mild and self-limiting
- Loose stools or increased bowel frequency: reported in 5 to 15 percent of subjects at higher doses
- Nausea: infrequent (less than 5 percent) at standard doses; more common at doses above 200 micromoles daily
- Taste or odor complaints: the isothiocyanate has a pungent, sulfurous taste and odor; encapsulated forms mitigate this

These adverse-event rates are drawn from pooled data across the clinical trial literature and are consistent with the expected effects of a dietary isothiocyanate on gastrointestinal function.

11.2 Goitrogenic potential

Isothiocyanates as a class are goitrogenic at high doses in animal models, interfering with thyroid iodide uptake and thyroid hormone synthesis. At dietary and standard supplemental doses of sulforaphane (up to 200 micromoles daily), clinically significant thyroid effects have not been reported in euthyroid subjects in clinical trials. However, individuals with pre-existing hypothyroidism, iodine deficiency, or autoimmune thyroid disease (Hashimoto's thyroiditis) should be monitored if consuming high-dose sulforaphane supplementation. The goitrogenic potential is primarily a class effect of isothiocyanates rather than a specific toxicity of sulforaphane [37].

11.3 Hepatic considerations

At very high doses in rodent studies (doses producing plasma concentrations substantially above those achieved by human supplementation), sulforaphane has produced mild hepatic enzyme elevations and, in some models, paradoxical hepatotoxicity attributed to excessive electrophilic stress and glutathione depletion. Clinical trials in humans at standard doses have not reported hepatotoxicity. The Axelsson et al. (2017) trial monitored liver function tests and found no clinically significant changes [10].

11.4 Pregnancy and lactation

The safety of supplemental sulforaphane during pregnancy and lactation has not been established in controlled studies. Cruciferous vegetable consumption during pregnancy is not contraindicated and is consistent with standard dietary guidelines; however, concentrated sulforaphane supplements at doses substantially exceeding dietary intake have not been studied for developmental or reproductive toxicity in humans.

11.5 Drug interaction safety

The CYP inhibition and glutathione modulation activities of sulforaphane create potential for pharmacokinetic drug interactions as described in Section 10. No severe drug interactions have been reported in published clinical trials, but concurrent use with narrow therapeutic index drugs (warfarin, cyclosporine, theophylline) warrants caution and monitoring.

11.6 Long-term safety

Long-term safety data (beyond 6 months of continuous supplementation) are limited. The longest published controlled trial is the 6-month Cipolla et al. (2015) prostate cancer recurrence study, which reported no serious adverse events attributable to sulforaphane [28]. Epidemiological data consistently associate higher cruciferous vegetable intake with reduced cancer incidence and cardiovascular mortality, providing indirect support for long-term safety of dietary sulforaphane exposure. Extrapolation of these epidemiological observations to concentrated supplement doses requires caution.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative cytoprotective compounds against sulforaphane, evaluated against five competency standards: Nrf2 activation potency, clinical evidence breadth, bioavailability and pharmacokinetic favorability, side-effect profile, and overall validation. The five compounds were selected as the principal dietary or nutraceutical Nrf2 activators or cruciferous-derived cytoprotective agents with substantive human pharmacology data, with priority on those that share sulforaphane's research positioning.

12.1 Curcumin

Mechanism: Curcumin (diferuloylmethane), the principal polyphenol of turmeric (*Curcuma longa*), activates Nrf2 through electrophilic modification of Keap1 cysteine residues and through Nrf2 stabilization via PI3K/Akt signaling. Additional mechanisms include NF-kappaB suppression, COX-2 inhibition, and STAT3 pathway modulation.

Nrf2 activation potency: Curcumin is approximately 13-fold less potent than sulforaphane in standardized NQO1 induction assays (CD value approximately 2.7 micromolar versus 0.2 micromolar for sulforaphane) [15]. The lower potency is compounded by poor oral bioavailability.

Clinical evidence breadth: Extensive. Over 200 clinical trials have examined curcumin across indications including osteoarthritis, inflammatory bowel disease, metabolic syndrome, depression, and cancer adjuvant therapy. Effect sizes have been modest and frequently not replicated in well-powered trials, attributed in part to poor bioavailability.

Bioavailability: Very low. Oral bioavailability of unformulated curcumin is less than 1 percent, owing to poor aqueous solubility, rapid intestinal and hepatic glucuronidation, and rapid systemic clearance. Bioavailability-enhanced formulations (phytosome, nanoparticle, piperine co-administration) improve absorption 5- to 50-fold but still achieve peak plasma concentrations in the low-nanomolar range, below the in vitro effective concentrations for Nrf2 activation.

Side-effect profile: Generally well tolerated. Gastrointestinal disturbance at high doses. Iron chelation concerns with chronic high-dose use. Rare hepatotoxicity reports with high-dose bioavailability-enhanced formulations.

Overall validation: Moderate. The very extensive clinical trial literature has produced mixed results, with the bioavailability limitation as the principal pharmacokinetic barrier. Curcumin is the most widely consumed Nrf2-activating nutraceutical globally but is less pharmacologically validated than sulforaphane at the molecular and clinical level.

Comparison to sulforaphane: Sulforaphane is substantially more potent as an Nrf2 activator, has dramatically higher oral bioavailability (70 to 80 percent versus less than 1 percent for unformulated curcumin), and has produced more mechanistically coherent clinical results. Curcumin has a broader clinical trial base by number but lower pharmacokinetic plausibility for systemic Nrf2-mediated effects.

12.2 3,3'-Diindolylmethane (DIM)

Mechanism: DIM is an acid condensation product of indole-3-carbinol (I3C), the indole glucosinolate hydrolysis product co-occurring with sulforaphane in cruciferous vegetables. DIM activates Nrf2 (less potently than sulforaphane), modulates estrogen metabolism (shifting the 2-hydroxyestrone to 16- α -hydroxyestrone ratio), and inhibits NF- κ B signaling.

Nrf2 activation potency: DIM activates Nrf2 but is substantially less potent than sulforaphane in NQO1 induction assays. DIM is classified as a bifunctional inducer (inducing both phase 1 and phase 2 enzymes), whereas sulforaphane is a monofunctional inducer (primarily phase 2) [38].

Clinical evidence breadth: Moderate. Clinical trials have examined DIM for cervical dysplasia (CIN), prostate cancer biomarkers, breast cancer prevention biomarkers, and hormonal balance in premenstrual syndrome. A Phase 3 trial (DIVA trial) in cervical dysplasia was the most advanced clinical program.

Bioavailability: Moderate. DIM is absorbed after oral administration, with bioavailability enhanced by microencapsulated formulations (BioResponse DIM). Peak plasma concentrations are in the low-micromolar range.

Side-effect profile: Generally well tolerated. Darkening of urine (a benign metabolite effect), gastrointestinal disturbance at high doses. Theoretical concern for estrogen-modulating effects in hormone-sensitive populations.

Overall validation: Low to moderate. The compound has produced Phase 2 and Phase 3 clinical data in cervical dysplasia and cancer biomarker endpoints but has not achieved regulatory approval. DIM is positioned primarily as a hormone-modulating rather than Nrf2-activating agent.

Comparison to sulforaphane: Sulforaphane is a substantially more potent Nrf2 activator. DIM has a complementary but distinct mechanism centered on estrogen metabolism modulation. The two compounds derive from different glucosinolate classes in the same plant family and are sometimes co-supplemented. Sulforaphane has a broader and more mechanistically diverse clinical evidence base.

12.3 Dimethyl fumarate (Tecfidera)

Mechanism: Dimethyl fumarate (DMF) is a synthetic fumaric acid ester that activates Nrf2 through electrophilic modification of Keap1 Cys151, the same principal cysteine targeted by sulforaphane. DMF also suppresses NF-kappaB signaling and modulates T-cell differentiation. It is approved by the FDA for relapsing-remitting multiple sclerosis (marketed as Tecfidera and Vumerity).

Nrf2 activation potency: High. DMF is a potent Nrf2 activator in cell-based assays, with effective concentrations in the low-micromolar range, comparable to sulforaphane. The active metabolite monomethyl fumarate (MMF) is the principal circulating Nrf2 activator after oral DMF administration [39].

Clinical evidence breadth: Extensive for multiple sclerosis. The DEFINE and CONFIRM Phase 3 trials in over 2,600 relapsing-remitting MS patients demonstrated significant reduction in annualized relapse rate and MRI lesion burden. DMF has not been studied broadly in cancer chemoprevention, metabolic disease, or autism.

Bioavailability: Good for the metabolite MMF after oral administration of DMF enteric-coated capsules. Rapid hydrolysis of DMF to MMF in the gut.

Side-effect profile: Significant. Flushing (40 percent), gastrointestinal disturbance (30 to 40 percent), lymphopenia (rare but potentially severe, with cases of progressive multifocal leukoencephalopathy reported in lymphopenic patients).

The side-effect burden is substantially greater than sulforaphane.

Overall validation: High for multiple sclerosis. DMF is the only Nrf2 activator with FDA approval for a clinical indication. However, the approval is for an autoimmune neuroinflammatory condition, not for the chemopreventive or metabolic indications where sulforaphane is studied.

Comparison to sulforaphane: DMF is the only Nrf2 activator with full regulatory approval and Phase 3 clinical validation, making it the most clinically validated compound in this comparator set. However, its side-effect burden (flushing, GI effects, lymphopenia) is substantially greater than sulforaphane, making it unsuitable for the preventive, dietary supplement, and general research contexts in which sulforaphane is used. The two compounds share the Keap1-Cys151 modification mechanism but differ in chemical class, side-effect profile, and clinical positioning.

12.4 EGCG (Epigallocatechin gallate)

Mechanism: EGCG, the principal catechin polyphenol of green tea (*Camellia sinensis*), activates Nrf2 through multiple mechanisms including oxidation-mediated Keap1 thiol modification, inhibition of EGFR and PI3K/Akt signaling, DNMT1 inhibition (epigenetic), and direct antioxidant activity.

Nrf2 activation potency: EGCG activates Nrf2 at concentrations above 50 micromolar in most cell-based assays, making it over 100-fold less potent than sulforaphane. The Nrf2-activating mechanism is secondary to the direct antioxidant and kinase-inhibitory activities [15].

Clinical evidence breadth: Extensive, though primarily for cardiovascular risk reduction, metabolic syndrome, and cancer chemoprevention. Over 100 clinical trials have examined green tea extracts or EGCG. Effect sizes for cancer chemoprevention have been modest in most randomized trials. A positive Phase 2 trial for prevention of progression from oral leukoplakia to oral cancer was notable.

Bioavailability: Low. Oral bioavailability of EGCG is approximately 2 to 5 percent, limited by poor stability, extensive hepatic methylation and glucuronidation, and efflux transport. Peak plasma concentrations after typical supplemental doses (400 to 800 mg EGCG) reach approximately 0.1 to 1 micromolar, below the concentrations required for Nrf2 activation.

Side-effect profile: Generally well tolerated at moderate doses. Hepatotoxicity has been reported with high-dose green tea extract supplements (typically above 800 mg EGCG daily), leading to cautionary labeling. Caffeine content of some green tea extracts adds stimulant effects.

Overall validation: Moderate to high for cardiovascular and metabolic endpoints; low for Nrf2-specific applications.

Comparison to sulforaphane: Sulforaphane is dramatically more potent as an Nrf2 activator (over 100-fold in standardized assays) and has much higher oral bioavailability. EGCG has a broader chemical biology (kinase inhibition, DNMT inhibition, direct antioxidant) but lower pharmacokinetic plausibility for Nrf2-mediated effects at achievable plasma concentrations.

12.5 Bardoxolone methyl (CDDO-Me)

Mechanism: Bardoxolone methyl is a synthetic triterpenoid and the most potent known small-molecule Nrf2 activator. It modifies Keap1 Cys151 (the same residue as sulforaphane) with subnanomolar potency in cell-based NQO1 induction assays. Additional mechanisms include NF-kappaB suppression, modulation of the TGF-beta/Smad pathway, and direct anti-inflammatory activity.

Nrf2 activation potency: Extremely high. The CD value for NQO1 induction in Hepa 1c1c7 cells is approximately 0.001 micromolar, approximately 200-fold more potent than sulforaphane [40].

Clinical evidence breadth: Limited but consequential. The BEAM Phase 2 trial in patients with chronic kidney disease and type 2 diabetes (227 patients, 52 weeks) demonstrated significant improvement in estimated glomerular filtration rate (eGFR). The subsequent BEACON Phase 3 trial in 2,185 patients with stage 4 chronic kidney disease and type 2 diabetes was terminated early due to excess cardiovascular serious adverse events (heart failure hospitalizations and deaths) in the bardoxolone methyl arm. A subsequent Phase 3 program (CARDINAL) in Alport syndrome (a genetic kidney disease in a younger, lower-risk population) met its primary endpoint of eGFR improvement.

Bioavailability: Good oral bioavailability at clinical doses.

Side-effect profile: Significant. The BEACON trial cardiovascular safety signal (fluid retention, heart failure exacerbation, hypertension) limits the clinical applicability to populations without cardiovascular comorbidity. Muscle spasms, hepatic enzyme elevations, and weight loss have been reported.

Overall validation: High for Nrf2 pathway proof-of-concept; moderate for clinical utility. The compound has demonstrated the most robust clinical Nrf2 activation of any agent but carries significant safety limitations.

Comparison to sulforaphane: Bardoxolone methyl is approximately 200-fold more potent as an Nrf2 activator than sulforaphane but carries substantially greater safety risk. Sulforaphane has a dramatically superior safety profile and is accessible as a dietary supplement, while bardoxolone methyl requires prescription use in a restricted patient population. The two compounds validate the Nrf2 pathway from opposite ends of the potency-safety spectrum.

12.6 Comparator summary

The five compounds span a broad range of Nrf2 activation potency, clinical development, and safety profiles. **Curcumin** is the most widely consumed but least pharmacokinetically plausible Nrf2 activator, limited by sub-1-percent oral bioavailability. **DIM** is a complementary cruciferous-derived compound with estrogen metabolism modulation as its primary mechanism. **Dimethyl fumarate** is the only FDA-approved Nrf2 activator (for multiple sclerosis) but carries significant side-effect burden. **EGCG** is a broad-mechanism polyphenol with low Nrf2 potency and low bioavailability. **Bardoxolone methyl** is the most potent Nrf2 activator known but has serious cardiovascular safety limitations.

Sulforaphane occupies a unique and favorable position in this comparator landscape: it is the most potent naturally occurring Nrf2 activator, has excellent oral bioavailability (70 to 80 percent), has the broadest clinical evidence base among dietary Nrf2 activators (over 80 interventional trials across cancer chemoprevention, autism, diabetes, infection, and environmental detoxification), and has the most favorable safety profile of any potent Nrf2 activator. The principal limitations relative to the comparators are the short plasma half-life (requiring multiple daily dosing for sustained effect), the variable bioavailability of glucoraphanin-based formulations, and the absence of any regulatory approval as a drug. For research applica-

tions requiring Nrf2 pathway activation in human subjects, sulforaphane remains the best-validated, most accessible, and safest option among the evaluated compounds.

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