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Sulforaphane and Cancer Prevention: A Comprehensive Study of Extraction, Structural Properties, and Therapeutic Potential

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Abstract

Cancer is a leading cause of mortality worldwide, primarily driven by uncontrolled cell proliferation, metastasis, and resistance to conventional therapies. Natural bioactive compounds have gained attention as safer and potentially effective complements to synthetic drugs. Sulforaphane (SFN), an isothiocyanate generated from glucoraphanin in cruciferous vegetables such as broccoli, cabbage, and cauliflower, has emerged as a promising anticancer agent. This review examines the structural properties, natural sources, extraction strategies, pharmacokinetics, and therapeutic mechanisms of SFN in cancer prevention and treatment. Advances in solvent-based, microwave-assisted, ultrasound-assisted, high-pressure, and green-solvent extraction have improved SFN recovery and purity. Mechanistically, SFN modulates carcinogen metabolism, inhibits phase I enzymes, induces phase II detoxification enzymes, activates Keap1-Nrf2-ARE signaling, regulates epigenetic modifications, and triggers apoptosis through intrinsic and extrinsic pathways. Preclinical studies indicate that SFN can suppress tumor initiation, progression, angiogenesis, and metastasis across multiple cancer types. Nanocarrier-based delivery systems, particularly polymeric micelles and related formulations, may further enhance stability, bioavailability, and targeted release. Collectively, SFN represents a promising nutraceutical and adjunctive therapeutic candidate. Future research should prioritize standardized extraction, dose optimization, long-term safety evaluation, and well-designed clinical trials.

Keywords: Sulforaphane; cruciferous vegetables; glucoraphanin; extraction methods; anticancer activity

1. Introduction

Cancer remains a formidable global health challenge and is among the leading causes of death worldwide, with nearly 10 million cancer-related deaths reported annually [1]. Despite substantial advances in surgery, radiotherapy, and chemotherapy, outcomes for many patients remain limited by tumor recurrence, metastasis, and the emergence of drug resistance [2]. Conventional cancer treatments can also produce severe adverse effects that compromise therapeutic tolerance and quality of life [3]. These challenges underscore the need for safer, more effective, and cost-efficient preventive and adjunctive strategies.

Dietary phytochemicals have gained considerable attention as potential agents for cancer prevention and adjunctive therapy. Among these, sulforaphane (SFN), a naturally occurring isothiocyanate produced through the hydrolysis of glucoraphanin and found predominantly in cruciferous vegetables such as broccoli and cauliflower, has emerged as a bioactive compound with multifaceted anticancer effects [4]. Preclinical and clinical evidence indicates that SFN can modulate carcinogen activation, detoxification enzymes, oxidative stress, apoptosis, and epigenetic regulation, supporting its potential role in cancer chemoprevention [5].

Recent advances in extraction, structural characterization, and nanocarrier-based delivery systems have improved SFN stability and bioavailability, thereby expanding its therapeutic potential [6]. Given its broad biological activity, low toxicity at dietary exposures, and natural origin, SFN is increasingly recognized as a promising preventive nutraceutical and adjunctive agent in oncology. This review evaluates the chemical characteristics, natural sources, extraction and stabilization techniques, pharmacokinetics, anticancer mechanisms, safety considerations, and future translational priorities for SFN.

2. Structure and Physicochemical Properties of Sulforaphane

Sulforaphane (SFN; IUPAC name: 1-isothiocyanato-4-(methylsulfinyl)butane) is a small, electrophilic organosulfur compound classified within the isothiocyanate family. Its molecular formula is $C_6H_{11}NOS_2$, and it has a molar mass of 177.29 $g \cdot mol^{-1}$[7,8]. Structurally, SFN consists of a four-carbon alkyl chain bearing a terminal isothiocyanate group (–N=C=S) and a methylsulfinyl (–S(=O)–CH_3) substituent at the ω-position. This arrangement imparts moderate polarity and significant electrophilicity at the carbon of the isothiocyanate moiety, which is central to its bioactivity [7]. SFN is a low-molecular-weight liquid exhibiting solubility in organic solvents such as dimethyl sulfoxide (DMSO), methanol, and acetonitrile and has measured logP values near zero, indicative of balanced hydrophilic-lipophilic properties that enable reasonable membrane permeability despite limited aqueous solubility [9].

2.1. Chemical Reactivity and Biological Implications

The electrophilic carbon within sulforaphane's isothiocyanate group (–N=C=S) exhibits high reactivity toward nucleophilic centers, especially thiol (–SH) groups present on cysteine residues of cellular proteins. This covalent modification process is central to sulforaphane's biological activity and proceeds via nucleophilic addition where the thiolate anion attacks the electrophilic carbon atom, forming a thiocarbamoyl adduct. This interaction underlies two interconnected biological mechanisms. First, sulforaphane selectively targets sensor cysteine residues on the regulatory Kelch-like ECH-associated protein 1 (Keap1), a substrate adaptor for Cullin-3-dependent ubiquitination of the transcription factor Nrf2. Covalent modification of these cysteines induces a conformational change in Keap1, thereby inhibiting Nrf2 ubiquitination and degradation. Consequently, stabilized Nrf2 translocates to the nucleus, where it binds antioxidant response elements (AREs) in the promoters of target genes, initiating a robust cytoprotective transcriptional program. This pathway upregulates phase II detoxification enzymes such as glutathione S-transferases and NAD(P)H:quinone oxidoreductase 1, enhances antioxidant defenses, and promotes cellular redox homeostasis [8,10].

Second, sulforaphane undergoes enzymatic conjugation with glutathione (GSH), primarily mediated by glutathione S-transferase (GST), forming SFN-GSH conjugates. These conjugates are further metabolized via the mercapturic acid pathway into cysteinylglycine, cysteine, and N-acetylcysteine conjugates, which are excreted in urine. This metabolic processing not only facilitates detoxification and elimination but also reflects the reversible or semi-persistent nature of SFN's thiol adducts, which is integral to its sustained activation of adaptive stress responses [11]. Additionally, these thiol modifications can transiently alter the redox status of cells. By modifying protein thiols and depleting GSH levels, SFN elicits mild oxidative stress that paradoxically triggers apoptosis in cancer cells while promoting survival pathways in normal cells. This hormetic effect is a key mechanistic foundation of SFN's chemopreventive and anticancer properties [12]. The high specificity of SFN for reactive cysteine residues, combined with the reversible dynamics of thiol conjugation, enables it to function as a potent inducer of cellular defense mechanisms with relatively low toxicity, distinguishing it from classical electrophilic toxins.

2.2. Stability, Biosynthesis, and Processing Effects

In plants, SFN is not stored as a free compound but exists primarily as its inert precursor glucoraphanin, a glucosinolate abundant in cruciferous vegetables such as broccoli and cabbage. The biosynthesis of glucoraphanin is a complex, multi-step process originating from the amino acid methionine [13]. This pathway includes side-chain elongation, core glucosinolate structure formation through oxidation, conjugation, carbon-sulfur cleavage, glycosylation, and sulfation, followed by secondary modifications via flavin-containing monooxygenases to yield glucoraphanin as the final product [13,14].

Upon disruption of plant tissue integrity, such as during chewing, chopping, or processing, glucoraphanin comes into contact with the enzyme myrosinase, a β-thioglucosidase that hydrolyzes glucoraphanin to release glucose and an unstable aglucone intermediate. This aglucone spontaneously rearranges to form sulforaphane, the biologically active isothiocyanate [13]. The efficiency of this conversion is influenced by accessory proteins such as epithiospecifier protein (ESP), which can direct hydrolysis toward nitrile formation rather than isothiocyanate. Moderate heat treatment can inactivate ESP, thereby favoring sulforaphane production, whereas high temperatures denature myrosinase and prevent sulforaphane formation altogether [13,15].

Chemical stability of sulforaphane is limited under conditions of prolonged heating, acidic pH, or oxidative environments. These vulnerabilities necessitate mild processing and extraction techniques coupled with stabilizing strategies like encapsulation or complexation with cyclodextrins to preserve activity during storage and delivery [16]. Importantly, mammals do not produce endogenous myrosinase, meaning conversion of glucoraphanin to sulforaphane is partially reliant on gut microbiota enzymatic activity. Variability in gut microbial composition impacts the bioavailability of sulforaphane from dietary sources, highlighting the interplay between processing, host biology, and therapeutic efficacy [17]. Thus, optimizing sulforaphane yield and stability involves careful control of food processing parameters, such as moderate heating to inactivate ESP while retaining myrosinase activity, and advancements in formulation technologies to protect sulforaphane from degradation, enhancing its chemopreventive potential.

2.3. Pharmacokinetics and Bioavailability

Following oral ingestion of SFN-rich foods or formulated supplements, sulforaphane is rapidly absorbed in the gastrointestinal tract. Once absorbed, SFN undergoes conjugation with glutathione (GSH) facilitated by glutathione S-transferases, forming SFN-GSH conjugates. These conjugates enter the mercapturic acid pathway, sequentially metabolizing into cysteinylglycine, cysteine, and N-acetylcysteine derivatives that serve as primary metabolites and are eventually excreted in the urine. Measurement of urinary N-acetylcysteine conjugates is widely used as a biomarker to assess systemic SFN exposure [18,19]. Pharmacokinetic studies indicate that sulforaphane exhibits a two-compartment model disposition with a terminal half-life of approximately 6 to 8 hours, demonstrating relatively rapid plasma clearance and mean residence times around 4 hours. Peak plasma concentrations (C_max) of sulforaphane and its metabolites are typically reached within 1 to 3 hours post-ingestion, although values vary depending on the dose, formulation, and food matrix [20].

Human studies reveal considerable interindividual variability in SFN bioavailability, primarily shaped by the presence and activity of myrosinase (either plant-derived or microbial), gut microbiota composition capable of glucoraphanin hydrolysis, and the food matrix effect. Notably, subjects consuming SFN precursors without active myrosinase experience lower systemic exposures compared to those ingesting myrosinase-active preparations [18,19,21]. Pharmacodynamic correlations demonstrate that SFN exposure induces expression of various phase II detoxification and antioxidant enzymes such as NAD(P) H: quinone oxidoreductase 1 (NQO1), glutathione peroxidase-1 (GPx-1), and heme oxygenase-1 (HO-1) in peripheral blood mononuclear cells, with temporal gene expression peaks corresponding to plasma SFN levels. The concentration for half-maximal gene induction (SC_50) varies from approximately 1.5 μM for NQO1 to above 40 μM for GPx-1, indicating differential sensitivity of target genes to SFN [20,21].

3. Natural Sources of Sulforaphane

Sulforaphane (SFN) is not stored in plants in its active form but is generated from the hydrolysis of its biosynthetic precursor glucoraphanin, an aliphatic glucosinolate derived from methionine. Glucoraphanin is predominantly found in members of the Brassicaceae family, commonly known as cruciferous vegetables, which include broccoli (*Brassica oleracea* var. *italica*), cauliflower (*B. oleracea* var. *botrytis*), cabbage (*B. oleracea* var. *capitata*), kale

(*B. oleracea* var. *sabellica*), brussels sprouts (*B. oleracea* var. *gemmifera*), and turnip (*Brassica rapa*). Mechanical disruption of plant tissues activates the enzyme myrosinase (β-thioglucosidase), catalyzing the conversion of glucoraphanin to SFN. When plant myrosinase is denatured during cooking, gut microbiota can partially mediate this conversion [22]. A schematic overview of the dietary sources and biosynthetic pathway of sulforaphane is presented in Figure 1. Broccoli sprouts, in particular, are considered the richest source, containing several-fold higher glucoraphanin content compared with mature florets. Other cruciferous vegetables, including cabbage, kale, Brussels sprouts, cauliflower, and turnip, also contribute substantially to dietary SFN intake. Following cellular disruption, the glucosinolate precursor glucoraphanin is converted into SFN by the action of endogenous myrosinase or gut microbial enzymes. The efficiency of this process is strongly influenced by agronomic factors, genetic background, and cooking methods. For instance, steaming preserves myrosinase activity and enhances SFN release, while prolonged boiling can lead to enzyme denaturation and significant loss of bioactive compound.

3.1. Broccoli and Broccoli Sprouts

Broccoli (*Brassica oleracea* var. *italica*) stands out as the most extensively studied and richest dietary source of glucoraphanin, the precursor of sulforaphane (SFN). Mature broccoli florets typically contain approximately 20–50 mg glucoraphanin per 100 g fresh weight (equivalent to about 0.36 to 0.88 μmol/g) under field and greenhouse cultivation conditions [13]. However, glucoraphanin concentration in broccoli florets shows considerable variability depending on genotype, environmental factors, and agricultural practices.

Broccoli sprouts, harvested 3–5 days after germination, exhibit markedly higher glucoraphanin concentrations, often 20- to 50-fold greater than mature broccoli heads, typically ranging from 200 to 1000 mg per 100 g fresh weight. This elevated content makes broccoli sprouts the most potent natural source of SFN identified to date [13,23]. These sprouts have become widely utilized in experimental research and clinical studies exploring SFN's chemopreventive and therapeutic properties. Processing and preparation methods are critical in preserving myrosinase activity and optimizing SFN availability from broccoli sources. For instance, mild heating can maintain enzymatic activity and enhance SFN yield, whereas high heat treatments denature myrosinase, reducing SFN formation [24].

3.2. Cabbage and Cauliflower

White and red cabbage (*Brassica oleracea* var. *capitata*) are widely consumed cruciferous vegetables containing appreciable levels of glucoraphanin. Studies report glucoraphanin concentrations in cabbage ranging from approximately 10 to 30 mg per 100 g fresh weight, with variations attributed to genotype, cultivation, and environmental factors [25]. Red cabbage, in particular, is notable not only for glucoraphanin but also for its rich anthocyanin content and other antioxidants, which may synergize with sulforaphane's chemopreventive activities, enhancing its functional properties [23].

Cauliflower (*Brassica oleracea* var. *botrytis*), especially its inflorescence, contains a diverse array of sulfur-containing compounds, including glucoraphanin and related glucosinolates. Glucoraphanin levels in cauliflower tend to be lower than in cabbage and broccoli, often around 10–20 mg per 100 g fresh weight; nevertheless, the enzymatic hydrolysis of these glucosinolates can yield sulforaphane and other bioactive isothiocyanates under appropriate conditions [26]. The glucoraphanin content and antioxidant profile of these vegetables vary significantly based on cultivar, plant part, storage, and preparation techniques, thereby influencing the overall potential for sulforaphane generation upon consumption.

3.3. Kale, Turnip, and Brussels Sprouts

Kale (*Brassica oleracea* var. *sabellica*) and turnip (*Brassica rapa*) are moderate sources of glucoraphanin. Turnip roots have been reported to contain approximately 20–35 mg glucoraphanin per 100 g fresh weight, contributing notably to dietary intake of SFN precursors [22]. Kale, especially young sprouts, exhibits higher glucoraphanin levels often comparable to or exceeding those in mature forms of broccoli, with some studies reporting glucoraphanin concentrations in kale sprouts around 70–80 μmol/g dry weight, which corresponds roughly to 15–25 mg per 100 g fresh weight when adjusted for moisture [27]. Brussels sprouts (*Brassica oleracea* var. *gemmifera*) are among the richest glucoraphanin-containing cruciferous vegetables after broccoli sprouts, typically containing 100–120 mg glucoraphanin equivalents per 100 g fresh weight, making them a significant dietary source of SFN [28]. The variations in glucoraphanin content across these vegetables reflect species

differences, agronomic conditions, and developmental stages, which should be considered when optimizing dietary strategies or sourcing materials for SFN extraction.

3.4. Non-traditional Sources: Papaya and Other Plants

While cruciferous vegetables remain the primary reservoirs for sulforaphane (SFN) precursors, recent research has identified alternative plant sources containing glucosinolate derivatives capable of yielding SFN or related isothiocyanates upon enzymatic hydrolysis. Notably, seeds of Chilean papaya (*Vasconcellea pubescens*) have been found to contain glucosinolates that can generate SFN and analogs, highlighting their emerging potential as nutraceuticals beyond traditional cruciferous matrices [29].

Additionally, certain radish and mustard cultivars produce glucoraphanin analogs and other glucosinolates, although typically at lower concentrations compared to broccoli and its sprouts. These non-traditional sources broaden the diversity of SFN precursors available for dietary and therapeutic applications but require further agronomic and biochemical characterization to optimize their utility [22]. The identification and characterization of these alternative glucosinolate-containing plants open avenues for exploration in biofortification, sustainable sourcing, and novel formulation strategies, which could enhance the accessibility and sustainability of SFN-based interventions.

3.5. Factors Affecting Sulforaphane Content

The concentration of glucoraphanin, the direct precursor of sulforaphane (SFN), in cruciferous vegetables is highly variable and influenced by multiple factors spanning plant genetics, cultivation, post-harvest handling, and food processing. Genotypic differences among cultivars can lead to significant variation in glucoraphanin content, underscoring the importance of selecting high-glucoraphanin varieties for both consumption and industrial extraction [30]. Environmental and agronomic factors, including soil sulfur availability, nitrogen-to-sulfur (N:S) ratios, light exposure, temperature, and irrigation, also play pivotal roles. For example, sulfur fertilization and balanced N:S ratios can enhance glucosinolate biosynthesis, thereby increasing glucoraphanin accumulation [24].

Post-harvest treatment and storage conditions critically affect SFN yield upon consumption. Mild steaming is beneficial as it inactivates epithiospecifier protein (ESP), which diverts glucoraphanin hydrolysis toward the formation of biologically inactive nitriles rather than active SFN. Conversely, prolonged boiling or high-temperature cooking promotes myrosinase denaturation and leaching of water-soluble compounds, significantly reducing SFN bioavailability [31]. The presence and activity of myrosinase is essential for converting glucoraphanin into SFN during ingestion. While plant myrosinase is often inactivated through cooking, gut microbiota can partially compensate by hydrolyzing glucoraphanin to SFN, although with considerable interindividual variability [30]. Additionally, other factors such as pH, reaction time, and the presence of cofactors like ascorbic acid influence both enzymatic hydrolysis efficiency and SFN stability, thereby affecting the final bioactive compound yield.

Cruciferous vegetables particularly broccoli sprouts, brussels sprouts, and cabbage form the primary dietary sources of sulforaphane (SFN). The amount of glucoraphanin, SFN's precursor, varies widely depending on species, genotype, developmental stage, and growth conditions. Post-harvest handling, storage, and culinary processing critically impact SFN yield, with mild steaming techniques favoring enzyme preservation and prolonged boiling reducing bioavailability. These factors highlight the necessity for targeted agricultural practices and optimized food preparation to maximize SFN intake. The broad diversity of natural sources also presents promising opportunities for biotechnological improvements and scalable extraction methods, which will be discussed in the upcoming section. A summary of natural dietary and non-traditional sources of sulforaphane, along with their glucoraphanin content, is presented in Table 1.

Table 1. Natural sources of sulforaphane and their glucoraphanin content.

Source (Plant/Part)	Glucoraphanin Content	Key Notes	References
Broccoli florets	20–50 mg/100 g fresh weight	Widely studied; glucoraphanin levels vary by genotype and cultivation	[13], [23]
Broccoli sprouts (3–5 days old)	200–1000 mg/100 g fresh weight	20–50 times higher glucoraphanin than mature broccoli; most potent SFN source	[13], [24]
Brussels sprouts	100–120 mg/100 g fresh weight	Rich in glucoraphanin; important dietary source	[28]

Kale sprouts	~70–80 µmol/g dry weight (~15–25 mg/100 g fresh)	High content in young sprouts	[27]
Turnip roots	20–35 mg/100 g fresh weight	Moderate source of glucoraphanin	[22]
Cabbage (white/red)	10–30 mg/100 g fresh weight	Red cabbage rich in anthocyanins, synergistic antioxidants	[25]
Cauliflower	10–20 mg/100 g fresh weight	Lower levels than broccoli and sprouts	[26]
Chilean papaya seeds	Variable (trace levels)	Emerging non-cruciferous source of glucosinolates	[29]

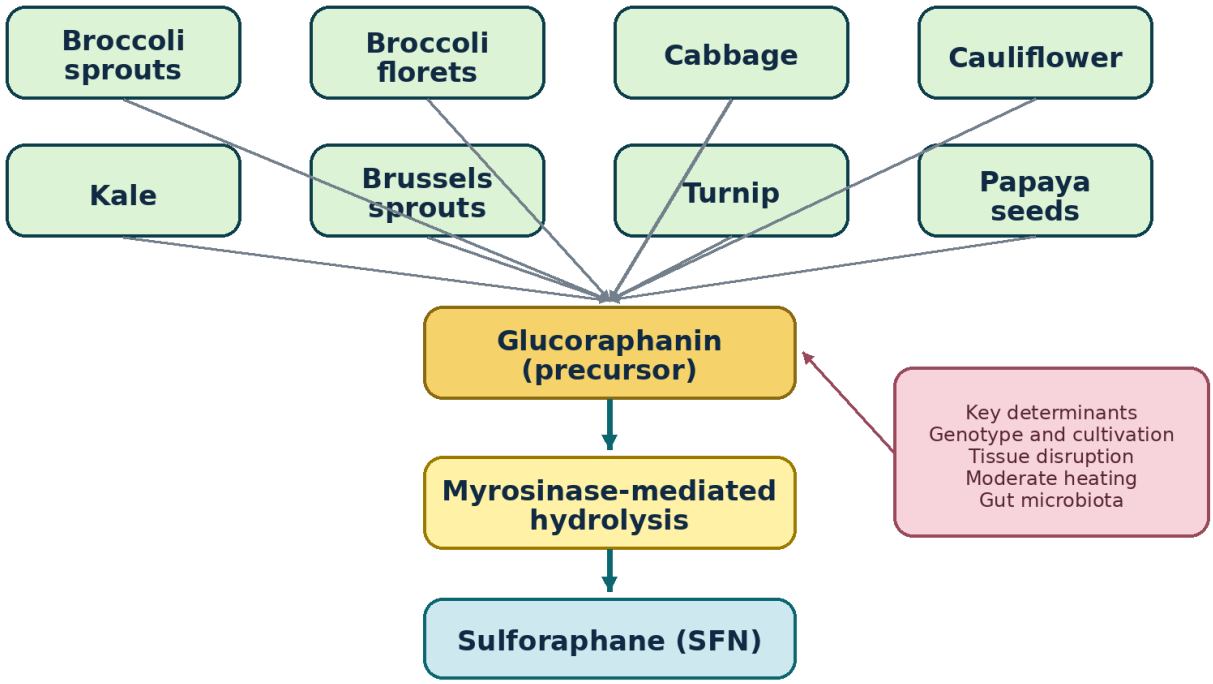

Figure 1. Major dietary sources and biosynthetic conversion of glucoraphanin to sulforaphane through myrosinase-mediated hydrolysis.

4. Extraction, Purification, and Stabilization of Sulforaphane

Accurate and high-yield extraction of sulforaphane (SFN) from plant matrices presents technical challenges due to SFN's enzymatic origin from glucoraphanin (via myrosinase), chemical lability (sensitivity to heat, oxidation, and extreme pH), and poor aqueous solubility. Successful recovery depends on two interconnected goals: (A) maximizing enzymatic conversion of glucoraphanin to SFN and (B) isolating and stabilizing free SFN with minimal degradation. This section reviews contemporary extraction techniques—both conventional and emerging—analytical methods for quantification and purification, as well as scale-up and formulation considerations [32].

Extraction methods play a pivotal role in determining the yield, stability, and bioactivity of sulforaphane. Conventional solvent extraction remains widely applied but is often constrained by solvent toxicity, long processing times, and risk of compound degradation. In contrast, advanced techniques such as microwave-assisted extraction (MAE) and ultrasound-assisted extraction (UAE) have significantly improved extraction efficiency while reducing processing time and preserving enzyme activity. More recently, green chemistry–based approaches, including deep eutectic solvents (DES) and supercritical CO_2 extraction, have demonstrated excellent recovery rates, environmental compatibility, and scalability for industrial applications. Additionally, non-thermal methods such as high-pressure processing (HPP) and pulsed electric fields (PEF) have emerged as promising alternatives for maintaining myrosinase activity and enhancing glucoraphanin hydrolysis. A comparative summary of these extraction strategies, along with their respective advantages and limitations, is presented in Table 2.

Table 2. Comparative advantages and limitations of major sulforaphane extraction methods.

Extraction Method	Main Principle	Advantages	Limitations	References

Solvent Extraction	Organic solvents (e.g., dichloromethane, ethyl acetate) after hydrolysis	Simple, widely used, compatible with chromatography	Toxic solvents, long processing, risk of SFN degradation	[32], [34]
Microwave-Assisted Extraction (MAE)	Rapid heating, enhanced mass transfer	High efficiency, short time, good yield	Risk of enzyme inactivation, SFN degradation if overheated	[33], [38]
Ultrasound-Assisted Extraction (UAE)	Acoustic cavitation disrupts cells	Preserves enzyme activity, high efficiency, eco-friendly	Requires optimization to prevent overheating	[39], [40]
Deep Eutectic Solvents (DES)	Green solvents with salting-out effect	High efficiency (>97%), reusable, eco-friendly	Limited regulatory approval, requires validation	[32], [41]
Supercritical CO_2 (SFE)	CO_2 + co-solvents under pressure	Solvent-free, scalable, high purity, eco-friendly	Expensive setup, needs strict parameter optimization	[34], [42]
High-Pressure Processing (HPP)	Non-thermal disruption, preserves enzymes	Maintains myrosinase activity, enhances yield	High capital cost	[42], [43]
Pulsed Electric Fields (PEF) / HVED	Electroporation or discharge disrupts cells	Improves glucoraphanin hydrolysis, energy-efficient	Technical complexity, limited data	[44], [45]

4.1 Two Prerequisite Steps: Controlled Hydrolysis and Matrix Pretreatment

Sulforaphane (SFN) is enzymatically generated from its precursor glucoraphanin through the action of myrosinase, making controlled enzymatic hydrolysis a fundamental initial step in extraction protocols. Optimal hydrolysis conditions strongly favor SFN formation over the generation of biologically inactive nitriles. These favorable conditions typically include a neutral to slightly acidic pH range (approximately 5 to 7), moderate temperatures (20–40 °C) to deactivate epithiospecifier protein (ESP) while preserving myrosinase activity, and well-defined incubation durations to maximize conversion efficiency without inducing non-enzymatic degradation [33,34]. Mechanical disruption techniques such as milling, grinding, blanching, or freeze-thawing are essential to bring the enzyme and substrate into close proximity, facilitating effective hydrolysis. In cases where plant-derived myrosinase activity is compromised due to heat processing, gut microbiota or exogenously supplied myrosinase can catalyze the conversion during or post-extraction [35].

Hydrolysis time significantly influences SFN yield. Short incubations, often around 15 to 60 minutes under optimized temperature and pH, achieve high molar conversion rates of glucoraphanin to SFN while suppressing competing degradation pathways [33,34]. Prolonged incubation may lead to SFN degradation or diminished enzyme activity. Metal ions such as Fe^{2+} bind with ESP to form complexes that promote nitrile formation, reducing SFN yields. Chelating agents like EDTA can mitigate this effect by sequestering metal ions, enhancing SFN production [36]. Careful monitoring and adjustment of these parameters during matrix pretreatment define the success of downstream SFN extraction and concentration steps.

4.2 Conventional Solvent Extraction and Its Limits

Traditional isolation of sulforaphane (SFN) from plant sources primarily involves organic solvent extraction using solvents such as dichloromethane, ethyl acetate, and hexane/ethanol mixtures following enzymatic hydrolysis. These solvents offer good compatibility with downstream purification methods, including solid-phase extraction (SPE), silica gel chromatography, gel permeation chromatography (GPC), and high-performance liquid chromatography (HPLC) [34]. However, conventional solvent extraction faces several notable limitations. The need for large volumes of organic solvents raises environmental and health concerns due to the toxicity and volatility of solvents like dichloromethane. Extended exposure to solvent and ambient conditions may induce thermal and oxidative degradation of the chemically labile SFN molecule, reducing overall yield. The processing times are often long, and solvent recovery adds further complexity and cost to the extraction workflow [32].

Recent improvements focus on optimizing solvent selection to reduce toxicity, such as substituting halogenated solvents with ethyl acetate or ethanol-containing mixtures, minimizing exposure time, and integrating mild physical assistance like sonication and microwave energy. These combined approaches enhance mass transfer and extraction efficiency while mitigating SFN degradation and solvent use [37]. Solid-phase extraction using silica cartridges with ethyl acetate as the washing solvent and dichloromethane as the elution solvent has shown superior selectivity and yield for SFN purification, with 4 mL dichloromethane providing optimal elution efficiency [34].While solvent extraction remains foundational for SFN isolation, evolving greener, faster, and safer methods are vital to minimizing environmental impact and improving industrial feasibility.

4.3 Microwave-Assisted Extraction (MAE)

Microwave-Assisted Extraction (MAE) harnesses microwave energy to rapidly heat the solvent and plant matrix, thereby enhancing mass transfer and significantly reducing extraction time. When applied to cruciferous

vegetables, MAE expedites glucoraphanin solubilization and, in conjunction with controlled enzymatic hydrolysis, markedly improves sulforaphane (SFN) yields [33]. Optimal parameters, including microwave power, exposure time, and solvent type, vary depending on the matrix. High microwave power or prolonged exposure risks degradation of SFN and inactivation of the vital enzyme myrosinase. Consequently, short microwave pulses and moderate power settings, combined with rapid cooling, are recommended to maximize yield and preserve enzyme functionality [37]. Recent studies demonstrate that MAE can reduce extraction times from several hours to minutes while maintaining or enhancing SFN content compared to conventional methods, owing to improved solvent infiltration and cell wall disruption. The careful balance of microwave parameters thus allows MAE to be a powerful and efficient technique for SFN extraction, with potential scalability for industrial applications [38].

4.4 Ultrasound-Assisted Extraction (UAE) and Combined Pretreatments

Ultrasound-Assisted Extraction (UAE) utilizes acoustic cavitation to enhance solvent penetration, disrupt cell walls, and improve mass transfer at comparatively mild temperatures. This makes UAE especially suitable for preserving myrosinase activity during the crucial pre-hydrolysis step or for assisting the direct extraction of formed sulforaphane (SFN). Recent research demonstrates that applying UAE to broccoli by-products or seeds significantly increases SFN recovery compared to passive solvent extraction methods [39]. Moreover, combining microwave-assisted extraction (MAE) pretreatment with UAE yields synergistic improvements in both extraction yield and processing speed. MAE disrupts plant tissues and solubilizes glucoraphanin effectively, thereby enhancing subsequent UAE efficiency. Optimization of UAE operational parameters such as ultrasound frequency, amplitude, duty cycle, solvent-to-solid ratio, and temperature—is vital to maintain enzyme integrity and avoid localized overheating that could inactivate myrosinase or degrade SFN [39]. Optimized UAE protocols have reported significant increases in total SFN yield, shorter extraction times, and enhanced energy efficiency, positioning UAE as a green, scalable, and rapid approach for SFN recovery in both laboratory and industrial settings [39,40].

4.5 Green Solvent Systems and Deep Eutectic Solvents (DES)

The increasing demand for sustainable and environmentally friendly extraction methods has led to the exploration of green solvents for SFN recovery. Among these, deep eutectic solvents (DES) particularly hydrophobic DES and salting-out assisted DES aqueous two-phase systems—have demonstrated significant promise for effective SFN extraction from broccoli and related matrices [41]. Deng et al. [2023] developed a novel salting-out assisted hydrophobic DES system that markedly improved SFN partitioning from broccoli extracts. Their approach used a DES composed of methyl trioctyl ammonium chloride and ethylene glycol, with the addition of inorganic salts (e.g., KH_2PO_4) to enhance SFN extraction efficiency via a salting-out effect. Under optimized conditions, they achieved extraction efficiencies exceeding 97%, surpassing traditional organic solvent methods. Activated carbon treatment allowed the recovery of over 82.5% of SFN from DES, facilitating solvent reuse and downstream processing [32].

Theoretical studies employing Kamlet-Taft parameters and density functional theory (DFT) revealed that the hydrogen bond accepting capacity, van der Waals interactions, and electrostatic forces inherent to hydrophobic DES contribute synergistically to SFN's solubilization and selective extraction. These findings uncover the underlying molecular mechanisms driving DES extraction performance, supporting DES's tunable polarity and solvent properties as key advantages for targeting weakly hydrophobic bioactive compounds [32,41]. DES systems offer benefits including non-volatility, biodegradability, low toxicity, and design flexibility, enabling enhanced matrix disruption and compatibility with downstream processing. Collectively, these attributes position DES as sustainable alternatives to hazardous organic solvents, aligning with green chemistry principles and industrial demands for safer extraction methods of heat- and oxidation-sensitive phytochemicals like SFN [32].

4.6. Supercritical and Subcritical Fluid Extraction

Supercritical carbon dioxide (CO_2) extraction, commonly modified with polar co-solvents such as ethanol, offers a solvent-free, tunable, and scalable method suitable for industrial-scale SFN recovery. Its advantages include minimal solvent residues, environmental safety, and alignment with regulatory requirements for nutraceuticals and pharmaceuticals. However, SFN's thermal and hydrolytic sensitivity necessitates precise optimization of extraction parameters including pressure, temperature, and co-solvent concentration to prevent degradation and maintain bioactivity [34,42].

Protocols typically involve pre-treatment such as degreasing and powdering of broccoli seeds or sprout materials followed by controlled acidic hydrolysis to convert glucoraphanin to SFN before SFE. Extraction pressures generally range from 100 to 400 bar, with temperatures carefully maintained below 50 °C to balance solvent density with compound stability. Polar co-solvents such as ethanol significantly enhance the solubility of polar or moderately hydrophobic molecules like SFN in supercritical CO_2, improving extraction efficiency substantially [32,42]. Subcritical water extraction, leveraging pressurized hot water below its critical point, emerges as another green technique for extracting bioactive compounds. Yet, its elevated temperatures (100–200 °C) pose challenges for thermolabile SFN, requiring stringent control to minimize degradation [42]. Collectively, SFE and subcritical fluid extraction stand out as sustainable, scalable, and regulatory-compliant methodologies capable of producing high-purity SFN extracts for use in food, pharmaceutical, and cosmetic applications, contingent upon meticulous parameter optimization.

4.7 Non-Thermal Cell Disruption Technologies

Non-thermal cell disruption technologies such as high-pressure processing (HPP), pulsed electric fields (PEF), and high-voltage electrical discharge (HVED) provide innovative approaches to enhance sulforaphane (SFN) extraction by facilitating plant cell breakage without heat-induced enzyme inactivation. These methods maintain myrosinase activity, enabling controlled enzymatic hydrolysis of glucoraphanin and improved SFN release.

HPP applies pressures typically ranging from 100 to 600 MPa, disrupting cell walls and increasing glucosinolate accessibility. Studies demonstrate that moderate HPP treatments in broccoli preserve myrosinase function, reduce epithiospecifier protein activity, and promote SFN formation, with optimized conditions achieving significantly higher yields than conventional extraction [42,43].

PEF enhances solvent penetration and accelerates extraction kinetics through electroporation-induced cell membrane permeabilization, reducing energy consumption relative to thermal methods. However, high capital costs and technical complexity slow widespread industrial adoption. Research on broccoli seed and sprout matrices shows that PEF pretreatment improves glucosinolate extraction efficiency and SFN yields, with potential for scale-up [44]. HVED uses intense electrical discharges to induce shock waves and cavitation, disrupting plant tissues effectively. It shares advantages with PEF and HPP, maintaining enzyme activity and reducing thermal degradation risks, though data on SFN extraction remain limited and warrant further exploration. Collectively, non-thermal technologies enable efficient extraction of SFN by preserving enzymatic pathways and improving mass transfer, positioning them as promising, sustainable alternatives to traditional heat-based extraction methods for producing high-quality SFN-rich extracts [42,45].

4.8 Analytical Workflows: Cleanup, Quantification, and Method Validation

Accurate quantification of sulforaphane (SFN) requires rigorous sample cleanup to address co-extracted matrix compounds. Standard approaches include liquid–liquid extraction, solid-phase extraction (SPE), and chromatographic purification techniques to isolate SFN prior to quantification [32,46]. Quantification employs high-performance liquid chromatography equipped with ultraviolet detection (HPLC-UV), diode array detection (DAD), or liquid chromatography-tandem mass spectrometry (LC-MS/MS), each offering distinct advantages in sensitivity, selectivity, and robustness. Method validation metrics—sensitivity (limit of detection and quantification), linearity, precision, recovery, and reproducibility—are essential and must be defined for each specific matrix and extraction protocol [47,48].

Advanced analytical workflows increasingly incorporate QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe) sample preparation combined with ultra-high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS). This technique enables rapid, multi-analyte detection with reduced solvent usage, streamlined cleanup, and enhanced throughput in complex vegetable matrices [47,48]. For example, validated QuEChERS-UHPLC-MS/MS methods have demonstrated SFN recoveries exceeding 95%, with low detection limits (down to 0.05 μg/kg), highlighting their applicability for rigorous quality control and bioavailability studies [47]. Laboratories must rigorously adapt and validate these protocols according to matrix composition and instrumental platforms to ensure inter-laboratory comparability, data reliability, and accurate SFN quantification [49].

4.9 Stabilization and Formulation Immediately Post-Extraction

Sulforaphane (SFN) is chemically unstable, prone to degradation via heat, oxidation, and changes in pH, necessitating prompt stabilization immediately after extraction to preserve its bioactivity [50,51]. Rapid solvent evaporation under reduced temperature and vacuum is commonly employed to minimize thermal degradation during concentration [52]. Encapsulation techniques, such as spray-drying or freeze-drying using protein or polysaccharide carriers, form microcapsules that enhance SFN stability and protect against environmental stressors [50,51]. Cyclodextrin inclusion complexes have been shown to improve SFN solubility and protect it from degradation by encapsulation within the hydrophobic cavity of cyclodextrin molecules [53]. Nanoscale delivery systems, including liposomes, polymeric micelles, and albumin nanoparticles, offer additional routes to enhance SFN stability and bioavailability. These nanocarriers provide physical protection and controlled release, improving simulated gastrointestinal retention and targeted delivery [51,54].

Kinetic studies reveal SFN degradation follows first-order kinetics, with faster decay at elevated temperatures and non-neutral pH. Preservation at low temperatures (below 10 °C) markedly reduces breakdown during storage, as shown in broccoli tissues and isolate formulations [52]. Combining careful extraction with immediate stabilization via encapsulation or complexation is vital for maintaining SFN's therapeutic potential in functional food, pharmaceutical, and supplement applications.

4.10 Comparative Advantages, Limitations, and Recommended Workflows

For laboratory-scale extraction, microwave-assisted extraction (MAE) or UAE combined with short controlled pre-hydrolysis protocols offer rapid processing and high SFN yields using relatively modest equipment. These methods enable effective glucoraphanin conversion and SFN recovery with reduced solvent consumption and processing times [33,47]. At the green industrial scale, salting-out assisted hydrophobic DES and supercritical fluid extraction (SFE) with green co-solvents demonstrate superior sustainability, scalability, and higher extraction efficiencies compared to traditional organic solvents. Tunable solvent polarity and enhanced matrix disruption provided by DES systems, as well as solvent-free processing by SFE, support eco-friendly production. However, these approaches require careful optimization of co-solvent type and processing parameters to maximize SFN partitioning and prevent degradation [32,42].

Formulation considerations are equally critical. Coupling extraction with encapsulation or complexation techniques such as cyclodextrin inclusion, protein/polysaccharide microencapsulation, or nanoscale carriers—can significantly enhance SFN's bioavailability and shelf stability. Stabilization immediately post-extraction protects SFN from thermal, oxidative, and hydrolytic degradation, optimizing its therapeutic efficacy in foods, supplements, and pharmaceuticals [42,54].

Despite advances, notable challenges remain: (i) substantial variability across laboratories stemming from differences in plant matrices, pretreatment, and hydrolysis conditions complicates direct comparison of extraction yields [52]; (ii) incomplete or inconsistent reporting of critical pre-hydrolysis parameters in older studies hinders reproducibility; and (iii) regulatory, toxicological, and residual solvent concerns related to novel solvents like DES require comprehensive evaluation before widespread industrial application [32,42]. Continued work to standardize protocols, integrate green processing technologies, and stabilize SFN in functional formulations will be essential to fully realize SFN's health potential in commercial applications.

Standardizing pre-hydrolysis protocols including harmonization of critical parameters such as pH, temperature, incubation time, and enzyme-to-substrate ratios would greatly improve comparability of sulforaphane (SFN) yield data between laboratories. Optimal conditions reported in the literature vary, with neutral to slightly acidic pH (around 5–7), moderate temperatures (20–40°C), and incubation times ranging between 30 minutes to a few hours. Controlling these factors minimizes formation of inactive nitriles and maximizes SFN conversion, as demonstrated by several studies employing response surface methodology for enzymolysis optimization [35,36,54].

Development of green solvents, particularly deep eutectic solvents (DES), holds substantial promise for sustainable SFN extraction. However, comprehensive environmental impact assessments, biodegradability studies, and toxicity profiling are essential prerequisites before industrial scale adoption to ensure safety and regulatory compliance [32].

Integrated processing technologies combining extraction and encapsulation offer a frontier to reduce SFN exposure to degradative stresses immediately post-extraction. Continuous or inline approaches incorporating microencapsulation or complexation with cyclodextrin or protein carriers could improve SFN stability and bioavailability, enabling more effective delivery in functional foods and therapeutics [54]. Finally, the establishment of Good Manufacturing Practice (GMP)-compatible extraction and purification pipelines remains critical for producing clinical-grade SFN preparations. Such standards are essential for supporting late-stage clinical trials and eventual commercialization of SFN-based health interventions [42]. Addressing these knowledge gaps through collaborative, multidisciplinary research will be key to unlocking the full translational potential of sulforaphane. An overview of the major sulforaphane extraction methods, highlighting their underlying principles, advantages, and limitations, is provided in Table 2.

5. Anticancer Mechanisms and Therapeutic Potential

SFN is a multi-targeted small molecule that exerts chemopreventive and therapeutic activities across a broad range of malignancies. Its anticancer effects arise from a constellation of molecular actions modulation of xenobiotic metabolism, redox regulation, epigenetic remodeling, cell-cycle control, induction of programmed cell death, suppression of angiogenesis and metastasis, interference with cancer stem-cell properties, and enhancement of conventional therapies. Below, these actions are summarized with recent, high-impact evidence and mechanistic detail to support translational development.

5.1 Modulation of Carcinogen Metabolism and Activation of Cytoprotective Programs (Nrf2/ARE)

A fundamental chemopreventive mechanism of sulforaphane (SFN) involves activation of the Keap1–Nrf2–ARE pathway. Under basal conditions, Nrf2 is bound to the Keap1 homodimer, which promotes ubiquitination and proteasomal degradation of Nrf2 via the Cul3-Rbx1 E3 ligase complex. This interaction is mediated by Keap1's cysteine-rich sensor domains, notably cysteine 151, which serve as redox-sensitive switches [55].

SFN, an electrophilic isothiocyanate, covalently modifies reactive cysteine residues on Keap1, especially C151. This modification disrupts Keap1's ability to target Nrf2 for degradation, resulting in increased Nrf2 stabilization and accumulation. Stabilized Nrf2 translocates to the nucleus, where it heterodimerizes with small Maf proteins and binds antioxidant response elements (ARE) in gene promoters, inducing transcription of phase II detoxifying enzymes (e.g., NAD(P)H quinone oxidoreductase 1 [NQO1], glutathione S-transferases [GSTs], heme oxygenase-1 [HO-1]) and antioxidant proteins [56,57].

This activation enhances cellular detoxification of procarcinogens and reactive oxygen species, reducing DNA damage and mutagenesis in early tumorigenic stages. Besides redox regulation, the Nrf2 pathway mediates anti-inflammatory and cytoprotective functions that modulate the tumor-promoting microenvironment [58,59]. Robust evidence underscores SFN as one of the most potent naturally occurring Nrf2 activators, exerting effects at nanomolar concentrations partly through rapid cellular uptake and glutathione conjugate interchange. Mutation of Keap1 cysteine 151 to serine abrogates SFN-mediated Nrf2 activation, highlighting this residue's critical sensor role [55].

5.2 Epigenetic Regulation and Gene-Expression Remodeling

Sulforaphane (SFN) modulates epigenetic landscapes by inhibiting histone deacetylases (HDACs) and reducing DNA methyltransferase (DNMT) activities, leading to re-expression of tumor suppressor genes such as Nrf2 and p21, as well as alterations in microRNA profiles that promote differentiation and apoptosis. These reversible epigenetic modifications restore key regulatory pathways frequently silenced in cancer and sensitize tumors to treatment [58,60]. SFN has been shown to inhibit HDAC activity, resulting in increased histone acetylation at promoter regions of tumor suppressor genes, facilitating their transcriptional activation. Concurrently, SFN decreases DNMT expression and activity, leading to hypomethylation and reactivation of silenced genes, including Nrf2 itself, enhancing cytoprotective responses [60]. Additionally, SFN impacts the expression of oncogenic and tumor-suppressive microRNAs, modulating cellular differentiation and apoptotic pathways. The integration of SFN into combinatorial epigenetic therapies has shown synergistic inhibition of cancer cell proliferation [61,62]. These findings underscore SFN's promising role as a dietary epi-therapeutic, capable of

remodeling the aberrant epigenome in cancer cells and enhancing responsiveness to chemotherapeutic interventions.

5.3 Cell-Cycle Arrest and Induction of Apoptosis

Sulforaphane (SFN) induces cell-cycle arrest primarily at the G1 and G2/M checkpoints by modulating the expression of key regulators. It downregulates cyclins such as Cyclin D1 and Cyclin B1, which are essential for progression through these phases, while upregulating cyclin-dependent kinase (CDK) inhibitors like p21^WAF1/CIP1 and p27, effectively halting cell proliferation [58]. Various studies report that SFN causes G2/M phase arrest involving reduced levels of cell cycle proteins including cyclin B1, cdc2, and cdc25c phosphatases, accompanied by increased p21 and p53 expression, which orchestrate this checkpoint control [63]. Concomitant with cell cycle arrest, SFN activates both intrinsic (mitochondrial) and extrinsic apoptotic pathways. It elevates pro-apoptotic Bax levels, promotes cytochrome c release from mitochondria, and activates caspases 9 and 3, culminating in cleavage of the PARP protein, a hallmark of apoptosis execution. This selective induction of programmed cell death targets cancer cells while sparing normal cells [64,65]. Collectively, these molecular effects suppress tumor cell proliferation and favor apoptotic elimination, underpinning SFN's potent anticancer activity across multiple experimental models.

5.4 Oxidative Stress, ROS Signaling and Metabolic Interference

Sulforaphane (SFN) transiently elevates reactive oxygen species (ROS) levels in malignant cells, disrupting redox homeostasis and inducing apoptosis. Cancer cells are often under intrinsic oxidative stress; the additional ROS burden imposed by SFN can push them beyond survival thresholds, triggering mitochondrial dysfunction, cytochrome c release, and activation of intrinsic apoptotic pathways [66,67]. Conversely, SFN activates nuclear factor erythroid 2-related factor 2 (Nrf2) in normal cells during the later phase, promoting transcription of antioxidant enzymes (e.g., HO-1, NQO1) that mitigate oxidative damage and create a therapeutic window distinguishing cancerous from normal cells [58,68].

Moreover, SFN perturbs cancer cell metabolism. It inhibits glycolytic enzymes, disrupts mitochondrial membrane potential, and affects redox balance, impairing energy production and biosynthesis essential for tumor growth [64,67]. Antioxidant enzyme activities such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) are often not significantly altered, suggesting that SFN selectively induces ROS in cancer cells without broadly compromising cellular antioxidant defenses [69]. This dual role of SFN inducing oxidative stress in tumors while enhancing antioxidant defenses in normal tissues underpins its selective cytotoxicity and positions SFN as a promising anticancer agent targeting redox vulnerabilities of malignant cells.

5.5 Anti-Angiogenic and Anti-Metastatic Actions

Preclinical studies reveal that sulforaphane (SFN) suppresses angiogenesis by downregulating hypoxia-inducible factor 1-alpha (HIF-1α) and vascular endothelial growth factor (VEGF), key drivers of tumor vascularization. SFN inhibits endothelial cell viability, migration, and tube formation—essential steps in new blood vessel development. In various tumor models, SFN reduces expression of matrix metalloproteinases (MMPs) that facilitate extracellular matrix degradation and tumor invasion. It also blocks epithelial–mesenchymal transition (EMT), curbing cancer cell motility and metastatic potential [70,71]. SFN's anti-angiogenic effects are partly mediated via inhibition of STAT3/HIF-1α/VEGF signaling pathways, as demonstrated in hepatocellular carcinoma cell models and chick embryo assays showcasing tumor growth suppression [71].

5.6 Targeting Cancer Stem Cells and Modulating Tumor Microenvironment

SFN effectively targets cancer stem-like cells (CSCs) by inhibiting critical stemness pathways including STAT3, Notch, and Wnt/β-catenin signaling. This inhibition reduces CSC self-renewal, sphere formation, and tumor-initiating capacity, potentially preventing relapse and metastasis. SFN also modulates inflammatory and immune signaling via Nrf2 and related pathways, reprogramming the tumor microenvironment toward an anti-tumor state, enhancing immune surveillance and reducing tumor-promoting inflammation [70,72]. Together, these properties support SFN's role as a multi-modal anticancer agent disrupting tumor progression at cellular and microenvironmental levels.

5.7 Chemosensitization and Radiosensitization

Sulforaphane (SFN) potentiates the efficacy of common chemotherapeutic agents such as cisplatin, paclitaxel, and doxorubicin, as well as radiation therapy, by sensitizing cancer cells to DNA damage and impairing DNA repair mechanisms. SFN reduces the fraction of cancer stem cells (CSCs), which are often resistant to therapy, and reverses epigenetic modifications linked to drug resistance. These combined actions lead to enhanced tumor cell apoptosis and impaired tumor progression when SFN is used as an adjuvant [73]. Mechanistically, SFN modulates multiple signaling pathways involved in cell survival and proliferation, including Akt/mTOR, NF-κB, and Wnt/β-catenin, and regulates key genes such as p53, p21, survivin, Bcl-2, and caspases to promote apoptotic responses. Co-treatment with SFN and chemotherapeutics exhibits synergistic inhibition of cancer cell proliferation, invasion, and metastasis across diverse cancer models [73,74].

SFN has also been shown to activate tumor-suppressive microRNAs (e.g., miR-124) that target oncogenic signaling such as IL-6R/STAT3, further enhancing chemosensitivity and reducing tumorigenic capacity in models such as gastric cancer [74]. The radiosensitizing effects of SFN include increased oxidative stress in cancer cells, impairments to DNA repair pathways, and stimulation of apoptosis in irradiated tumors. These effects highlight SFN's promise as a combination adjuvant that may allow lowering chemotherapeutic or radiation doses, reducing toxicity while maintaining therapeutic efficacy.

5.8 In Vivo Evidence and Human Studies

Extensive animal model research demonstrates sulforaphane's (SFN) efficacy in reducing tumor incidence, growth, and metastasis across multiple cancer types including breast, lung, prostate, and colon cancers. Key mechanistic biomarkers such as induction of phase II detoxifying enzymes, reduction in proliferation marker Ki-67, and increased apoptosis have been consistently modulated following SFN treatment. In murine xenograft models, SFN significantly suppressed tumor growth, diminished cancer stem cell populations, and impaired metastatic dissemination, underpinning its therapeutic potential [75].

Early phase human clinical trials primarily utilizing broccoli sprout extracts or purified SFN preparations report biological activity, including modulation of detoxification enzymes and reduction in proliferation indices, with favorable safety and tolerability profiles. Randomized controlled trials are underway to define clinical efficacy, optimal dosing, and target patient populations in various cancer types [76]. Despite promising results, challenges remain including dose standardization, bioavailability optimization, and identification of predictive biomarkers. Larger, multi-center clinical studies with well-defined endpoints are essential for translating SFN's preclinical promise into clinical practice.

6. Limitations, Context Dependency, and Safety

Sulforaphane (SFN) exhibits multifaceted, dose- and context-dependent anticancer activities that require careful consideration for translational development. While SFN's activation of the Nrf2 pathway in normal tissues confers cytoprotective, antioxidant, and anti-inflammatory benefits, chronic, persistent Nrf2 activation in certain cancer contexts may paradoxically support tumor progression, chemoresistance, and proliferation a phenomenon recognized as the "Nrf2 paradox" [58,77]. The beneficial effects largely depend on transient, tightly regulated Nrf2 activation. In contrast, aberrant Nrf2 signaling or mutations in the Keap1-Nrf2 axis found in various tumors can lead to constitutive Nrf2 stabilization, fostering an environment conducive to cancer cell survival and resistance to chemotherapy or radiation [78].

Bioavailability of SFN is another critical factor influencing clinical outcomes. SFN is formed from the precursor glucoraphanin via myrosinase enzymatic hydrolysis, which can be endogenous or gut microbiota-derived. Variability in myrosinase source and activity, differences in gut microbial composition among individuals, and the food matrix or formulation used can drastically affect SFN's systemic absorption and biological efficacy [58,68].

Formulation strategies—including encapsulation, use of stable analogs, and co-administration of synergistic compounds—are under development to overcome these limitations, aiming to standardize delivery and improve therapeutic windows [79]. Safety data from clinical trials to date indicate that SFN is generally well tolerated at dietary and supplemental doses without serious adverse effects reported. However, long-term safety and potential

off-target effects at pharmacologic or high supplemental doses remain to be rigorously evaluated in larger, controlled clinical trials, particularly given the complex interplay with the Nrf2 pathway [58,68].

7. Conclusions and Future Perspectives

Sulforaphane (SFN), a naturally occurring isothiocyanate derived from the hydrolysis of glucoraphanin in cruciferous vegetables, has emerged as a potent multi-target anticancer compound. Its ability to regulate xenobiotic metabolism, activate the Keap1–Nrf2–ARE signaling pathway, modulate epigenetic mechanisms, induce cell-cycle arrest and apoptosis, and inhibit angiogenesis, metastasis, and cancer stem cell renewal underscores its broad-spectrum therapeutic potential. Unlike conventional chemotherapeutics, SFN offers a dual advantage—selective cytotoxicity toward cancer cells while enhancing protective antioxidant defenses in normal tissues. Advances in extraction strategies such as microwave-assisted, ultrasound-assisted, green solvent systems, and supercritical CO_2 methods, combined with stabilization and nanoformulation approaches, have significantly improved SFN yield, purity, stability, and bioavailability. Preclinical evidence strongly supports SFN's chemopreventive and therapeutic roles across various cancer models, and early-phase clinical trials confirm its biological activity and safety. However, variability in bioavailability, context dependency of Nrf2 activation, and lack of standardized dosing remain critical barriers to clinical translation.

Looking forward, several avenues must be prioritized to realize SFN's translational and industrial potential. First, optimization and scale-up of extraction technologies using sustainable, eco-friendly approaches such as deep eutectic solvents and supercritical fluids are essential for industrial-level production of high-purity SFN. Second, clinical validation and dose standardization through large, multi-center randomized trials are required to establish efficacy, safety, and therapeutic regimens across different cancers. Third, formulation advancements, particularly nanoencapsulation, polymeric micelles, and cyclodextrin complexes, should be further developed to overcome instability and variability in bioavailability. Fourth, mechanistic insights into SFN's epigenetic regulation, modulation of tumor microenvironment, and targeting of cancer stem-like cells will expand its therapeutic scope and improve combinatorial strategies with existing chemotherapies and radiotherapies. Fifth, crop improvement and microbial engineering for enriched glucoraphanin and myrosinase production offer sustainable and cost-effective solutions for large-scale SFN sourcing. Sixth, long-term safety evaluations must be performed to fully address the "Nrf2 paradox" and ensure that chronic or high-dose exposure does not inadvertently promote tumor progression in specific contexts. Finally, techno-economic and life-cycle analyses are necessary to assess the industrial feasibility and environmental benefits of SFN production from agricultural waste streams, supporting its integration into circular bioeconomy frameworks.

Declarations

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