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Review

Sulforaphane: a natural organosulfur having potential to modulate apoptosis and survival signalling in cancer

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Abstract
Owing to its ever-growing range of pharmacological advantages, sulforaphane, an isothiocyanate from cruciferous vegetables such as broccoli, is becoming increasingly popular. This review aims to provide a thorough understanding and a current update on the application of sulforaphane in cancer treatment. Sulforaphane interacts with many signaling molecules that control various pathways in malignant cells, including angiogenesis, apoptosis, cell cycle arrest, metastasis, and inflammation pathways. This review examines the effects of this isothiocyanate on inflammatory mediators, caspases, MMPs, cytokines, and the proteins Bax and Bcl-2. Furthermore, the advantages of nanotechnology and synergistic effects in sulforaphane applications are also reviewed. As per evidence, sulforaphane is a shining example of how ethno-pharmacological expertise can be used to create modern medications.

Keywords Sulforaphane · Isothiocyanate · Chemoprevention · Nanotechnology · Organosulfur

1 Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, with its incidence rising despite advancements in diagnosis and treatment [1]. Conventional therapies, including chemotherapy, radiation, and targeted treatments, have significantly improved patient outcomes, yet they are often accompanied by severe side effects, drug resistance, and

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limited efficacy in certain cancers [2, 3]. These challenges underscore the urgent need for alternative or complementary approaches that enhance treatment efficacy while minimizing adverse effects. In recent years, naturally derived compounds have gained substantial interest in oncology due to their ability to modulate multiple cellular pathways with relatively low toxicity [4–7]. Among these natural compounds, sulforaphane (SFN)-a bioactive isothiocyanate found in cruciferous vegetables like broccoli-has demonstrated exceptional anticancer potential [8]. Unlike other well-known phytochemicals such as curcumin and resveratrol, which are limited by poor bioavailability or restricted molecular targets [9, 10], SFN exhibits a broad spectrum of anticancer effects. It influences multiple cellular pathways simultaneously, including apoptosis induction, inhibition of survival signaling (NF-κB and PI3K/Akt), and modulation of oxidative stress responses [11]. Additionally, SFN's ability to cross the blood–brain barrier and epigenetically regulate gene expression sets it apart from many other plant-derived compounds [12].

Despite promising preclinical and clinical findings, several research gaps remain. Questions regarding optimal dosing, stability, and interindividual variability in metabolism and bioavailability need further investigation [13]. Moreover, SFN's efficacy in different cancer types and its potential for synergistic effects with existing therapies require more extensive clinical validation [14]. This review aims to provide a comprehensive analysis of SFN's role in cancer therapy by summarizing its molecular mechanisms, potential clinical applications, and limitations. Additionally, we highlight emerging strategies, including nanodelivery and combination therapies, that may enhance SFN's therapeutic potential. By addressing these critical gaps, this review contributes to the growing body of research supporting the use of SFN as a viable candidate for cancer treatment and prevention.

2 Chemistry and pharmacokinetics of SFN

Chemically, SFN is 1-isothiocyanato-4-methylsulfinylbutane (Fig. 1), an organosulfur that belongs to the isothiocyanate group. It is formed when glucoraphanin is converted to SFN by the enzyme myrosinase [15].

Glucoraphanin, a food-bound version of SFN, is present in numerous vegetables, including mustard, turnip, radish, watercress, cauliflower, kale, and broccoli. The approximate molecular weight of SFN is 177.28 g/mol. The chemical formula of SFN is $C_6H_{11}NOS_2$, and its average melting point is 74.6 °C, although it can vary between 58.6 °C and 91.2 °C. It dissolves in methanol, DMSO, and solvents that resemble water.

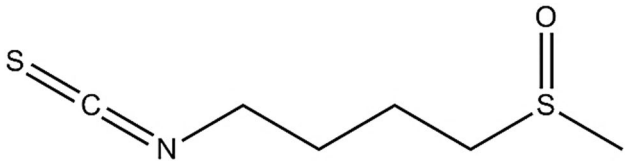
Various methods have been reported for the laboratory preparation of SFN. In one study conducted by Vermeulen et al., 1,4-dibromobutane (Fig. 2) was used as a starting material for the synthesis of SFN [16]. Alternately, it can be prepared by nucleophilic ring opening of a thiolanium salt (Fig. 3) by an azide anion [17]. Regarding the pharmacokinetics, Wang et al. (2012) reported that the plasma concentration of SFN decreased biexponentially [18].

3 Apoptotic and survival signaling modulation in cancer

3.1 Fas-FasL pathway activation by SFN

SFN has been well-known for its anticancer properties, including its capacity to cause apoptosis in tumor cells (Table 1) (Fig. 4) [19]. Various signaling pathways control the latter process, mainly the Fas/Fas ligand (Fas/FasL) signaling pathway [20]. The Fas/FasL pathway is a crucial apoptotic signaling mechanism that plays a significant role in eliminating damaged or malignant cells [21]. Fas (CD95) is a death receptor that, upon binding to its ligand FasL (CD95L), triggers a cascade of intracellular events leading to programmed cell death. SFN has been shown to upregulate Fas expression, promoting apoptosis in various cancer models [22]. However, the precise molecular mechanisms underlying this activation require further elaboration. Recent studies indicate that SFN enhances Fas expression both directly and indirectly through intermediaries such as reactive oxygen species (ROS) and transcription factors like nuclear factor kappa B (NF-κB) and p53 [23, 24]. In breast cancer cells (MDA-MB-231), SFN-mediated Fas activation is accompanied by increased ROS production, which in turn stimulates NF-κB translocation into the nucleus, enhancing Fas transcription [20]. Similarly, in ovarian cancer cells, SFN has been reported to stabilize p53, which binds to the Fas promoter region and increases Fas gene expression [25]. These findings suggest that

Fig. 1 Chemical structure of sulforaphane



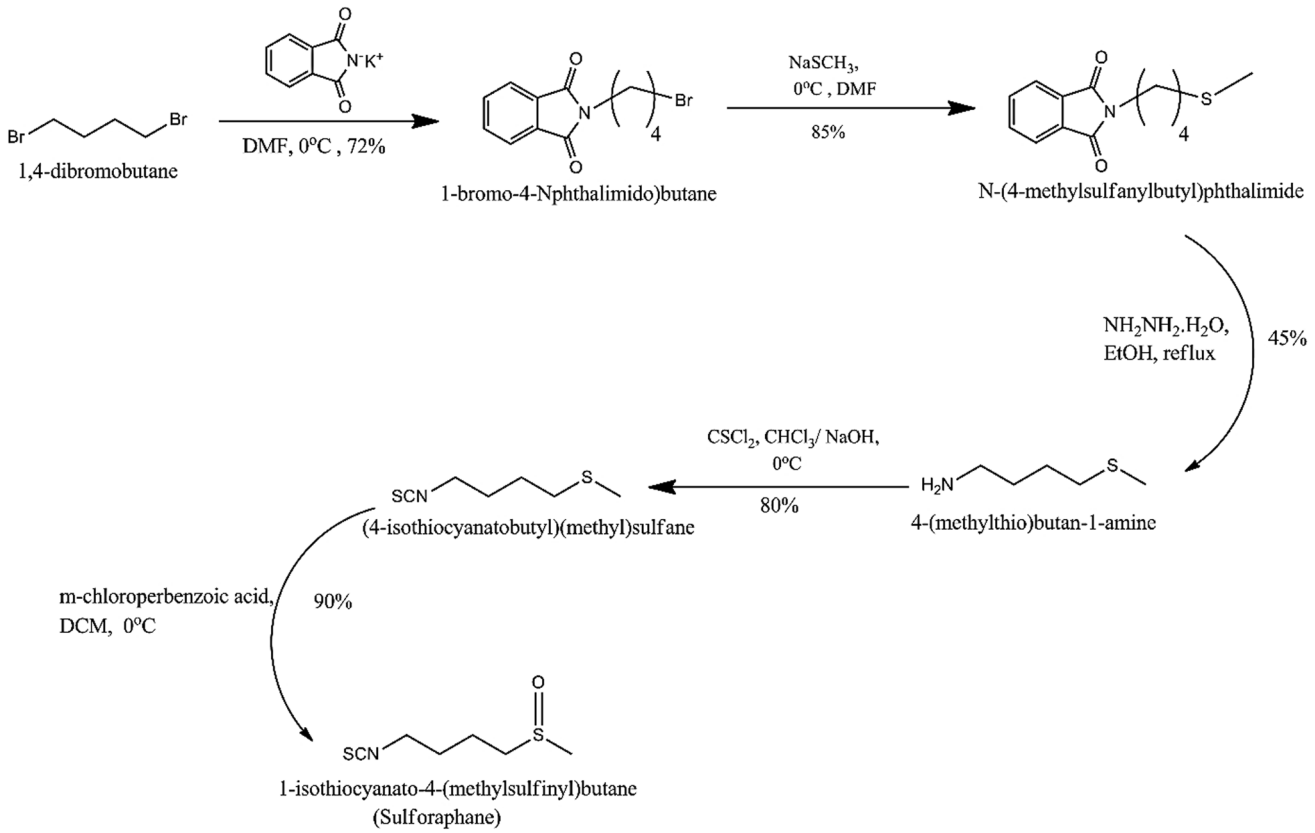


Fig. 2 Chemical synthesis of sulforaphane

SFN's effect on the Fas/FasL pathway is not solely a direct receptor-ligand interaction but is also modulated through oxidative stress and transcriptional regulation.

Beyond its direct role in apoptosis initiation, Fas/FasL signaling intersects with caspase activation and mitochondrial pathways. Upon FasL binding, caspase-8 is recruited to the Fas-associated death domain (FADD), initiating a caspase cascade leading to cell death [26]. In some cancers, SFN has been observed to amplify this response by simultaneously activating mitochondrial-mediated apoptosis through the Bcl-2/Bax ratio shift [27]. In ovarian and breast cancer models, SFN treatment has led to a 2.5-fold increase in Bax expression and a 40% reduction in Bcl-2, thereby enhancing cytochrome c release and further promoting caspase activation [28]. These dual effects—Fas/FasL activation and mitochondrial pathway modulation—highlight SFN's multifaceted approach to inducing apoptosis in cancer cells. According to Yamada et al. (2017), Fas-mediated apoptosis plays a role in healthy and diseased cellular processes, including survival and differentiation [29]. Therefore, developing potent treatments targeting the Fas/FasL system may be crucial in the fight against cancer. Pro-apoptotic genes such as FAS were expressed more frequently when SFN was present [22]. Breast cancer cells (MDA-MB-231) appear to undergo apoptosis by upregulating the Fas ligand, which activates caspase-8 and caspase-3 and causes PARP to be proteolytically cleaved [30]. Reversible mRNA modification via N6-methyl adenine (M6A) has been shown to have a significant impact on numerous pathways, including tumorigenesis and mammalian apoptosis pathways. Methyltransferase-like 3 (METTL3) is primarily responsible for controlling the methylation of m6A RNA [31]. Bi et al. reported that METTL3 overexpression in some cancers, such as ovarian cancer, decreases the apoptosis rate [23]. SFN reduces the expression of METTL3 and further activates the FAS/FADD apoptosis pathway in some cancers, such as breast cancer and ovarian and endometrial ovarian cancer (Fig. 5) [31, 32].

Several studies have demonstrated SFN's role in modulating Fas-mediated apoptosis across different cancer types: breast cancer (MDA-MB-231 and MCF-7 cells): SFN increased Fas expression by 2.3-fold, leading to significant caspase-8 and caspase-3 activation [33]; ovarian cancer (A2780 and OVCAR-3 cells): SFN enhanced FasL expression and induced apoptosis in a dose-dependent manner, with a 30% increase in Fas-mediated cell death observed at 10 μM SFN [31]; prostate cancer (DU145 cells): SFN treatment resulted in a 45% increase in Fas receptor levels, promoting apoptosis via caspase-8 activation [34]; Leukemia (HL-60 cells): SFN-mediated Fas upregulation led to

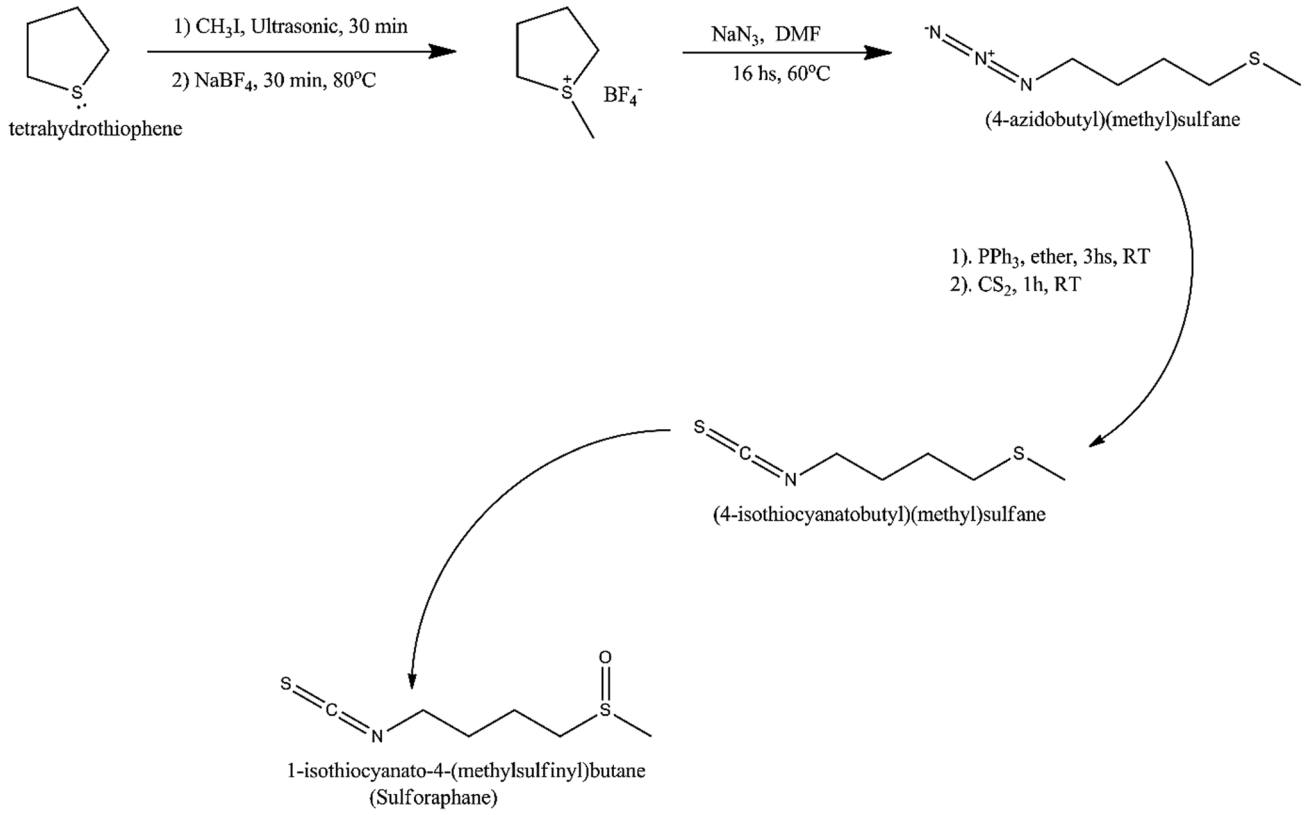


Fig. 3 Synthesis of sulforaphane by ring opening of a thiolanium salt by an azide anion

a 60% increase in apoptotic cell death, confirmed by flow cytometry analysis [35]. These findings highlight the concentration-dependent effects of SFN, where higher doses tend to produce stronger Fas activation, but also emphasize the variability in response depending on the cancer type and cellular context.

Despite these promising findings, several limitations exist regarding SFN's ability to modulate the Fas/FasL pathway. First, cancer-type specificity in which SFN-induced Fas activation appears to be more pronounced in certain cancers (e.g., breast and ovarian cancer) but less effective in highly aggressive or resistant tumors [36]. Second, dose and duration dependence in which studies indicate that prolonged SFN exposure (> 48 h) or concentrations exceeding 15 µM may lead to adaptive resistance mechanisms, where cancer cells downregulate Fas to evade apoptosis [13]. Third, ROS-dependent variability in which SFN's reliance on ROS signaling for Fas activation could make it less effective in cancers with high endogenous antioxidant capacity, such as melanoma and pancreatic cancer [37].

In summary, SFN activates the Fas/FasL apoptotic pathway through both direct Fas upregulation and indirect regulation via ROS and transcription factors like NF-κB and p53. It further enhances apoptosis by interacting with mitochondrial and caspase-dependent pathways, making it a versatile anticancer agent. While substantial evidence supports its efficacy, dose optimization, cancer-type specificity, and potential resistance mechanisms must be addressed in future research. Understanding these nuances will be crucial for translating SFN into clinically effective cancer therapies.

3.2 Modulating the Bcl2-Bax pathway by SFN

The possible signaling pathways that regulate the anticancer effects of SFN have been well documented in Table 1 and Fig. 5 [49]. It is suggested that the Bcl-2/Bax pathway promotes apoptosis in tumor cells. Bcl-2 and Bax are proteins that regulate apoptosis, and a shift in their balance can affect cell survival. Understanding the targeting of

Table 1 The anticancer activities of sulforaphane against various cancers

S. No.	Type of cancer	Subjective model	Physiological effect	Mechanism of action	References
1	Breast cancer	MDA-MB-231 and ZR-75-1 cells	Apoptosis induction, anti-proliferative effect, cell cycle arrest	↓ROS, ↓cyclin B1/Cdc2, ↓CDC25C, ↑CDK5R1	[38]
2	Intrahepatic cholangiocarcinoma	HuCCT-1 and HuH28 cells	Apoptosis induction, anti-proliferative effect, cell cycle arrest	↑G2/M, ↓VEGFA, ↓VEGFR2, ↓HIF-1α, and iNOS, ↓$Ki67^{+}$, ↑$TUNEL^{+}$, ↑ p21 and p-Chk2, ↓ p-Cdc25C	[39]
3	Prostate cancer	DU145 and PC-3 cells	Anti-autophagy, anti-proliferative effect	↑Bax, ↑Caspase 8, ↑Caspase 3, ↑JNK, and NRF2, ↓Bcl-2 – (in DU145 cells), ↑Bax and NRF2, ↓JNK, ↓Caspase 8, and Bcl-2 -(in PC-3 cells)	[40]
4	Bladder cancer	RT4, RT112, T24, and TCCSUP cell lines	Tumor growth inhibition, anti-proliferative effect	↓AKT/mTOR, ↑Acetylation of histone H3	[41]
5	Skin squamous cell carcinoma	SSCC cell line (SCC-13)	Anti-proliferative effect	↑miR-199a-5p, ↓Sirt1 and CD44ICD mRNA	[42]
6	Breast cancer	MDA-MB-231 and MDA-MB-157 cells	Anti-metastasis	↓Paxillin, ↓IQGAP1, ↓FAK, ↓PAK2, and ROCK, ↓MEK and ERK	[24]
7	Gastric cancer	Human gastric cancer AGS cells	Anti-metastasis	↓AP-1 and NF-κB, ↓p38 MAPK and Erk1/2, ↑ROS/(p38 MAPK, Erk1/2)	[43]
8	Oral squamous carcinoma	UPCI-SCC-172 cells	Apoptosis induction, cell cycle arrest	↑ROS, ↓MMP, ↓HDAC	[44]
9	Gastric cancer	BGC-823 and MGC-803 cell lines	Apoptosis induction	↑p53, ↑p21, ↑Bax and ↑caspase-3, ↓CDK2	[27]
10	Hepatocellular Carcinoma	Hep3B	Apoptosis induction	↑Bax, ↑caspase 3, ↓TrxR, ↓PI3K/Akt	[45]
11	Prostate cancer	LNCaP (wild-type p53) and PC-3 (p53 deficient) cells	Apoptosis induction	↓cIAP1, ↓cIAP2 and ↓XIAP, ↑Apaf-1, ↑E2F1, ↑Bax	[26]
12	Breast cancer	MDA-MB-231, MDA-MB-468, MCF-7, and T47D cells	Apoptosis induction	↑caspase 8, ↑caspase 3, and ↑poly (ADP-ribose) polymerase, ↓ Bcl-2	[33]
13	Breast cancer	MCF-7 and MDA-MB-231 cells	Anti-autophagy, Anti-proliferative effect, apoptosis induction	↑$p21^{WAF1}$ and $p27^{KIP1}$, ↓cyclin A, ↓cyclin B1 and Cdc2, ↑caspase 3, ↑Bax, ↓Bcl-2	[46]
14	Prostate cancer	PC-3 cells, PC-3 xenografts in mice	Apoptosis induction	↑Bax, ↓Bcl-2, ↑caspases 3, 9, and 8	[28]
15	Urinary bladder cancer	T24 human bladder cancer line	Apoptosis induction	↑caspase 9 and 3, ↑ Nrf2, ↑Bax, ↓Bcl-2, ↑GRP78 and ↑C/EBP-homologous protein (CHOP)	[36]
16	Hepatocellular carcinoma	HepG2 human hepatocellular carcinoma cells	Apoptosis induction	↑Bip/GRP78, ↑XBP-1, ↑caspase 12, ↑CHOP/GADD153	[47]
17	Ovarian cancer	A2780 and OVCAR cell lines	Anti-proliferative effect, apoptosis induction	↑Bax, Cyto-c, and Caspase-3, ↓Bcl-2, ↓Akt and NF-κB, ↑P53 and P27	[48]

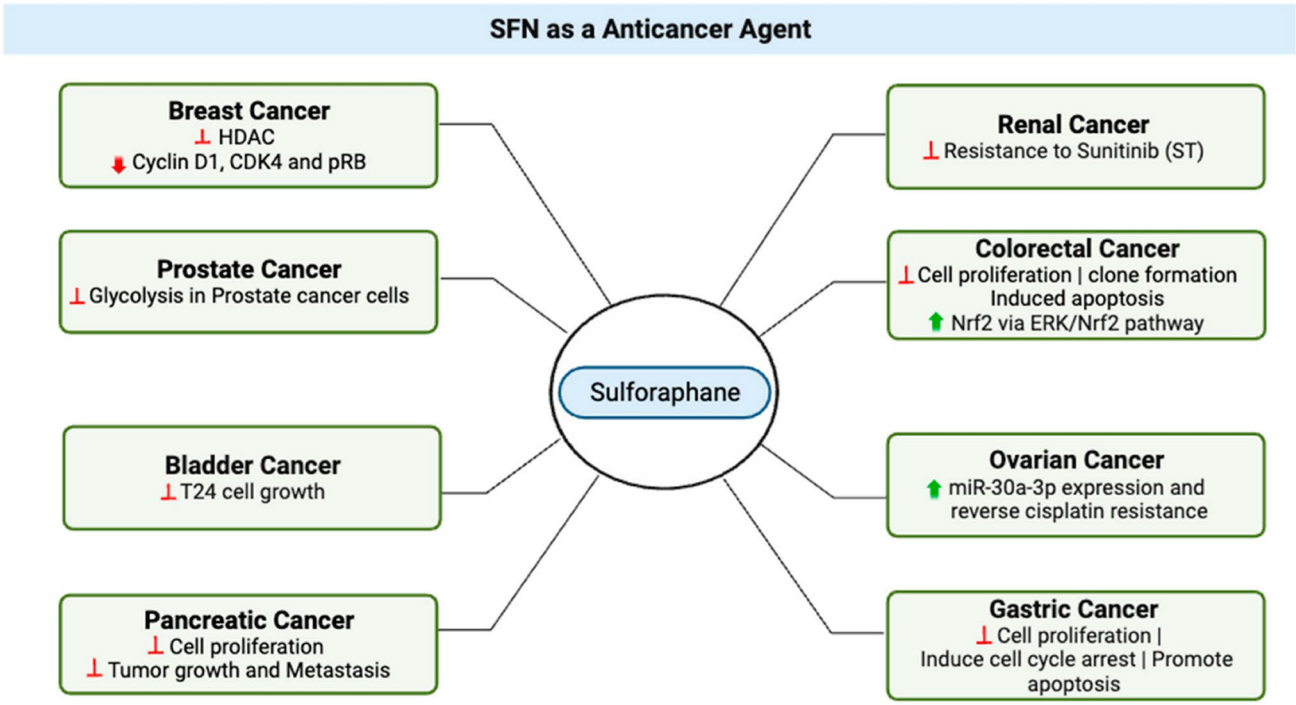


Fig. 4 Different mechanisms in different cancers mediate the chemopreventive effects of sulforaphane

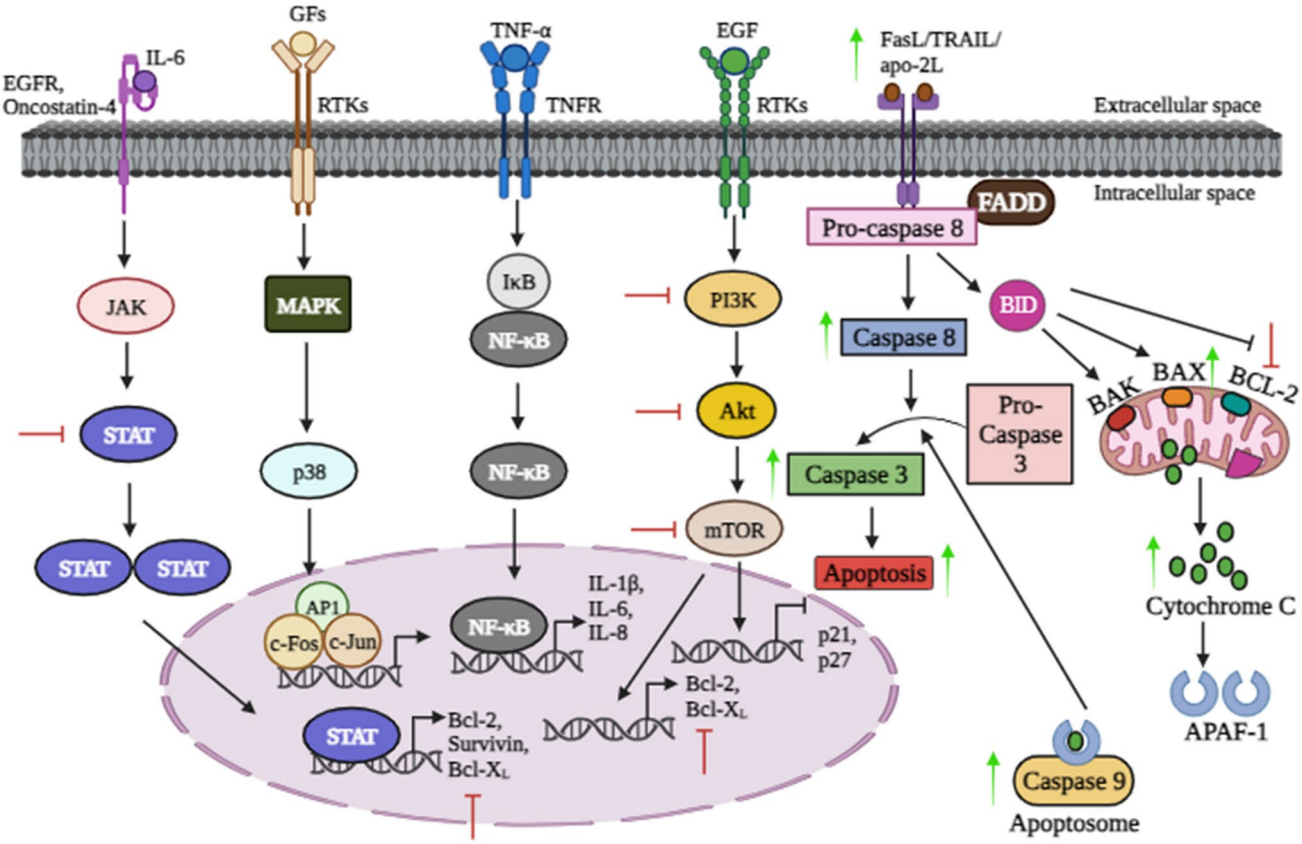


Fig. 5 Mechanisms of apoptosis and survival signaling modulation in different cancers by sulforaphane. The green and red arrows represent the activation and inhibition effects exerted by sulforaphane (GF-growth factor; JAK-Janus kinase; RTK-receptor tyrosine kinase; EGFR-epidermal growth factor receptor; TNFR-tumor necrosis factor-α receptor)

the Bcl-2/Bax pathway has become an essential strategy in cancer research [50]. SFN modulates the Bcl-2/Bax axis through multiple regulatory pathways, including NF-κB, PI3K/Akt, and ROS-mediated signaling [25]. SFN inhibits NF-κB activation, leading to reduced transcription of Bcl-2 and Bcl-xL, thus decreasing cell survival [51]. SFN suppresses PI3K/Akt signaling, resulting in the activation of FOXO3a, which in turn downregulates Bcl-2 and upregulates Bax [52]. In addition, SFN-induced oxidative stress stimulates p53 activation, which directly enhances Bax expression and promotes apoptosis [53].

Recent studies provide robust quantitative data demonstrating SFN's impact on the Bcl-2/Bax ratio: In breast cancer cells (MDA-MB-231 and MCF-7), SFN (10 μM, 48 h) increased Bax expression by 2.5-fold and decreased Bcl-2 levels by 45%, enhancing apoptosis [54]. In gastric cancer cells (AGS, BGC-823), SFN (15 μM) led to a 40% reduction in Bcl-2 and a 65% increase in Bax, correlating with heightened caspase-3 activity [55]. In prostate cancer cells (DU145), SFN treatment resulted in a 50% decrease in Bcl-2 and a threefold increase in Bax, triggering cytochrome c release and caspase activation [11]. Overexpression of Bax and decreased expression of Bcl-2 were linked to SFN-induced apoptosis (Fig. 3) [28, 52].

SFN-mediated Bcl-2/Bax modulation interacts with other key apoptotic mechanisms, including caspase activation, ROS accumulation, and mitochondrial dysfunction [56]. In caspase cascade, SFN-induced Bax upregulation facilitates cytochrome c release, activating caspase-9, which in turn activates caspase-3, leading to apoptosis [36]. In mitochondrial activation pathway, Bax translocation to the mitochondria disrupts membrane potential, leading to apoptosis-inducing factor (AIF) release, amplifying apoptosis [57]. Further, in ROS mediated apoptosis pathway, SFN-induced ROS accumulation activates ASK1/JNK signaling, which phosphorylates Bax, enhancing its mitochondrial localization and promoting apoptosis [58]. In pancreatic cancer cells, SFN increased ROS production by 50%, amplifying Bax-mediated apoptosis [58]. In gastric cancer cells, SFN treatment led to dose-dependent Bax/Bcl-2 alterations and the upregulation of apoptotic signaling proteins, including cytochrome c, Casp-3, Casp-8, and PARP-1 [59]. Similarly, in esophageal cancer cells, SFN induced apoptosis and inhibited cell migration through the MSK2/CREB/Bcl-2 and cadherin pathways [60]. SFN elevated the Bax/Bcl-2 ratio in glioblastoma cells, resulting in cytochrome C release and apoptosis [61, 62]. Furthermore, SFN induces bladder cancer cell apoptosis via a mitochondrial pathway mediated by ROS, which includes altering the Bax/Bcl-2 ratio [59]. SFN-induced apoptosis in human colon cancer cells (HT29 cells) has been associated with the overexpression of Bax, cytochrome c release into the cytoplasm, and poly (ADP-ribose) polymerase (PARP) proteolytic cleavage [63]. In MDA-MB-468, MCF-7, and T47D cells, apoptosis appears to be initiated by an intrinsic mitochondrial route. In these cell lines, SFN promotes the cleavage of Casp-9, Casp-3, and PARP, inhibits Bcl-2, and releases cytochrome c into the cytosol from the mitochondria [33]. In an in vivo investigation of human ovarian cancer, Bcl-2 was markedly inhibited upon SFN treatment. When SFN was present in cells at varying concentrations, Bax was upregulated by the dose, which aided in the death of tumor cells [25]. SFN downregulates Bcl-2 in a concentration-dependent manner [52]. In an in vivo study on human ovarian cancer, Bcl-2 was found to be significantly inhibited when SFN was administered. According to Kan et al., Bax was upregulated in cells in a dose-dependent manner when exposed to varying concentrations of SFN, which helped cause cancer cells to die [25]. According to another study, bcl-2 expression in these ovarian cancer cells can be decreased by treatment with a combination of epigallocatechin gallate and SFN [64]. SFN downregulates Bcl-2 in a concentration-dependent manner [52]. Among human non-small cell lung cancer (NSCLC) cells, SFN-cysteine (SFN-Cys), a metabolite of SFN, has been shown to increase and decrease the expression of Bax and Bcl-2, respectively [65].

SFN modulates Bcl-2/Bax expression through multiple regulatory levels, including transcriptional regulation, post-translational modifications, and proteasome degradation. In transcriptional regulation: SFN increases Bax transcription via p53 and FOXO3a activation while suppressing Bcl-2 gene expression through NF-κB inhibition [66]. In post-translational modifications: SFN phosphorylates Bax at Ser184, enhancing its mitochondrial translocation [67]. SFN induces Bcl-2 phosphorylation at Ser70, marking it for ubiquitin-proteasomal degradation [68]. In proteasomal degradation: SFN enhances the degradation of Bcl-2 and Mcl-1 via the ubiquitin–proteasome system, shifting the balance toward apoptosis [69]. This multi-level regulation underscores SFN's role as a powerful apoptosis inducer.

One of the major challenges in apoptosis-targeted cancer therapy is cellular resistance, often mediated by upregulation of anti-apoptotic proteins like Mcl-1 and Bcl-xL [70]. SFN counteracts resistance through first downregulation of Mcl-1 and Bcl-xL, such as in lung cancer cells (A549), SFN (10 μM) decreased Mcl-1 expression by 50%, enhancing apoptosis [52]. In colorectal cancer models, SFN downregulated Bcl-xL by 35%, sensitizing tumors to chemotherapy [70]. Second, sensitizing drug-resistant cancer cells, such as SFN enhances chemosensitivity by inhibiting survival pathways (PI3K/Akt, NF-κB) [70]. In triple-negative breast cancer, SFN co-treatment with doxorubicin reduced tumor cell viability by 65% compared to doxorubicin alone [71]. Third, inhibition of survival signaling pathways such as SFN

directly inhibits Akt phosphorylation, leading to reduced expression of Mcl-1 and Bcl-xL, sensitizing cells to apoptosis [72]. These findings position SFN as a promising agent for overcoming therapy resistance in aggressive cancers.

3.3 Targeting the PI3K-Akt-mTOR pathway

SFN, a natural compound present in cruciferous vegetables, including brussels sprouts, broccoli, and cabbage, has gained attention for its promising health benefits, including its role in targeting the PI3K-Akt-mTOR pathway. The latter pathway is a crucial signaling pathway involved in cell growth, proliferation, survival, and metabolism [52, 73]. SFN affects the abovementioned pathway through multiple mechanisms. One key aspect is its ability to modulate phosphoinositide 3-kinase (PI3K), a key enzyme in the pathway that phosphorylates lipids and activates downstream signaling. SFN was shown to abolish PI3K activity, thereby disrupting the signaling cascade [74, 75]. Akt, also known as protein kinase B, is another important component of the PI3K-Akt-mTOR pathway. SFN was shown to suppress Akt activation by inhibiting its phosphorylation. Akt plays a central role in regulating cell viability and growth, and dysregulation of Akt signaling is associated with various cancers, such as bladder cancers and polycystic ovarian cancers [76, 77]. Furthermore, SFN influences the mammalian target of rapamycin (mTOR) protein, a downstream target of Akt. mTOR is a key regulator of cellular processes, including protein synthesis and autophagy. SFN has been found to inhibit mTOR activation, resulting in the inhibition of cell growth and proliferation [35, 78]. Additionally, the ability of SFN to target the PI3K-Akt-mTOR pathway has implications beyond cancer treatment. It may be relevant in the context of neurodegenerative diseases, cardiovascular disorders, and metabolic conditions where this signaling pathway plays a critical role [79, 80]. Studies have indicated that SFN's modulation of the PI3K-Akt-mTOR signaling cascade contributes to its anticancer properties. By interfering with signaling events within this pathway, SFN can induce cell cycle arrest, promote apoptosis, and inhibit the uncontrolled growth of cancer cells [79].

3.4 Targeting the JAK-STAT3 signaling pathway

The JAK-STAT3 pathway is a critical signaling cascade involved in cell growth, differentiation, and the immune response. Studies have shown interactions between SFN and the JAK-STAT3 pathway [81]. SFN interferes with the initial step of the JAK-STAT3 pathway and can modulate downstream signaling events. SFN improves chemotherapy efficacy by targeting cancer stem cell-like properties via the miR-124/IL-6R/STAT3 axis [82, 83]. STAT3 is translocated to the nucleus and regulates the expression of various genes involved in cell survival, proliferation, and inflammation. Studies suggest that SFN inhibits the phosphorylation and activation of STAT3, preventing its transcriptional activity [84]. By inhibiting STAT3 activation, SFN can contribute to the suppression of antiapoptotic signals, promoting programmed cell death in cancer cells [62]. SFN interferes with the survival and proliferation of cancer cells by targeting Nrf2 via the ERK-JNK pathway [37]. The impact of SFN on the JAK-STAT3 pathway is not limited to cancer. It has cytoprotective effects in various diseases, including neurodegenerative disorders, where inflammation and cell survival pathways play crucial roles [85]. The preventive effects of SFN on JAK and STAT3 activation make SFN a promising candidate for further research on the development of therapeutic strategies targeting diseases associated with dysregulated JAK-STAT3 signaling, including certain cancers and inflammatory conditions. However, it is important to note that research in this field is ongoing, and more studies are required for a deeper understanding of the molecular mechanisms and potential therapeutic applications of SFN in modulating the JAK-STAT3 pathway.

3.5 Inducing apoptosis via autophagy modulation

Autophagy contributes to the health and function of cells by degrading and recycling cellular constituents. Studies have shown various pathways by which SFN modulates autophagy. A study revealed that SFN inhibits the mammalian target of rapamycin (mTOR). mTOR activation suppresses autophagy. By inhibiting mTOR, SFN promotes the initiation of autophagy, allowing cells to break down and recycle cellular components [35, 86, 87]. According to a different study, SFN can activate AMP-activated protein kinase (AMPK), an enzyme that senses energy and is involved in controlling the equilibrium of energy within cells. Autophagy is linked to AMPK activation, and the effect of SFN on AMPK enhances its capacity to promote autophagic activities [88, 89]. SFN modulates the expression and activity of crucial proteins involved in the autophagy process in breast cancer cells (HDAC6), pancreatic cancer cells, etc. SFN has been shown to upregulate the expression of LC3-II, a hallmark of autophagosome maturation, and Beclin-1, a protein essential for autophagosome formation [72, 90]. The antioxidant properties of SFN also contribute to its role in autophagy modulation in pancreatic

cancer cells. By decreasing oxidative stress within cells, SFN may help prevent the accumulation of damaged cellular components that could trigger autophagic responses [72, 91]. The induction of autophagy by SFN is of particular interest in the context of different diseases, including neurodegenerative disorders, cancer, and metabolic conditions. The property of autophagy aligns with the potential therapeutic benefits of SFN in maintaining cellular health and preventing the progression of diseases linked with cellular dysfunction. However, while preclinical studies have shown promise, more studies are required to obtain in-depth information about the mechanisms and therapeutic implications of SFN-induced autophagy in diverse health contexts [48, 92].

4 Synergistic and nanodelivery aspects

Recently, the administration of various natural molecules as adjuvants during chemotherapeutic treatment has been shown to lead to various positive outcomes, including increased efficacy and reduced adverse effects [93]. Various studies have reported that the application of SFN as an adjuvant has a remarkable benefit during chemotherapeutic treatment. For instance, the combination of 5-fluorouracil and SFN potentiates autophagy by augmenting LC3-II protein expression, which ultimately results in decreased proliferation and the induction of apoptosis in MDA-MB-231 cells [94]. SFN inhibits NF-κB and PI3K/Akt survival pathways, reducing multidrug resistance in various cancers [83]. In colorectal cancer cells, SFN reversed resistance to 5-fluorouracil by downregulating Bcl-2 and Mcl-1 [23].Compared with SFN or DOX treatment alone, treatment with SFN (4 mg/kg) combined with DOX strongly decreased tumor growth [14]. Moreover, the use of SFN as an adjuvant has also been shown to mitigate DOX-induced cardiotoxicity by increasing mitochondrial activity. In a BALB/c mouse tumor model, the therapeutic efficacy of SFN as an adjuvant with DOX on tumor formation was comparable to that in an in vitro model [95]. SFN has been shown to increase the cytotoxicity of doxorubicin, paclitaxel, and cisplatin by modulating drug efflux pumps, oxidative stress, and apoptosis pathways [13]. In breast cancer models, SFN co-treatment with doxorubicin reduced tumor growth by 65% compared to doxorubicin alone [71]. Burnet and his colleagues reported that cotreatment with SFN (2.5–15 mM) and DTX reduced cancer stem cell (CSC) expression by inhibiting NF-κB activity and retrogressive aldehyde dehydrogenase-positive (ALDH +) enrichment in TNBC patients [71]. Similarly, the PTX-SFN combination reduced the viability of breast cancer cells with concomitant activation of cell cycle progression in G1 and cell death [32]. SFN promotes autophagy-mediated apoptosis, which enhances the efficacy of chemotherapy in resistant tumors [72]. In pancreatic cancer cells, SFN co-treatment with gemcitabine tripled apoptosis rates compared to gemcitabine alone [95].

Nanotechnology-based drug delivery has significantly improved the bioavailability, stability, and targeted delivery of natural compounds used in cancer therapy [96, 97]. Among these, curcumin, resveratrol, quercetin, and SFN have been widely studied for their anticancer properties [98]. While curcumin and resveratrol demonstrate potent anti-inflammatory and antioxidant effects, their poor solubility and rapid metabolism limit their therapeutic potential [98]. Nanocompounding has been used to overcome these limitations, leading to improved pharmacokinetics and enhanced tumor-targeting ability [97] such as encapsulation in liposomes and polymeric nanoparticles has enhanced curcumin's bioavailability by over 20-fold, improving its anticancer efficacy [99],nanocarriers such as solid lipid nanoparticles (SLNs) have significantly improved resveratrol's metabolic stability and sustained its release in tumor models [100], quercetin-loaded chitosan nanoparticles have exhibited a threefold increase in anticancer activity compared to free quercetin [101], and SFN has been successfully incorporated into polymeric micelles, gold nanoparticles, and liposomal carriers, enhancing its cellular uptake, bioavailability, and anticancer potential [54].

When comparing SFN to these nanocompounded natural compounds, SFN demonstrates unique advantages, including its ability to modulate multiple signaling pathways, cross the blood–brain barrier, and synergize with chemotherapeutic agents [53]. Moreover, unlike curcumin and resveratrol, which require high doses to achieve therapeutic effects, SFN remains bioactive at relatively low concentrations when delivered through nanocarriers [13]. Several studies have shown that the delivery of the SFN system through NP-based treatments such as selenium, tellurium, gold-coated Fe_3O_4, PEGylated Fe_3O_4, monomethoxypol, Fe^{2+} and Fe^{3+} in breast cancer led to efficient antitumor effects by decreasing tumor cell viability [102–106]. Surprisingly, the stimulation of apoptosis via the overexpression of the proapoptotic Bak and Bax proteins and decreased expression of the antiapoptotic Bcl-2 and Bcl-xL proteins promoted this improved anticancer effect. Moreover, other studies have also reported that treatment with SFN-coated selenium and tellurium nanoparticles is more efficacious than treatment alone [103, 107, 108]. Overall, SFN nanoparticle therapy shows high therapeutic efficacy in cancer cells, and thus, synergistic treatment with other chemopreventive drugs coated with NPs may offer a

more efficacious approach. Furthermore, the use of PVA/PEG400 hydrogels containing SFN nanoliposomes in dermal dressings has been shown to promote wound healing [109].

Nanotechnology has revolutionized the therapeutic potential of SFN and other natural compounds by enhancing their stability, bioavailability, and tumor-targeting capabilities. Compared to curcumin and resveratrol, SFN demonstrates superior bioactivity at lower concentrations, stronger synergy with chemotherapeutics, and broader pathway modulation. Its synergistic effects extend to enhancing drug efficacy, overcoming resistance, and triggering apoptotic mechanisms, making it a promising candidate for future clinical applications. Further research into optimized nanoformulations and combination therapies will be critical for fully harnessing SFN's anticancer potential.

5 Safety aspects

Several animal studies have reported that the administration of SFN (a single oral 150 µmol dose or 7.5 µmol for 21 days orally, 50 mg/kg intraperitoneally) has no adverse effects, as evidenced by the lack of apparent changes in animal health, food intake or body weight [11]. However, extremely high doses of SFN (250–300 mg/kg) were found to cause sedation and muscular dysfunction in an in vivo model [110, 111]. This observation concludes that the therapeutic dose of SFN was 191.58 mg/kg, whereas the deadly dose was 212.67 mg/kg [110]. Numerous in vivo investigations using greater dosages of SFN should highlight the toxicity that requires careful consideration when determining therapeutic or preventive indices and performing risk–benefit analyses. Socala et al. [110] reported the LD_{50} value of SFN in mice to be 213 mg/kg i.p. (1203 µmol/kg). Adverse effects such as marked drowsiness and hypothermia (at 150–300 mg/kg), dysfunction of motor coordination (at 200–300 mg/kg), reduction in skeletal muscular strength (at 250–300 mg/kg), and fatalities (at 200–300 mg/kg) were reported when the toxicity profile of SFN in a mouse model was investigated. Interestingly, human clinical trials have verified that SFN is relatively nontoxic, does not show apparent toxicity at small doses, and is slightly unsafe at large doses. However, more extreme levels have not been explored because the Food and Drug Administration (FDA) only allows the use of SFN at 200 µmol in chosen clinical trials [13]. Broccoli sprout extracts containing SFN were well tolerated and did not significantly affect the administration of a 25 µmol SFN dosage orally every eight hours for seven days (a total of 21 doses), according to randomized clinical phase I research [13]. Additionally, a six-week randomized, double-blind, placebo-controlled clinical investigation revealed that taking 30 mg of SFN daily could safely alleviate depression symptoms caused by cardiac procedures. The reported adverse effects were mild to moderate in intensity [112]. Another randomized clinical pilot study revealed that giving patients with advanced pancreatic cancer 200 µmol/day of SFN-rich extracts for up to 20 weeks did not cause any adverse events (POUDER trial) [113]. Similarly, a phase II trial confirmed the safety of broccoli sprout extracts high in SFN for men with recurrent prostate cancer [13]. SFN medication (200 µmol/day for 20 weeks) was found to be safe in this trial, with the exception of one instance in which recurring prostate cancer patients experienced grade 2 constipation. In a clinical experiment, a single patient in the 200 µmol SFN dose group experienced grade 2 nausea [114]. Consistently, two side effects related to headaches and bloating were observed in two subjects treated with 200 µmol SFN in a double-blind study [115]. Yamashita et al. [99] also reported that patients had a severe burning sensation in the back of their throat and the posterior portion of their tongue after receiving 100 µmol SFN orally. Similar to previous clinical trials, patients also reported nausea, heartburn, and gastrointestinal pain at larger dosages. It is necessary to conduct extensive research on safe and effective dosages of SFN because mild to moderate adverse effects have been recorded at larger doses.

Based on current evidence, the recommended safe and effective doses for SFN are 20–40 mg/day (~ 100–200 µmol SFN) from dietary sources or supplements (General health benefits), 100–200 µmol/day for up to 20 weeks, as supported by clinical trials (Cancer prevention and adjunct therapy), and 250–300 mg/kg in animal models; equivalent human dose should not exceed 200 µmol/day without medical supervision (Maximum tolerable dose). SFN demonstrates a strong safety profile at moderate doses, with long-term supplementation (30–200 µmol/day) being well tolerated in clinical studies. However, high doses may lead to gastrointestinal discomfort, metabolic variability, and potential thyroid interactions. Future research should focus on individualized dosing strategies, long-term clinical trials, and nanodelivery systems to optimize SFN's therapeutic potential.

6 Conclusion and future perspectives

The information in this review makes it quite evident that sulforaphane's ability to interfere with cancer cell signaling makes it a viable candidate for the design of innovative anticancer drugs. Therefore, it is necessary to ascertain and calculate how the right dosage affects the pharmacodynamic properties of the drug. Future studies should, however, investigate the further therapeutic uses of sulforaphane using a variety of omics techniques, including transcriptomics, proteomics, systems biology, genomics, epigenomics, and metabolomics. Furthermore, by examining the structure–activity connections and utilizing contemporary synthetic metal complexation, a sulforaphane-based therapeutic option for treating many cancer types may be achieved. Furthermore, research is needed to determine the clinical effectiveness of sulforaphane in various nanoformulations against various cancer types.

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Declarations

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