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Review Article

Sulforaphane's Rhythm: A Natural Note in Cancer's Downfall

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Abstract

Sulforaphane (SFN), a phytochemical constituent of cruciferous vegetables, has emerged as a compelling candidate in the therapeutic landscape of cervical carcinoma. Exhibiting selective cytotoxicity, SFN orchestrates apoptosis and cell cycle arrest via modulation of pivotal signaling cascades, including JNK/p38 MAPK and Wnt/β-catenin, while concurrently attenuating cancer stem cell phenotypes. It augments radiosensitivity by compromising DNA repair fidelity through inhibition of Rad51 and MDC1, thereby potentiating radiotherapeutic outcomes. SFN further exerts epigenetic influence by regulating microRNAs such as miR-1247-3p and modulating chromatin architecture, culminating in transcriptional repression of oncogenic drivers. The article represents a comprehensive elucidation of SFN's pleiotropic mechanisms, with particular emphasis on its capacity to counteract HPV-mediated inflammation through Nrf2 activation and NF-κB suppression—key modulators of oxidative and inflammatory stress in cervical oncogenesis. Preclinical investigations substantiate its antitumor efficacy with negligible off-target toxicity. Owing to its favorable pharmacokinetic profile, dietary accessibility, and minimal adverse effects, SFN holds promise as both a chemopreventive and adjunctive therapeutic agent. This synthesis underscores SFN's potential to surmount therapeutic resistance and recurrence, advocating for its integration into future multimodal cervical cancer regimens pending rigorous clinical validation.

Keywords: sulforaphane (sfn); cervical cancer; human papillomavirus (hpv); apoptosis; cell cycle arrest; nrf2/nf-κb signaling; oxidative stress; chemoprevention etc

1.Introduction

Cervical cancer remains a major global health concern, particularly in developing countries where access to HPV vaccination and early screening is limited. Despite advances in chemotherapy and radiotherapy, treatment efficacy is often hindered by drug resistance, toxicity, and recurrence. This has led to increased interest in bioactive phytochemicals with anticancer potential. Sulforaphane (SFN), a naturally occurring isothiocyanate found in cruciferous vegetables such as broccoli and Brussels sprouts, has demonstrated promising anticancer effects across various malignancies, including cervical cancer. SFN induces G2/M phase cell cycle arrest in cervical cancer cells by downregulating Cyclin B1 and promoting the formation of the GADD45β/CDC2 complex, thereby delaying mitosis and suppressing proliferation [1]. In addition to cell cycle modulation, SFN influences apoptotic pathways through the MAPK signaling cascade, mediated by the downregulation of miR-1247-3p, leading to increased apoptosis and reduced viability in HeLa cells [2]. These molecular interactions highlight SFN's ability to reprogram oncogenic signaling and promote programmed cell death. Furthermore, SFN has shown synergistic effects when combined with conventional chemotherapeutic agents such as cisplatin and 5-fluorouracil, enhancing cytotoxicity while reducing adverse effects [3]. This combinational approach suggests that SFN may serve as an effective adjuvant in cervical cancer therapy. Taken together, these findings underscore the therapeutic potential of Sulforaphane as a multi-targeted agent in cervical cancer management, warranting further preclinical and clinical investigation.

2.Apoptosis & Cell Death

2.1. Induces apoptosis via mitochondrial dysfunction:

Sulforaphane (SFN) induces apoptosis in cervical cancer cells primarily through mitochondrial dysfunction and activation of intrinsic apoptotic pathways. Upon SFN treatment, HeLa cells exhibit hallmark features of apoptosis, including chromatin condensation, formation of apoptotic bodies, and accumulation in the sub-G1 phase of the cell cycle [4]. Mechanistically, SFN downregulates anti-apoptotic proteins such as Bcl-2 and Bcl-xL, while upregulating pro-apoptotic Bax, thereby disrupting

mitochondrial membrane potential and promoting cytochrome c release. This mitochondrial imbalance leads to the activation of caspase-9, followed by caspase-3, culminating in the cleavage of poly (ADP-ribose) polymerase (PARP) and β-catenin, which are critical for DNA repair and cell adhesion, respectively [4]. Importantly, the use of z-DEVD-fmk, a caspase-3 specific inhibitor, significantly attenuates SFN-induced apoptosis, confirming the central role of caspase-3 in this process. These findings underscore SFN's ability to trigger intrinsic apoptotic signaling via mitochondrial destabilization, making it a promising candidate for targeted cervical cancer therapy.

2.2. Caspase Activation by Sulforaphane:

Sulforaphane (SFN) initiates apoptosis in cervical cancer cells through the intrinsic mitochondrial pathway, prominently involving the activation of Caspase-9 and Caspase-3. SFN disrupts mitochondrial membrane integrity, leading to the release of cytochrome c into the cytosol. This event triggers the formation of the apoptosome complex, which activates Caspase-9, the initiator caspase of the intrinsic pathway [5]. Activated Caspase-9 subsequently cleaves and activates Caspase-3, the key executioner caspase responsible for dismantling cellular structures. SFN-treated HeLa cells exhibit cleavage of poly (ADP-ribose) polymerase (PARP) and β-catenin, both substrates of Caspase-3, confirming its activation [5], [6]. These molecular events are accompanied by chromatin condensation, DNA fragmentation, and formation of apoptotic bodies—hallmarks of programmed cell death. Importantly, the use of z-DEVD-fmk, a Caspase-3-specific inhibitor, significantly reduces SFN-induced apoptosis, validating the central role of Caspase-3 in SFN-mediated cytotoxicity [5]. Additional studies have shown that SFN also upregulates Bax and downregulates Bcl-2, further amplifying mitochondrial dysfunction and caspase activation [6,7]. These findings collectively highlight SFN's ability to trigger apoptosis via a well-orchestrated caspase cascade, reinforcing its potential as a targeted therapeutic agent in cervical cancer.

2.3. Nuclear Fragmentation & Chromatin Condensation

Sulforaphane (SFN) induces apoptosis in cervical cancer cells through both biochemical and morphological changes, including nuclear fragmentation and chromatin condensation—hallmarks of late-stage apoptosis. These changes are clearly observed in SFN-treated HeLa cells using DAPI staining and fluorescence microscopy, where nuclei appear condensed and fragmented [8]. Mechanistically, SFN activates the intrinsic apoptotic pathway, leading to mitochondrial dysfunction and release of cytochrome c, which triggers caspase-9 and subsequently caspase-3 activation. Caspase-3 cleaves nuclear substrates such as PARP and lamin proteins, resulting in disassembly of the nuclear envelope and DNA fragmentation [9]. Additionally, SFN influences epigenetic regulators such as HDAC1 and DNMT3B, which are involved in chromatin remodeling. By downregulating these enzymes, SFN promotes a more open chromatin structure that facilitates apoptotic signaling and nuclear breakdown [10]. These combined effects reinforce SFN's role in orchestrating both molecular and structural dismantling of cancer cells.

2.4. Bax/Bcl-2 Ratio and Apoptotic Shift:

Sulforaphane (SFN) promotes apoptosis in cervical cancer cells by modulating the balance between pro-apoptotic and anti-apoptotic proteins—specifically by increasing the Bax/Bcl-2 ratio. This shift is critical in tipping the cellular fate toward programmed cell death. SFN upregulates Bax, a pro-apoptotic member of the Bcl-2 family, which promotes mitochondrial outer membrane permeabilization (MOMP). Concurrently, SFN downregulates Bcl-2, an anti-apoptotic protein that normally inhibits cytochrome c release and caspase activation. The resulting increase in the Bax/Bcl-2 ratio facilitates mitochondrial dysfunction, leading to the release of apoptogenic factors such as cytochrome c and apoptosis-inducing factor (AIF) [11]. Immunohistochemical studies in cervical squamous cell carcinoma have confirmed that Bax expression intensifies in invasive stages, while Bcl-2 expression is more prominent in pre-invasive lesions, suggesting SFN's role in pushing cells beyond the survival threshold [12]. Moreover, genomic analyses have revealed missense mutations in the BAX gene and transitional mutations in Bcl-2, further implicating these proteins in cervical carcinogenesis and SFN's therapeutic targeting [13]. This Bax/Bcl-2 modulation is a key mechanism by which SFN induces mitochondrial-mediated apoptosis, reinforcing its potential as a selective and effective anticancer agent.

2.5. Cytochrome c Release and Mitochondrial Apoptosis

Sulforaphane (SFN) promotes apoptosis in cervical cancer cells by triggering mitochondrial outer membrane permeabilization (MOMP), which leads to the release of cytochrome c into the cytosol—a pivotal event in the intrinsic apoptotic pathway. Once released, cytochrome c binds to Apaf-1, forming the apoptosome, which activates caspase-9, followed by caspase-3, initiating the execution phase of apoptosis [14].In HeLa cells treated with SFN, Western blot analysis confirms a dose-dependent increase in cytosolic cytochrome c, accompanied by upregulation of Bax and downregulation of Bcl-2, further destabilizing mitochondrial integrity [14]. This mitochondrial disruption is also associated with loss of membrane potential, as shown by JC-1 staining assays, and correlates with increased DNA fragmentation and apoptotic body formation. Additional studies in colon and oral squamous carcinoma cells support these findings, demonstrating that SFN-induced apoptosis involves cytochrome c release, PARP cleavage, and activation of mitochondrial caspases, reinforcing its role as a mitochondrial-targeting anticancer agent [15], [16].

2.6.ER Stress-Mediated Apoptosis Induced by Sulforaphane

Sulforaphane (SFN) induces apoptosis in cervical cancer cells not only through mitochondrial pathways but also by triggering endoplasmic reticulum (ER) stress, a critical cellular mechanism that responds to misfolded protein accumulation and calcium imbalance. In HeLa cells, SFN treatment leads to the upregulation of key ER stress markers such as GRP78, CHOP, and Caspase-12, indicating activation of the unfolded protein response (UPR) and subsequent apoptotic signaling [17].The ER stress pathway initiated by SFN involves three major sensors: PERK, IRE1, and ATF6. SFN activates PERK, which phosphorylates eIF2α, leading to selective translation of ATF4 and transcriptional activation of CHOP, a pro-apoptotic transcription factor. CHOP promotes mitochondrial dysfunction and enhances the expression of Bax, further amplifying apoptosis [18]. Additionally, SFN-induced ER stress activates Caspase-12, which is localized to the ER membrane and specifically mediates ER-associated apoptosis. This caspase cascade complements the mitochondrial pathway, resulting in robust and irreversible cell death in cervical cancer cells [19]. These findings underscore SFN's ability to engage multiple apoptotic pathways, making it a potent and multifaceted anticancer agent.

3. Cell Cycle Arrest

3.1. Arrest cells at G2/M phase:

Sulforaphane (SFN), a dietary isothiocyanate derived from cruciferous vegetables, has been shown to induce G2/M phase cell cycle arrest in various cancer types, including cervical cancer. Cheng et al. [20] demonstrated that SFN treatment in HeLa, Cx, and CxWJ cells leads to a dose-dependent accumulation of cells in the G2/M phase, mediated by downregulation of Cyclin B1 and upregulation of GADD45β, which disrupts the Cyclin B1/CDC2 complex essential for mitotic entry. This mechanism halts cell cycle progression and promotes mitotic delay. Complementing these findings, Chang et al. [21] showed that SFN induces G2/M arrest in ovarian cancer cells via CDC2 downregulation and dissociation of the Cyclin B1/CDC2 complex, suggesting a conserved mechanism across gynecological malignancies. Furthermore, Kamal et al. [22] reviewed SFN's broader anticancer actions, highlighting its ability to arrest the cell cycle at both G1 and G2/M phases and enhance the efficacy of chemotherapeutics like paclitaxel and gemcitabine through synergistic interactions. Collectively, these studies underscore SFN's potential as a chemopreventive and therapeutic agent targeting cell cycle checkpoints in cervical and other cancers.

3.2. Sulforaphane Downregulates Cyclin B1 and CDC2 to Induce G2/M Arrest:

Sulforaphane (SFN), a dietary isothiocyanate derived from cruciferous vegetables, exerts potent anticancer effects by targeting key regulators of the cell cycle. One of its most consistent mechanisms is the downregulation of Cyclin B1 and CDC2, which disrupts the Cyclin B1/CDC2 complex essential for mitotic entry and progression. In PA-1 ovarian cancer cells that SFN treatment leads to significant downregulation of both Cyclin B1 and CDC2, confirmed by western blot and co-immunoprecipitation. This disruption of the Cyclin B1/CDC2 complex results in metaphase arrest and impaired mitotic spindle formation, contributing to G2/M phase arrest.[23]In cervical cancer cells (HeLa, Cx, CxWJ), showing that SFN downregulates Cyclin B1, while CDC2 levels remain stable. However, SFN upregulates GADD45β, which binds CDC2 and inhibits its kinase activity, functionally mimicking CDC2 suppression and reinforcing mitotic delay.[24]. A study archived on Semantic Scholar confirmed that SFN delays cancer progression by downregulating Cyclin B1, dissociating the Cyclin B1/CDC2 complex, and upregulating GADD45 proteins, reinforcing G2/M arrest and apoptosis.[25] Additional mechanistic insights from Chang et al. (2013) emphasize SFN's role in CDC2 kinase inhibition, which blocks phosphorylation of mitotic substrates and prevents chromosomal segregation. This reinforces SFN's dual targeting of Cyclin B1 and CDC2 as a conserved anticancer strategy across gynecological malignancies.[26]

3.3. Sulforaphane Upregulates GADD45β and Disrupts Cell Cycle Progression

Sulforaphane (SFN), a bioactive compound derived from cruciferous vegetables, disrupts cell cycle progression by upregulating GADD45β, a stress-inducible gene involved in checkpoint control and DNA damage response. [27] demonstrated that SFX-01, a stabilized form of SFN, significantly increases GADD45β expression in models of myeloproliferative disorders, leading to inhibition of CDC2 (CDK1) activity and suppression of cyclin D1 via STAT1-mediated signaling, ultimately resulting in cell cycle arrest. In cervical cancer cells, [28] showed that SFN induces GADD45β in a dose-dependent manner, which binds directly to CDC2 and disrupts the Cyclin B1/CDC2 complex, a critical driver of G2/M transition. This interaction halts mitotic progression and reinforces SFN's antiproliferative effects. Supporting these findings, [29] reported that SFN triggers ROS-dependent signaling in pancreatic cancer cells, activating GADD45β and contributing to sub-G1 accumulation and mitotic delay. Additionally, [30] observed SFN-induced cell cycle arrest and apoptosis in HT29 colon cancer cells, consistent with stress-responsive pathway activation, although GADD45β was not directly measured. Collectively, these studies highlight GADD45β as a central mediator of SFN-induced cell cycle disruption across diverse cancer models.

3.4. Sulforaphane Inhibits DNA Synthesis in S-Phase

Sulforaphane (SFN) has been shown to inhibit DNA synthesis by arresting cancer cells in the S-phase of the cell cycle, thereby suppressing proliferation and promoting apoptosis. Wang et al. [31] demonstrated that SFN induces S-phase arrest in gastric cancer cells via a p53-dependent mechanism, leading to upregulation of p21 and downregulation of CDK2, a key regulator of DNA replication. This disruption impairs the transition through S-phase and halts DNA synthesis. Supporting this, Abassi Joozdani et al. [32] showed that SFN directly interacts with DNA through groove binding and intercalation, altering DNA conformation and potentially interfering with replication machinery. In glioblastoma models, Li et al. [33] reported that SFN-cysteine analogs downregulate CDK4/CDK6 and disrupt tubulin polymerization, contributing to cell cycle arrest and impaired DNA synthesis. Additionally, Gamet-Payrastre et al. [34] observed SFN-induced cell cycle arrest in HT29 colon cancer cells, consistent with suppressed DNA replication and enhanced apoptotic signaling. Collectively, these findings confirm that SFN inhibits DNA synthesis during S-phase through both transcriptional regulation and direct molecular interference, reinforcing its role as a potent anticancer agent.

4.Gene Expression & Epigenetics

4.1. Downregulates miR-1247-3p, a key oncogenic microRNA:

Sulforaphane (SFN), a bioactive isothiocyanate derived from cruciferous vegetables, exerts anticancer effects by modulating key microRNAs, including miR-1247-3p, a known oncogenic regulator. In a pivotal study by Luo et al. [35], SFN treatment of HeLa cervical cancer cells led to significant downregulation of miR-1247-3p, resulting in activation of the MAPK signaling pathway, suppression of cell proliferation, and induction of apoptosis. Using next-generation sequencing (NGS), qRT-PCR, and Western blot analysis, the study confirmed that SFN disrupts the oncogenic function of miR-1247-3p, which normally suppresses MAPK pathway components. Further supporting this, Su et al. [36] reviewed SFN's broader epigenetic mechanisms, highlighting its ability to modulate noncoding RNAs, including oncogenic microRNAs, through inhibition of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs). These epigenetic changes restore tumor suppressor gene expression and disrupt malignant signaling networks. SFN's impact on miR-1247-3p fits within this framework, suggesting a dual mechanism of transcriptional repression and post-transcriptional regulation. Additionally, emerging evidence from preclinical models [37] confirms that SFN-induced miRNA reprogramming contributes to its antiproliferative and pro-apoptotic effects across multiple cancer types. The consistent downregulation of miR-1247-3p and concurrent MAPK activation positions SFN as a promising candidate for miRNA-targeted

therapy, especially in malignancies where miR-1247-3p is upregulated and drives tumor progression.

4.2. Sulforaphane Activates MAPK Signaling via miRNA Modulation

Sulforaphane (SFN), a bioactive compound from cruciferous vegetables, exerts anticancer effects by modulating microRNA expression and activating key signaling pathways such as MAPK (Mitogen-Activated Protein Kinase). In a foundational study by Luo et al. [38], SFN was shown to downregulate miR-1247-3p in HeLa cervical cancer cells, thereby relieving its inhibitory effect on MAPK pathway components. This led to increased phosphorylation of ERK and JNK, promoting apoptosis and suppressing proliferation. The study employed next-generation sequencing, qRT-PCR, and Western blotting to confirm that SFN's anticancer activity is mediated through miRNA-dependent activation of MAPK signaling. Expanding on this, Wang et al. [39] demonstrated that SFN modulates dendritic cell function through microRNA regulation, including suppression of miR-155-5p and induction of miR-194-5p, which indirectly influence MAPK and JAK/STAT3 signaling. Although focused on immune cells, this study reinforces the concept that SFN's miRNA-mediated signaling modulation is a generalizable mechanism across cell types. Su et al. [40] further reviewed SFN's epigenetic mechanisms, highlighting its ability to inhibit DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), thereby altering the expression of noncoding RNAs such as microRNAs. This epigenetic reprogramming contributes to the reactivation of tumor suppressor pathways and the activation of MAPK signaling, positioning SFN as a multifaceted therapeutic agent. Together, these studies confirm that SFN activates MAPK signaling through targeted miRNA suppression and epigenetic remodeling, offering a promising strategy for cancer therapy.

4.3. Alters expression of tumor suppressor genes (e.g., p53):

Sulforaphane Alters Expression of Tumor Suppressor Genes (e.g., p53)

Sulforaphane (SFN), a naturally occurring isothiocyanate, has been shown to modulate the expression of key tumor suppressor genes, notably p53, which plays a central role in cell cycle regulation, DNA repair, and apoptosis. In a recent study by Li et al. [41], SFN treatment in glioblastoma cells led to significant transcriptional changes, including upregulation of p53-associated apoptotic pathways. RNA sequencing and qPCR analyses revealed that SFN activated stress-responsive genes and enhanced nuclear localization of p53 downstream effectors, contributing to apoptotic cell death. This effect was linked to SFN-induced endoplasmic reticulum stress and unfolded protein response (UPR), which indirectly stabilized p53 activity. Complementing this, Gwon et al. [42] demonstrated that SFN influences colorectal cancer cell proliferation through Nrf2 activation in a p53-dependent manner. In HCT116 cells expressing wild-type p53, SFN promoted mitochondrial biogenesis and reduced apoptosis, whereas in p53-knockout cells, SFN enhanced apoptotic signaling. These findings suggest that SFN's impact on p53 is context-dependent, capable of either promoting survival or triggering cell death based on cellular stress thresholds. Further mechanistic insights are provided by Lenzi et al. [43], who reviewed SFN's pleiotropic effects across cancer models. They noted that SFN exerts cytostatic and cytotoxic effects through modulation of multiple molecular targets, including p53, and that its efficacy is not strictly dependent on p53 mutation status. SFN was shown to potentiate chemotherapy-induced cytotoxicity and reinforce tumor suppressor pathways, making it a promising adjunct in cancer therapy.

4.4. Sulforaphane Modulates Histone Acetylation and Methylation Patterns:

Sulforaphane (SFN), a potent isothiocyanate derived from cruciferous vegetables, exerts significant epigenetic effects by altering histone acetylation and methylation, thereby influencing gene expression in cancer cells. [44] demonstrated that SFN inhibits histone deacetylases (HDACs), leading to increased acetylation of histone H3 and H4 tails. This chromatin relaxation facilitates transcriptional activation of tumor suppressor genes such as p21 and Bax, contributing to cell cycle arrest and apoptosis. Building on this, explored SFN's effects in malignant melanoma, showing that SFN not only reduces HDAC activity but also modulates histone acetyltransferases (HATs) and histone methyltransferases (HMTs)[45] . Their findings revealed SFN-induced changes in lysine acetylation and methylation marks, such as H3K9ac, H3K4me3, and H3K27me3, which are critical for regulating transcriptional accessibility. These modifications were associated with reduced cell viability and enhanced apoptotic signaling, underscoring SFN's therapeutic potential. The interdependence between histone modifications and DNA methylation. SFN was shown to reverse promoter hypermethylation and restore active chromatin states, particularly in genes involved in cell cycle regulation and differentiation.[46] The compound's ability to simultaneously modulate multiple epigenetic layers positions it as a promising agent for nutritional epigenetic therapy and cancer chemoprevention.

4.5. Proliferation & Migration

Suppresses proliferation of HeLa cells (dose-dependent):

Sulforaphane Suppresses Proliferation and Migration of HeLa Cells (Dose-Dependent)

Sulforaphane (SFN) exhibits potent antiproliferative and antimigratory effects on HeLa cervical cancer cells, with its efficacy increasing in a dose-dependent manner. [47], SFN significantly reduced HeLa cell viability by modulating key molecular targets involved in cell cycle progression, apoptosis, and epigenetic regulation. Quantitative PCR analysis revealed downregulation of proliferation-associated genes such as cyclin B1, CDK1, and c-Myc, while upregulating tumor suppressors like p21 and Bax. SFN also inhibited the activity of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), leading to chromatin remodeling and re-expression of silenced apoptotic genes. SFN induces cell cycle arrest and apoptosis in a dose-dependent fashion, mediated by reactive oxygen species (ROS) accumulation and mitochondrial dysfunction[48]. In HeLa cells, SFN treatment elevated levels of cleaved caspase-3 and PARP, while reducing mitochondrial membrane potential and increasing γH2AX expression, indicative of DNA damage. These effects were reversed by ROS scavengers, confirming the role of oxidative stress in SFN-induced cytotoxicity. SFN's broader anticancer mechanisms, emphasizing its ability to suppress migration and invasion through inhibition of epithelial-mesenchymal transition (EMT) markers such as Snail, Twist, and MMP-9. In HeLa cells, SFN reduced migratory capacity by downregulating matrix metalloproteinases and interfering with cytoskeletal dynamics[49]. These findings collectively support SFN's dual role in inhibiting proliferation and migration, making it a promising candidate for cervical cancer chemoprevention and therapy.

4.6. Sulforaphane Reduces Colony Formation Capacity

Sulforaphane (SFN) significantly impairs the colony-forming ability of cancer cells, reflecting its potent anti-proliferative and cytotoxic properties. As demonstrated by Wang et al. [53], SFN treatment in gastric cancer (GC) cell lines BGC-823 and MGC-803 led to a marked reduction in colony formation in a dose-dependent manner. This suppression was attributed to SFN-induced S-phase cell cycle arrest and apoptosis, mediated through a p53-dependent pathway. Western blot analysis revealed increased expression of p53, p21, Bax, and cleaved caspase-3, alongside decreased levels of CDK2, indicating disruption of cell cycle progression and activation of apoptotic machinery. Building on this, Cho et al. [54] reported similar findings in pancreatic cancer cells, where SFN reduced clonogenic survival by triggering ROS-mediated DNA damage and mitochondrial dysfunction. SFN treatment elevated γH2AX levels and disrupted mitochondrial membrane potential, leading to irreversible cell cycle arrest and apoptosis. These effects were reversed by antioxidant pretreatment, confirming the role of oxidative stress in SFN's anti-colony-forming action. Furthermore, Liu et al. [55] reviewed SFN's broad-spectrum anticancer effects, highlighting its ability to inhibit anchorage-independent growth in soft agar assays across multiple cancer types. SFN was shown to interfere with oncogenic signaling pathways such as PI3K/Akt and MAPK, further contributing to its suppression of colony formation and tumorigenic potential.

4.7. Sulforaphane Impairs Cytoskeletal Dynamics via Ezrin Downregulation:

Sulforaphane (SFN) disrupts cancer cell motility and structural integrity by impairing cytoskeletal dynamics, primarily through the downregulation of Ezrin, a key membrane-cytoskeleton linker protein. As reported by Coutinho et al. [56], SFN treatment in cancer stem cells (CSCs) led to significant suppression of Ezrin expression, which in turn destabilized actin filament organization and impaired cellular polarity. Ezrin, a member of the ERM (Ezrin-Radixin-Moesin) family, is crucial for anchoring the actin cytoskeleton to the plasma membrane and facilitating signal transduction pathways that regulate migration and invasion. SFN-induced Ezrin downregulation was associated with reduced filopodia formation and diminished focal adhesion assembly, thereby limiting metastatic potential. Building on this, Mundy [57] investigated SFN's effects on microtubule dynamics and centrosome positioning in epithelial cancer cells. The study revealed that SFN interferes with tubulin polymerization, alters centrosome orientation, and reduces cell velocity and directionality in scratch wound assays. These cytoskeletal disruptions were accompanied by changes in upstream regulators such as Rap1GAP, a tumor suppressor that modulates cell adhesion and migration. The combined effect of Ezrin suppression and microtubule destabilization contributes to SFN's robust anti-migratory and anti-invasive profile. Together, these findings underscore SFN's ability to target structural and signaling components of the cytoskeleton, making it a promising agent for anti-metastatic therapy in epithelial cancers.

5.Synergistic Effects

5.1. Sulforaphane Enhances Efficacy of Chemotherapeutics (e.g., Docetaxel)

Sulforaphane (SFN) has demonstrated synergistic anticancer effects when combined with conventional chemotherapeutics, notably docetaxel (DCT). As reported by Peñata-Taborda et al. [58], low-dose SFN combined with DCT significantly enhanced therapeutic efficacy in prostate cancer cell lines (LNCaP and PC-3). The SFN:DCT combination reduced cell viability to levels comparable with DCT monotherapy, but at half the IC_{50} concentration, indicating a potentiating effect. Mechanistically, SFN amplified caspase-3 activation (2.4 ± 0.75 RFU vs. 2.1 ± 0.47 RFU for DCT alone), increased ROS production, and reduced mitochondrial mass, suggesting that SFN sensitizes cancer cells to docetaxel by targeting metabolic vulnerabilities and apoptotic pathways. Building on this, Kim et al. [59] explored SFN's role in triple-negative breast cancer (TNBC), where it enhanced the anticancer activity of taxanes (including docetaxel) by targeting cancer stem cells (CSCs). SFN suppressed IL-6 secretion and reversed CSC expansion typically induced by taxane treatment, thereby improving long-term therapeutic outcomes and reducing recurrence risk. These findings underscore SFN's potential as a chemosensitizer, capable of lowering the required dose of cytotoxic drugs while maintaining efficacy, thereby minimizing adverse effects and overcoming resistance mechanisms.

5.2. Sulforaphane Sensitizes Cells to Radiation-Induced Apoptosis:

Sulforaphane (SFN) enhances the sensitivity of cancer cells to radiation-induced apoptosis, making it a promising radiosensitizer in oncologic therapy. As reviewed by Sailo et al. [60], SFN modulates multiple signaling pathways—including Akt/mTOR, NF-κB, and Wnt/β-catenin—that are commonly activated in radioresistant tumors. By downregulating anti-apoptotic proteins such as Bcl-2 and survivin, and upregulating pro-apoptotic mediators like p53, p21, and caspases, SFN primes cancer cells for enhanced apoptotic response following radiation exposure. This chemosensitizing effect is particularly evident in cancers of the bone, brain, and breast, where SFN synergistically augments radiation efficacy while minimizing damage to surrounding healthy tissue. SFN treatment in glioblastoma cells activated the ATF4–CHOP axis of the unfolded protein response (UPR), a pathway known to amplify radiation-induced stress and apoptosis[61]. SFN pre-treatment led to increased nuclear translocation of CHOP and elevated expression of ER stress markers, which sensitized glioma cells to subsequent radiation. Importantly, SFN showed minimal cytotoxicity in normal astrocytes, suggesting a favorable therapeutic window for combination therapy.

Together, these findings highlight SFN's potential to overcome radioresistance, enhance tumor control, and reduce the required radiation dose, thereby improving therapeutic outcomes and minimizing side effects.

5.3. Reverses drug resistance by modulating ABC transporters:

Sulforaphane (SFN) has emerged as a potent modulator of ATP-binding cassette (ABC) transporters, which play a central role in multidrug resistance (MDR) by actively effluxing chemotherapeutic agents out of cancer cells. As reviewed by Coutinho et al. [62], SFN downregulates the expression of key ABC transporters such as ABCB1 (P-glycoprotein) and ABCG2, thereby enhancing intracellular drug accumulation and restoring chemosensitivity. This effect is particularly relevant in cancer stem cells (CSCs), which often exhibit elevated ABC transporter activity and contribute to tumor relapse and therapy failure. SFN's ability to suppress ABC transporter expression is linked to its modulation of Wnt/β-catenin and NF-κB signaling pathways, both of which regulate MDR gene transcription. Supporting this, Sailo et al. [63] demonstrated that SFN enhances the efficacy of chemotherapeutic agents by inhibiting ABC transporter-mediated efflux, leading to increased drug retention and apoptosis in resistant cancer cells. Their comprehensive review highlights

SFN's role in chemosensitization, showing that it not only downregulates ABCB1 and ABCG2 but also interferes with Akt/mTOR and MAPK pathways that sustain drug resistance phenotypes. Together, these findings position SFN as a promising adjunct in cancer therapy, capable of reversing drug resistance and improving the therapeutic index of conventional anticancer agents.

6.Oxidative Stress & Detoxification

6.1.SFN Increases Intracellular ROS, Promoting Oxidative Damage

Sulforaphane (SFN), though widely recognized for its antioxidant-inducing properties, can paradoxically act as a pro-oxidant in cancer cells, leading to oxidative stress and apoptosis. As demonstrated by Ferreira de Oliveira et al. [64], SFN treatment in p53-null MG-63 osteosarcoma cells significantly increased intracellular reactive oxygen species (ROS) levels in a dose-dependent manner. At concentrations ≥10 μM, SFN impaired glutathione recycling by inhibiting glutathione reductase (GR) and suppressing glutathione peroxidase (GPx) gene expression and activity. This disruption of redox homeostasis led to elevated ROS accumulation, caspase-3 activation, and early apoptotic events, confirming SFN's cytotoxic potential via oxidative damage. Extending these findings, Liang et al. [65] showed that SFN induces a pro-oxidative state in human T-cells, marked by increased ROS and depleted glutathione (GSH) levels. This oxidative shift resulted in global cysteine sulfenylation and targeted oxidation of transcription factors like STAT3, impairing inflammatory signaling and promoting apoptosis. Notably, the effects were reversible with antioxidant supplementation, confirming the ROS-dependent nature of SFN's cytotoxicity. Together, these studies highlight SFN's dual role: while it activates detoxification pathways in normal cells via Nrf2, it can overwhelm antioxidant defenses in cancer cells, leading to selective oxidative damage and cell death—a mechanism exploitable for cancer therapy.

6.2. Sulforaphane Activates Nrf2 Pathway, Boosting Antioxidant Defenses

Sulforaphane (SFN) is a potent activator of the Nrf2 (nuclear factor erythroid 2–related factor 2) pathway, which governs the transcription of over 200 genes involved in antioxidant defense, detoxification, and cellular protection. As demonstrated by Kubo et al. [66], SFN enhances Nrf2 translocation into the nucleus, where it binds to antioxidant response elements (AREs) in the promoter regions of genes such as Prdx6, catalase, and GSTπ. This activation restores Nrf2/ARE signaling disrupted by aging and oxidative stress, leading to increased expression of cytoprotective enzymes and improved resistance to UVB-induced toxicity. SFN upregulates Nrf2-mediated antioxidant enzymes in colorectal cancer cells, including HO-1 and NQO1, in both p53-wild-type and p53-knockout models. The study confirmed SFN's ability to modulate redox balance and mitochondrial function through Nrf2 activation, highlighting its dual role in cytoprotection and metabolic regulation[67].SFN modifies cysteine residues on Keap1, the cytoplasmic repressor of Nrf2, thereby releasing Nrf2 to initiate transcription of phase II detoxification enzymes such as UGT, GSTs, and NQO1. This cascade enhances cellular resilience against oxidative and xenobiotic stress[68].SFN-induced Nrf2 activation in human T-cells leads to increased glutathione synthesis and ROS neutralization, while simultaneously suppressing inflammatory signaling via STAT3 oxidation. These effects were shown to be reversible with antioxidant supplementation, confirming the redox-dependent nature of SFN's action[69].Finally, Metabolic Therapy [70] summarized preclinical evidence showing that SFN activates Nrf2 by inhibiting Keap1, resulting in elevated expression of detoxifying enzymes and reduced oxidative damage across multiple cancer models. SFN's ability to modulate Nrf2 makes it a promising agent for chemoprevention, anti-aging therapy, and inflammation control.

6.3. Phase II Detox Enzymes (e.g., GST, NQO1)

Sulforaphane (SFN), a bioactive isothiocyanate derived from cruciferous vegetables, is a well-established inducer of Phase II detoxification enzymes, which play a critical role in neutralizing reactive metabolites and enhancing cellular resilience. As described by Vitafenix [71], SFN activates the Nrf2–ARE pathway, leading to transcriptional upregulation of key detox enzymes including GST, NQO1, and UGT. This activation occurs via covalent modification of cysteine residues on Keap1, releasing Nrf2 to translocate into the nucleus and initiate gene expression. These enzymes catalyze conjugation reactions that render electrophilic toxins water-soluble for excretion, thereby reducing oxidative and xenobiotic stress. SFN's potency in human keratinocytes, where it significantly increased GST and NQO1 activity after 48 hours of exposure. Their study emphasized the importance of the isothiocyanate functional group in SFN's detoxifying action, showing that synthetic derivatives were less effective than native SFN[72]. SFN-rich broccoli sprout extract upregulated GSTM1 and NQO1 in human airway epithelial cells, with a dose-dependent increase in gene expression. This was further validated in a pilot clinical trial, where oral epithelial cells showed a twofold increase in NQO1 after SFN supplementation[73]. SFN's ability to elevate intracellular glutathione (GSH) levels, enhancing the substrate pool for GST-mediated detoxification. Their findings support SFN's role in maintaining redox balance and protecting against environmental insults[74].Finally, a randomized controlled trial summarized by Metabolic Therapy [75] showed that daily intake of SFN-rich broccoli sprout beverages significantly increased urinary excretion of airborne pollutants, correlating with elevated GST and NQO1 activity. These results underscore SFN's translational potential in clinical detoxification protocols.

6.4. Sulforaphane Inhibits Phase I Enzymes That Activate Procarcinogens:

Sulforaphane (SFN) plays a critical role in blocking carcinogen activation by inhibiting Phase I enzymes, particularly cytochrome P450s (CYPs), which are responsible for converting procarcinogens into reactive intermediates. [76], SFN interferes with the initiation stage of carcinogenesis by downregulating CYP1A1, CYP1B1, and CYP3A4, thereby reducing the bioactivation of polycyclic aromatic hydrocarbons and heterocyclic amines. This inhibitory effect complements SFN's induction of Phase II detoxification enzymes, creating a dual-action chemopreventive profile. SFN's ability to suppress Phase I enzyme activity in liver and colon cancer models. Their study showed that SFN treatment led to decreased expression of CYP1A2 and CYP2E1, enzymes commonly involved in the metabolic activation of aflatoxins and nitrosamines[77]. This suppression was mediated through Nrf2-dependent transcriptional repression and epigenetic modulation. SFN-rich broccoli sprout extract reduced CYP1A1 expression in human breast epithelial cells, thereby lowering DNA adduct formation and mutagenic potential[78]. The study emphasized SFN's role in blocking initiation rather than merely suppressing tumor progression. SFN's impact on benzo[a]pyrene metabolism, showing that SFN inhibited CYP1A1-

mediated activation and enhanced conjugation via GST, leading to reduced genotoxicity in lung epithelial cells[79].

SFN acts as a monofunctional inducer, selectively inhibiting Phase I enzymes while upregulating Phase II enzymes. Their work laid the groundwork for SFN's classification as a blocking agent in carcinogen metabolism[80].

7.Signaling Pathways

7.1. Suppresses PI3K/Akt/mTOR signaling:

Sulforaphane (SFN) exerts potent anticancer effects by suppressing the PI3K/Akt/mTOR signaling pathway, a central axis regulating cell survival, proliferation, and metabolism. As reviewed by Liu et al. [81], SFN inhibits phosphorylation of Akt and mTOR, leading to downstream suppression of cell cycle regulators and induction of apoptosis. This pathway is frequently hyperactivated in various cancers, and SFN's ability to downregulate it contributes to its tumor-suppressive properties. In breast cancer models, demonstrated that SFN reduced PI3K/Akt/mTOR activity, promoting autophagy and apoptosis while enhancing the efficacy of chemotherapeutic agents. Their nanomedicine-based approach showed improved bioavailability and synergistic tumor suppression[82]. SFN, alone and in combination with formononetin, significantly reduced PI3K, Akt, and mTOR expression in HeLa cervical cancer cells, resulting in enhanced ROS generation and apoptotic signaling. This dual-agent strategy amplified SFN's impact on cell cycle arrest and cytotoxicity[83]. SFN's effects in endometrial cancer, confirming that SFN downregulated Akt and mTOR while modulating EMT markers. Proteomic analysis revealed that SFN altered kinase networks, reducing migration and invasion in vitro and in xenograft models[84]. Finally SFN suppressed PI3K/Akt signaling in glioblastoma cells, contributing to ER stress and apoptosis. SFN treatment led to increased CHOP expression and mitochondrial dysfunction, reinforcing its role in targeting survival pathways[85].

7.2. Modulates NF-κB Pathway, Reducing Inflammation:

Sulforaphane (SFN) exerts strong anti-inflammatory effects by modulating the NF-κB signaling pathway, which plays a pivotal role in regulating immune responses, cytokine production, and chronic inflammation. As demonstrated by Sailo et al., SFN inhibits the phosphorylation and degradation of IκBα, preventing the nuclear translocation of NF-κB p65, thereby suppressing transcription of pro-inflammatory genes such as TNF-α, IL-6, and IL-1β. This results in reduced inflammatory cytokine secretion and diminished oxidative stress in cancer and immune cells [86]. In macrophage models, SFN was shown to attenuate LPS-induced NF-κB activation, leading to decreased expression of COX-2 and iNOS, and promoting a shift toward an anti-inflammatory phenotype [87]. Similarly, in human bronchial epithelial cells, SFN suppressed NF-κB signaling and reduced neutrophil recruitment, suggesting its utility in respiratory inflammatory disorders [88]. In colon cancer cells, SFN downregulated NF-κB target genes involved in proliferation and angiogenesis, including VEGF and MMP-9, thereby linking its anti-inflammatory action to anti-metastatic effects [89]. SFN also demonstrated protective effects in neuroinflammation models, where it reduced microglial activation and inhibited NF-κB-mediated neurotoxic cytokine release [90]. Furthermore, SFN's modulation of NF-κB is partly mediated through Nrf2 cross-talk, where activation of antioxidant response elements indirectly suppresses NF-κB-driven inflammation, Activates JNK and p38 MAPK Pathways

Sulforaphane (SFN) modulates key stress-responsive signaling cascades by activating the JNK and p38 MAPK pathways, which are involved in inflammation, apoptosis, and immune regulation. As demonstrated by Deramaudt et al., SFN pretreatment of macrophages exposed to Staphylococcus aureus led to phosphorylation of JNK and p38 MAPK, enhancing bactericidal activity and reducing intracellular pathogen survival. This activation was associated with downregulation of proinflammatory microRNAs (miR-142-5p and miR-146a-5p) and suppression of cytokines such as IL-1β, IL-6, and TNF-α, indicating SFN's role in fine-tuning immune responses through MAPK signaling [92]. In colorectal cancer cells, SFN was shown to activate MAPK/AP-1 signaling, leading to reduced IL-6 expression and inhibition of cell proliferation and invasion [93]. Similarly, in hepatoma HepG2 cells, SFN enhanced ARE-mediated transcription of antioxidant genes via p38 MAPK-dependent phosphorylation of Nrf2, demonstrating its dual role in stress response and detoxification [94]. Further evidence from breast cancer models revealed that SFN-induced JNK activation promotes apoptosis through mitochondrial disruption and caspase-3 cleavage [95]. In neuronal cells, SFN activated p38 MAPK and JNK to mitigate oxidative damage and support neuroprotection, highlighting its therapeutic potential beyond oncology [96]. Collectively, these findings underscore SFN's ability to engage JNK and p38 MAPK pathways as part of its multifaceted mechanism, contributing to inflammation control, apoptosis induction, and cellular defense.

7.3.Inhibits Wnt/β-Catenin Signaling, Reducing Stemness

Sulforaphane (SFN) exerts potent anti-cancer effects by inhibiting Wnt/β-catenin signaling, a pathway crucial for maintaining cancer stem cell (CSC) properties and tumor progression. Bernkopf et al. demonstrated that SFN suppresses Wnt/β-catenin activity in colorectal cancer cells by interfering with β-catenin–TCF transcriptional complex formation, independent of upstream β-catenin degradation. SFN treatment reduced expression of canonical Wnt target genes such as AXIN2 and LGR5, both markers of stemness, and induced nuclear β-catenin sequestration into transcriptionally inactive chromatin domains. This disruption of Wnt signaling led to decreased proliferation and enhanced apoptosis in SW480, DLD1, and HCT116 cells [97]. In breast cancer stem-like cells, SFN downregulated β-catenin and cyclin D1, impairing self-renewal and mammosphere formation, indicating suppression of CSC traits [98]. Similarly, SFN reduced stemness in prostate cancer by targeting Wnt/β-catenin and SHH pathways, leading to diminished ALDH1 activity and CD44 expression [99]. In glioblastoma models, SFN inhibited Wnt signaling and reduced SOX2 and Nestin, key regulators of neural stemness, thereby sensitizing cells to chemotherapeutics [100]. Moreover, SFN synergized with doxorubicin in cardiac models by modulating Wnt/β-catenin and antioxidant responses, suggesting broader implications in stemness and stress adaptation [101].

These findings highlight SFN's ability to attenuate cancer stemness through targeted inhibition of Wnt/β-catenin signaling, offering a promising strategy for overcoming therapy resistance and tumor recurrence.

7.3. Selectivity & Safety

Exhibits selective cytotoxicity toward cervical cancer cells, sparing normal epithelial cells

Sulforaphane (SFN) demonstrates selective cytotoxicity by preferentially targeting cervical cancer cells while sparing normal epithelial cells,

underscoring its therapeutic safety profile. Luo et al. showed that SFN significantly inhibited proliferation and induced apoptosis in HeLa cells via downregulation of miR-1247-3p, which in turn activated the MAPK signaling pathway. Importantly, SFN exhibited minimal cytotoxicity toward non-cancerous cervical epithelial cells, suggesting a tumor-specific mechanism of action. These findings were validated through flow cytometry, Western blot, and qRT-PCR analyses, confirming SFN's ability to modulate gene expression and promote cancer cell death without harming normal tissue [102].In a comparative study, SFN induced dose-dependent apoptosis in HeLa cells while maintaining viability in normal keratinocytes, highlighting its selective oxidative stress induction in malignant cells [103]. Similarly, SFN treatment led to G2/M cell cycle arrest in cervical cancer cells, with no significant impact on non-transformed cells, indicating differential checkpoint sensitivity [104].Further evidence from in vivo models revealed that SFN reduced tumor volume in xenografted cervical cancer mice without affecting surrounding healthy tissues, reinforcing its low systemic toxicity [105]. Additionally, SFN's selective action was attributed to its ability to modulate ROS levels and mitochondrial membrane potential specifically in cancer cells, sparing normal cells from oxidative damage [106]Together, these studies affirm SFN's selective cytotoxicity and safety, making it a promising candidate for cervical cancer therapy with minimal off-target effects.

8.Future Benefit of Sulforaphane Treatment in Cervical Cancer

Sulforaphane (SFN) holds significant promise as a future therapeutic agent for cervical cancer, offering a multi-targeted approach with minimal toxicity. Luo et al. provided compelling evidence that SFN suppresses cervical cancer cell viability and induces apoptosis via downregulation of miR-1247-3p and subsequent activation of the MAPK signaling pathway. Using next-generation sequencing (NGS) and bioinformatics analysis, the study identified SFN's ability to modulate key oncogenic transcripts and microRNAs, suggesting its potential for precision medicine applications. These findings lay the groundwork for SFN's integration into cervical cancer treatment regimens, especially for patients resistant to conventional therapies [107]In a recent study, SFN was shown to enhance radiosensitivity in cervical cancer cells by activating LATS2 and inhibiting homologous recombination repair via suppression of Rad51/MDC1 nuclear recruitment, thereby improving radiotherapy outcomes [108]. Additionally, SFN's ability to modulate epigenetic regulators and oxidative stress pathways positions it as a candidate for chemo-radioprotective strategies [109].SFN also demonstrated efficacy in reducing tumor stemness and recurrence by targeting Wnt/β-catenin and Notch pathways, which are often upregulated in cervical cancer stem-like cells [110]. Moreover, its anti-inflammatory and antioxidant properties, mediated through Nrf2 activation and NF-κB inhibition, suggest long-term benefits in preventing HPV-induced carcinogenesis and progression [111].Collectively, these studies highlight SFN's potential to transform cervical cancer therapy by offering a safe, multi-modal, and biologically precise intervention that complements existing treatments and addresses unmet clinical needs.

9.Conclusion:

Sulforaphane (SFN) is a potent phytochemical with selective cytotoxicity against cervical cancer cells, sparing normal epithelial tissue. It activates stress-responsive pathways like JNK and p38 MAPK, promoting apoptosis and immune modulation. SFN inhibits Wnt/β-catenin signaling, reducing cancer stemness, self-renewal, and metastatic potential. It enhances radiosensitivity by disrupting DNA repair proteins such as Rad51 and MDC1.SFN modulates oncogenic microRNAs, including miR-1247-3p, contributing to transcriptional reprogramming. Through Nrf2 activation and NF-κB suppression, it supports antioxidant defense and reduces HPV-driven inflammation. In vivo studies confirm its tumor-reducing effects with minimal systemic toxicity. Its epigenetic influence adds value in long-term cancer prevention strategies. SFN's oral bioavailability and dietary origin make it accessible and safe. It complements existing therapies and may reduce treatment-related side effects. Future clinical validation is needed to establish its role in personalized oncology. Overall, SFN offers a multi-targeted, low-toxicity approach to cervical cancer therapy.

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