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Review

Sulforaphane: The Principal Broccoli Phytochemical as a Cancer Challenger

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Abstract

Broccoli has long been reported to exert a positive impact on human health. It contains high levels of isocyanates, the most important of which is sulforaphane (SFN). Numerous studies have demonstrated that SFN can be used as an effective supplement for treating a variety of diseases. In addition, it is known to possess anti-cancer properties such as chemopreventive properties against gastrointestinal, breast, lung, bladder, prostate, and other cancers. The reported data indicates that broccoli could be a potent inhibitor of cancer development and progression and can be used alone or in combination with other isocyanates or conventional anti-cancer medications. Because *in vivo* studies of SFN's effects are scarce, this review provides an overview of the beneficial effects of SFN on different malignant tumor cells performed mostly *in vitro* with an expectation that the results will incite research in humans.

Keywords

Broccoli; sulforaphane; cancer; chemoprevention

1. Introduction

Broccoli is the most well-known member of the cruciferous vegetable family Brassicaceae. It was first cultivated in the Eastern Mediterranean region [1] and has been a popular vegetable since Roman times. Currently, it is a staple of several people's daily diets in a variety of countries. Manchali et al. [2] have published a comprehensive analysis of the history and health advantages of cruciferous vegetables. Broccoli has been named *"Crown Jewel of Nutrition"* because of its high level of vitamins, minerals, phytochemicals, and a variety of components with significant antioxidant activity [3,4]. For instance, broccoli sprouts contain several isothiocyanates, the most important of which is sulforaphane (SFN). Glucoraphanin is a glucosinolate that is further hydrolyzed to SFN, which is its precursor [5]. Phytochemicals, in general, and SFN, in particular, have been demonstrated to have favorable health qualities in diseases of the gastrointestinal system, diabetes, obesity, and even neurodegenerative problems [6]. SFN protects against cardiovascular disease, osteoporosis, and autism. [7]. Furthermore, research has indicated that SFN has an immunomodulatory impact; the administration of SFN suppressed the generation of pro-inflammatory cytokines by human mononuclear cells in a concentration-dependent manner [8]. Other studies have reported lower levels of tumor necrosis factor (TNF), interleukin (IL)-6, and C-reactive protein (CRP) in support of SFN's anti-inflammatory characteristics [9]. A well-established relationship has been reported between chronic inflammation and the modification of signaling pathways, leading to cancer development [10]. Infection and inflammation account for around 25% of cancer triggers [11]. One of the elements promoting tumor cell proliferation and migration is the presence of inflammatory cells in the tumor microenvironment [12]. In addition, an immune dialogue exists between mononuclear and tumor cells that may be influenced by numerous drugs and phytochemicals [13]. In addition, SFN can attenuate inflammation [14] and acquire the function of cancer chemoprevention. Because high consumption of broccoli is linked to a low risk of cancer [15], SFN was included in the group of *"Green Chemopreventers*," a term given to plants or dietary phytochemicals that can prevent the development of gastrointestinal tract, breast, ovaries, lungs, and prostate cancers [6-19]. Intricate mechanisms exist by which SFN exerts its carcinopreventive effects [20]. Studies have reported that SFN targets the cancer cells by its anti-inflammatory, cytotoxic, pro-apoptotic, and anti-mitotic capacities, as well as nuclear factor erythroid 2-related factor 2 (Nrf2) that acts as a regulator of antioxidant proteins [21-23]. In addition, it has been reported that SFN targets cancer stem cells [24] and their miRNAs (non-coding RNAs that govern gene expression) [25]. Another mechanism by which SFN may inhibit cancer progression is by inducing cell cycle arrest and death [18]. I Immunomodulatory characteristics of SFNs influence the immune-colon cancer cell cross-talk [26]. A combination of SNF and nanostructured lipid carriers improved *in vitro* and *in vivo* SFN release, antioxidant activity, and apoptotic values [27]. Nandini et al. [28] stated the use of SFN as a possible anti-cancer therapy for specific tumor entities. In this review, we will survey studies on SFN as a chemopreventive agent and the underlying molecular mechanisms. In addition, we anticipate that the data presented will attract researchers' attention and pave the way for increased human studies, leading to the inclusion of SFN to the list of cancer medications.

2. Animal and Clinical Trials

The pharmacological and therapeutic characteristics of SFNs have primarily been investigated *in vitro* or in animal models, and to a lesser extent, in humans, although the number of trials varies between reports. According to Yagishita et al., [29] over 3,000 rodent studies were recorded until the early 1900s, whereas clinical trials in humans were around 50. Clarke et al. [20] published an early overview of human research with SFN in 2008. A recent study based on PubMed, EMBASE, and the Cochrane Library reported 16 human studies, 4 animal studies, and 65 *in vitro* research papers [30]. The findings of clinical trials with two isothiocyanates, namely, SFN and phenethyl isothiocyanate, were examined by Palliyaguru et al. [31]. Both of them, according to the authors, could be used as an extra tool in treating a wide range of disorders, including cancer. Except for one patient, the primary goal of reducing PSA levels to less than 50% was not accomplished in a cohort of 20 patients with recurrent prostate cancer who were treated with 200 μM/day of SFN reach extracts (SFN-re) for 20 weeks [32]. Amjad et al. [17] analyzed the efficacy of SFN and other dietary treatments on the development and progression of prostatic cancer in individuals up to the beginning of 2015, concluding that an SFN-enriched diet can prevent prostate cancer. Abbaoui et al. [33] investigated the effects of SFN and broccoli sprouts on healthy volunteers, women undergoing reduction mammoplasty, and healthy smokers. They reported a high oral bioavailability of SFN, resulting in biologically active plasma and urine concentrations. Based on the well-established link between inflammation and obesity, López-Chillón et al. [9] conducted a study on 40 obese adults who were administered 20 to 25 g/day broccoli sprouts for 10 weeks. It was reported that inflammatory markers such as interleukin (IL)-6 and C-reactive protein (CRP) were considerably reduced. Altogether, research in humans appears to be restricted. More clinical and epidemiological investigations involving broad demographic groupings are required to obtain convincing results. Given the compelling outcomes observed with cancer cells treated with SFN, it is clear that more research is needed in humans.

3. Cancers of the Gastrointestinal Tract

Cruciferous vegetables, particularly SFN, exert anti-cancer action against gastrointestinal malignancies [34] by controlling detoxifying enzymes, stimulating apoptosis, and inhibiting cancer cell proliferation by inducing cell cycle arrest. According to Johnson [35], increasing cruciferous vegetable diet can reduce the risk of stomach cancer by 19% and colorectal cancer by 8%.

3.1 Cancers of the Mouth and Esophagus

Treatment with SFN reduced the growth of tongue tumors generated by 4-nitroquinoline-1-oxide (4NQO) in a mouse model [36], which was attributed to the activation of the NRF2 pathway and reduced oxidative damage [37]. Inhibition of the expression of cathepsin S [38] and downregulation of metalloproteinases MMP-1 and MMP-2 activities, which are elevated and associated with poor prognosis in several malignancies, including oral carcinoma [39], can prevent the motility and migration of oral cancer cells. SFN was found to significantly reduce the expression of hypoxia-inducible factor-1 alpha, a carcinogenesis marker, in human tongue squamous carcinoma cells [40]. Only a few studies are present on the effect of SFN on esophageal cancer. Qazi et al. [41] used SFN to treat Barret esophageal adenocarcinoma cells (BEAC) and

reported that the survival, cell cycle arrest, and apoptosis were reduced in a dose-and-time-dependent manner. A combination of this drug with paclitaxel boosted its activity and reduced its efflux. Similarly, treatment of BEAC-bearing immunodeficient mice with SFN considerably reduced the tumor growth, which was attributed to the stimulation of caspase 8 and P21, as well as the inhibition of Hsp 90, a protein that activates a variety of proliferative proteins implicated in tumor development, according to the authors. Because the NRF2 pathway was activated, esophageal squamous carcinoma cells treated with SFN displayed higher apoptosis and autophagy [42]. These findings suggest that SFN could be effective in the chemoprevention of oral and esophageal cancers.

3.2 Gastric Cancer

Gastric adenocarcinoma is one of the deadly malignancies [43]. In its early stage, surgery is advised, and efforts are being made to prevent and inhibit its development. The application of nutritional isocyanates, such as SFN, has demonstrated encouraging effects *in vitro*. The treatment of gastric cell lines (BGC-823 and MGC0803) with SFN reduced the proliferation by arresting the cell cycle in the S phase and increased apoptosis by elevating the levels of p53 and p21. In addition, the expression of SDK2 (cyclin-dependent kinase 2) was reduced [44]. SFN is known to suppress the Hh (Hedgehog) pathway, which serves as a transmitter of signals from the cell membrane to the nucleus, thus promoting apoptosis and decreasing the proliferation of gastric cancer stem cells [45]. Furthermore, SFN promotes apoptosis in gastric cancer cell lines (AGS and MKN450) in a dose-dependent manner, but not in normal HF2FF gastric cell lines. These effects are ascribed to altered expression of transcription factors CDX1, CDX2, and the gene regulators miR-9 and miR-326. According to Wang et al. [46], SFN improved the effect of cisplatin on gastric cancer cells by activating miR-124, allowing the anti-cancer agent to be used at lower concentrations. The findings of these and other trials support the idea that SFN could be employed as a therapeutic adjuvant for gastric cancer treatment.

3.3 Colorectal Cancer

Despite the significant efforts to develop a cure for colorectal cancer (CRC), it remains a fatal disease [47]. It has been observed that eating a diet high in vegetables and fruits can help lower the risk of CRC [48]. SFN, like other types of cancer, exerts its carcinopreventive effect on CRC via several mechanisms. SFN suppressed the proliferation of three CRC lines, namely, SW480, DLD1, and HCT116, according to Bernkopf et al. [49], by inhibiting the Wnt-catenin signaling pathways, which comprises a set of proteins that convey the signals through cell surface receptors and are highly expressed in CRC cells. Because of the overexpression of Nrf2 and increased glucuronosyltransferases (UGT1A) levels, SFN treatment suppressed cell proliferation, accelerated apoptosis, and reduced migratory activity in HT-29 and SW480 CRC cells [50]. The anti-cancer effect of SFN on HT-29 human colon cancer cells is ascribed partially to block the expression of microsomal prostaglandin E synthase-2 and COX-2, resulting in inhibited cell proliferation, arrested sub-G1 phase of the mitotic cycle, and activated detoxifying enzymes, based on the observation that CRCs express a high level of prostaglandin E2 [51, 52]. In addition, SFN targets the oncoprotein SKP2, which promotes cell proliferation by degrading the cyclin-dependent kinase inhibitor p27 (KIP1) [53]. SFN, with its ability to lower oxidative stress via triggered Nrf2 synthesis,

could prevent cancer in individuals with Lynch syndrome, who have a reduced mismatch gene repair capacity due to elevated oxidative stress [54].

3.4 Pancreatic Cancer

In comparison to other cancers, pancreatic duct adenocarcinomas are thought to be highly resistant to standard treatment. These characteristics may be attributable to the action of cancer stem cells, which are responsible for the rapid growth and migration of tumors [55]. The IL-8/CXCR1 axis, a pro-inflammatory cytokine with two receptors-CXCR1 and CXCR2, is active in pancreatic stem cells and is linked to rapid tumor growth and poor prognosis [56], has received considerable attention. Pancreatic cancer stem cells can be detected by signaling pathways that are sensitive to natural phytochemicals, including SFN, and so could be employed as therapeutic agents in addition to traditional treatments [55]. Furthermore, SFN suppressed the protein transcription factor NF-kappa B (nuclear factor kappa B), causing the resistance to apoptosis in tumor-initiating cells in pancreatic cancer [57]. Moreover, SFN increased the TRAIL activity, inhibiting tumor growth and metastasis by stimulating apoptosis. SFN was also able to target highly treatment-resistant pancreatic adenoma cells by boosting autophagy, a process that requires reactive oxygen [58]. In addition, SFN affects the oncoprotein SKP2, thus promoting cell proliferation by degrading the cyclin-dependent kinase inhibitor p27 (KIP1) [53]. Injection of SFN-treated pancreatic cancer cells (Panc-1, AsPc-1, and BxPc-3) to mice in a pancreatic cancer xenograft model demonstrated reduced cell proliferation and enhanced apoptosis, as well as inhibited tumor formation. These results are ascribed to the ability of SFN to disrupt protein-protein interactions in the Hsp90 (heat shock protein) complex [42]. Because of the high death rate among individuals with pancreatic tumors and their treatment resistance, researchers should consider adding SFN to the standard therapy.

3.5 Hepatocellular Carcinoma

Hepatocellular carcinoma is a highly aggressive cancer with a high death rate [59]. Effective preventative measures, including the use of SFN, have been implemented. Treatment with SFN resulted in increased apoptosis and decreased viability of hepatocarcinoma HepG2 cells. The anti-apoptotic Bcl-2 and Bcl-XL proteins, as well as caspase-3 activation, were found to be responsible for this effect [60]. SFN downregulates cyclin-dependent kinase enzymes CCND1, CCNB1, CDK1, and CDK2 and inhibits cell growth and cell cycle arrest in HepG2 and Huh-7 human liver cancer cell lines. Administration of SFN to liver cancer-bearing mice suppressed tumor cell proliferation and tumor angiogenesis [61]. In addition, SFN induced apoptosis in human liver carcinoma cells and other malignancies by inhibiting the activity of PFKFB4 (6-phosphofructo-2-kinase/fructose-2, 6-biphosphatase-4), a protein found in high numbers in cancer cells and required for their survival and development in hypoxic media [62]. Another possibility to explain the carcinopreventive impact of SFN is its ability to produce DNA damage and change the formation of the mitotic spindle in liver cancer HepG2 cells, resulting in death and reduced proliferation [63]. SFN is known to inhibit the NF-kB pathway, overexpressed during radiation, thus improving the radiosensitivity of hepatocellular carcinoma cells and resulting in increased malignant cell death [64]. It is possible that SFN can be used as a new synergistic strategy in treating hepatocellular carcinoma in the future.

4. Breast Caner

Despite modern approaches for preventing and treating breast cancer, it is still one of the most common malignant tumors in women [65]. Based on the positive effect of phytochemicals on carcinogenesis *in vitro*, micronutrients, alone or in combination, have been studied as a supplemental therapeutic approach to the standard breast cancer therapy. SFN impacts breast cancer cells in a variety of ways, including triggering the cell cycle arrest in the G2/M phase [66]. Application of SFN to breast ductal carcinoma ZR-75-1 cells resulted in a G1/S arrest, which was caused by the activation of SERTAD1 (cyclin-dependent kinase 4) [67]. SFN inhibits the self-renewal potential, invasiveness, and proliferation of breast cancer stem cells [64, 68, 69]. These effects were more pronounced when SFN was embedded in nano-carriers. The loading of SFN and tamoxifen in nanostructured lipid carriers improved the intestinal permeability and bioavailability of both drugs, whereas the toxicity of tamoxifen was reduced [70]. Experiments with mice bearing triple-negative breast cancer (TNBC) demonstrated that SFN inhibited the proliferation of malignant stem cells by suppressing numerous stem cells-related oncogenes, including the formation of Crypto/Alk4 protein complex [71] and even eliminating breast cancer stem cells by inhibiting the translocation of NF-kB p65 and p52 downregulation [72]. Treatment of MDA-MB-453 and MDA-MB-456 TNBC cells with SFN not only inhibited the cell proliferation, increased apoptosis, and cell cycle arrest in the G2/M phase but also up-and downregulated their genome, the most overexpressed being Egr1, an active tumor suppressor gene [73]. A combination of three phytochemicals with confirmed anti-cancer effects, i.e., sulforaphane, piperine, and thymoquinone (extracted from black seed, *Nigella sativa*), exerted a more pronounced activity in breast cancer compared to their effects when administered alone [65]. Moreover, SFN increased the paclitaxel-mediated apoptosis by activating the apoptosis-induced pathways such as caspase-3, -8, and -9, and cytochrome C, as well as enhancing the activity of additional anti-cancer agents, such as docetaxel and gemcitabine [74]. Although SFN alone inhibited the growth of human breast cancer cells (MCF-7) and induced apoptosis by downregulating the anti-apoptotic Bcl-2 and the pro-inflammatory *COX-2* genes, this effect was better expressed when SFN was administered together with gemcitabine [75]. In mice bearing triple-negative breast cancer, a combination of SFN and paclitaxel reduced the tumor volume and prevented the formation of secondary tumors [72]. A combination of SFN with 5-fluorouracil significantly reduced the number of MDA-MB-231 triple-negative breast cancer cells by inducing autophagic cell death [76]. Similarly, MDA-MB-231 cells were treated with a combination of SFN and doxorubicin encapsulated in liposomes, which resulted in improved endocytotic uptake of both drugs and strong synergistic activity, thus reducing the cytostatic dosage [77]. The anti-breast cancer activity of SFN is supported by the findings presented above, and its use in clinical studies should be considered.

5. Bladder Cancer

Leone et al. showed that isothiocyanates, particularly SFN, can prevent bladder cancer by acting on malignant cells via different mechanisms [78]. Treatment of human bladder cancer cells with broccoli sprout extracts containing SFN and other isocyanates resulted in a mitotic arrest in the S and M phases as well as apoptosis, which was comparable to the synthetic SFN activity [79]. In rats with N-butyl-N-(4-hydroxybutyl) nitrosamine-induced bladder cancer, a freeze-dried aqueous extract of broccoli sprouts inhibited the development of cancer in a dose-dependent

manner [80]. According to Wang, the high activity of the oncogene promoter protein-coding gene *FAT1* is linked to a worse 5-year survival rate in patients with bladder cancer [81]. SFN-mediated inhibition of *FAT1* expression in bladder cancer cells reduced cell survival and migration, as well as increased apoptosis. The potential of SFN to enhance the reactive oxygen species (ROS) activity, inducing higher apoptosis in bladder cancer cells, is similar to that of other malignant situations [82]. Because the rapamycin (mTOR) pathway is linked to the development of bladder cancer, Justin et al. [83] inhibited it by treating RT112, UMUC3, TCCSUP bladder cancer cells with 2.5 μM SFN for 24 h and found that it reduced the cell growth and proliferation when given alone or in combination with everolimus, an mTOR inhibitor. Furthermore, after 8 weeks of treatment with everolimus, the cancer cells displayed increasing resistance, as evident from the increased mTOR activity, which was reversed by the addition of SFN.

6. Prostate Cancer

Prostate cancer is one of the most frequent malignant disorders in males; efforts are being taken to prevent and treat it. For example, Mokbel et al. [84] examined the anti-cancer activity of a few isocyanates, including SFN, and concluded that they could be useful as a prostate cancer adjuvant. In comparison with controls, mice with transgenic prostate adenocarcinoma treated with 6 μM of SFN thrice a week showed a 23 to 28% lower incidence of prostate intercellular hyperplasia and pulmonary metastases, decreased cell proliferation, and increased apoptosis. Similarly, treatment of androgen-free prostate cancer cells (DU-145) with SFN reduced the phosphorylation of the Rb (retinoblastoma) protein, which stimulates the mitotic cycle, and blocked the G1-S phase. Thus, the development of cancer cells decreased, whereas cancer cell death was increased [85]. According to Hsu et al., SFN enhanced the expression of cyclin D2 by inhibiting the activity of DNA methyltransferases, followed by an anti-proliferative action on LnCap prostate cells [86]. Cancer development is connected to abnormal histone deacetylase function, resulting in increased histone acetylation. SFN has been demonstrated to decrease the activity of deacetylases in the prostate, bolstering its chemopreventive repute [87].

7. Lung Cancer

Lung cancer, an aggressive malignancy with a high fatality rate, is strongly linked to long-term smoking. Phytochemicals, such as SFN, can prevent the development of lung cancer. SFN inhibited the PI3K/Akt/mTOR pathway, lowering cancer cell survival and inducing apoptosis in H727 and H720 bronchial carcinoid cell lines. The effect was stronger when a combination of SFN and acetazolamide was used [24]. SFN has been demonstrated to cause cell death in a few lines of small-cell lung cancer cells by ferroptosis, a type of cell death distinct from apoptosis. It occurs when the cysteine/glutamate antiporter SLC7A11 is inhibited [88]. Lung cancer stem cells (LCSCs) have been studied, particularly for the role of miR-19, which regulates gene expression. Its overexpression induced tumor growth by stimulating the actions of LCSCs. SFN inhibits not only miR-19 but also the Wnt/β catenin pathway, thus inhibiting LCSC activity and tumor development [89]. SFN targets LCSCs by a few mechanisms [90]. A study of the effect of SFN on the development of A549 non-small lung cancer cell line demonstrated that 30, 60, and 90 μM SFN exerted a dose-dependent effect on G2/M arrest and cell death, with lower D1 cyclin content detected at higher concentrations [91]. Similarly, treatment of A549 non-small cell lung cancer

cells with both allyl isocyanate and SFN decreased their proliferation and migration, as well as enhanced apoptosis and formation of intracellular ROS [92].

8. Ovarian Cancer

Despite medical efforts to find a cure for ovarian cancer, it remains one of the most lethal gynecological cancers [93]. The ability of SFN and other nutritional isocyanates to inhibit cancer cell proliferation, impact cell cycle arrest, and induce apoptosis qualifies them as chemopreventers. This ability increases the likelihood of using them as adjuvants in ovary cancer therapy. The downregulation of the cyclin B1/CDC2 complex, active at this stage of cell mitosis, blocked the cell cycle in PA-1 ovarian cancer cells treated with SFN [94]. Others have reported similar findings [95]. Cisplatin is one of the most commonly used medications to treat ovarian cancer; however, the clinical experience revealed that drug resistance in malignant cells reduced its effectiveness. SFN can significantly overcome the resistance of A2780 and IGROV1-R10 ovarian cancer cells to cisplatin-induced DNA damage by increasing the expression of micro-RNA (miR), which is lower in cisplatin-resistant cells [96]. The capacity of SFN to overcome A2780 cells' resistance to cisplatin was explained in another investigation by the downregulation of the Nrf2 pathway; however, this impact was not detected in the SKOV3 ovarian cancer line [97]. This finding suggests that SFN does not always restore cisplatin resistance, at least in ovarian cancer cells.

9. Dosage (Table 1)

Table 1 Doses of SFN used in different experiments.

In vitro studies Type of cancer cells	Dosage	Effects	Ref
AGS and MKN450 gastric cancer	112 and 125 µg/mL for IC 50	Increased paclitaxel apoptosis	[74]
Panc-1, AsPc-1, and BxPc-3 pancreatic cancer	10-15 µM	Activated Nrf2 pathway and increased apoptosis	[42]
SW620 colon cancer	10-50 µM for cell viability 26 µM (24 h;, 24.4 µM (48 h;, 18 µM (72 h; for IC 50	Dose-dependent suppression of cell viability and proliferation	[98]
HCT116 colon cancer	5-15 µmol/L	Activated apoptosis	[99]
Caco-2 cells, colorectal carcinoma	1-20 µM	Dose-dependent suppression of cell development	[100]
RT112, UMUC3, TCCSUP bladder cancer	2.5 µM for 24 h or 8 weeks	mTOR inhibition with reduced cell growth and proliferation	[83]

MCF-7,MDA-MB-231, SK-BR-3, human breast carcinoma	50-20 µM	Cell cycle arrest from G1 to S phase with inhibited cell migration and apoptosis	[66]
DU-145 prostate carcinoma cells	0.1 µM-0.9 µM	Inhibited cell growth	[85]
A549 non-small lung carcinoma	30, 60 and 90 µM for 24 h	Dose-dependent effect on G2/M arrest	[91]
MDAH 2774 and SKOV-3 ovary carcinoma	8 µM for 3 days	Downregulation of cyclin B1/CDC2 complex and decreased mitosis	[95]
In vivo studies			
20 patients with prostate cancer	SFN-re 200 µM/daily for 20 weeks	<50% decrease in PSA level in 1 out of 20 patients	[32]
Colorectal carcinoma-bearing mice	400 µM/kg daily for 3 weeks	70% reduction of tumor weight	[101]
Triple-negative breast cancer-bearing mice	50 mg/kg/daily for 8 weeks	Inhibited malignant stem cells proliferation	[71]

According to Yagashita et al. [29], the median effective dose of SFN administered orally is 113 µmol/kg, whereas *in vivo* doses higher than 60 µM/kg have been used for detecting apoptosis in carcinogenesis. Treatment of human breast cancer cells MCF-7, MDA-MB-231, and SK-BR-3 with 5-20 µM SFN induced apoptosis and increased p21 and p27-cyclin-dependent kinase inhibitors of cell cycle arrest from G1 to S phase. Cell migration and apoptosis were inhibited in MDA-MB-231 cells treated with SFN 10-40 µM [66]. In human trials, young smokers who consumed 250 g of broccoli per day experienced enhanced DNA repair [31]. Castro et al. [71] reported that the administration of 50 mg SFN/kg for 5 weeks before and 3 more weeks after tumor cell inoculation inhibited the proliferation of malignant stem cells. The mean tumor weight was reduced by 70% in immunodeficient mice bearing primary human CRCs after daily administration of SFN at a dose of 400 µM/kg for 3 weeks [101]. The development of colorectal (Caco-2) cancer cells was suppressed in a concentration-dependent manner when cultivated in the presence of 1 to 20 µM SFN [100]. The exposure of HCT116 colon cancer cells to 15 µM/L SFN for 72 h resulted in 95% inhibition of cell proliferation, whereas 5 and 10 µM/L SFN reduced the G1 phase cell distribution and activation of apoptosis [99]. SFN at concentrations of 10 to 15 µM suppressed the viability and proliferation of SW620 colon cancer cells in a time-and dose-dependent manner. The IC50 was reached with 26 µM (24 h), 24.4 µM (48 h), and 18 µM (72 h) [98]. SFN at doses of 01 µM to 0.9 µM inhibited the growth inhibition of human prostate cancer cells DU-145 [85].

10. Side Effects

Because of its wide consumption, negative side effects have been rarely associated with broccoli. However, Latte et al., [102] based on their *in vitro* and animal investigations, caution that broccoli and its extracts may exert certain undesired genotoxic effects, which have not been established or detected in humans. Clinical trials to assess the health benefits of broccoli and SFN

resulted in a safety profile [6, 25]. A review of the research led to the conclusion that the health benefits of broccoli and its isothiocyanates are far superior; its combined culinary and medicinal properties should be greatly valued and utilized. However, Liang et al. [103] caution against its widespread use because of its double role as an antioxidant acting via the Nrf2-keap1 pathway. Once activated by SFN, the pathway prevents oxidative damage caused by cancer cells and acts as a pro-oxidant on T cells, and impedes their immune anti-cancer activity. Moreover, Nrf2 activation in certain cancers may induce malignant cell proliferation, inhibit apoptosis, and even promote their chemo-and radio-resistance [104]. The negative effects of SFN and other natural isocyanates, such as curcumin and resveratrol, have been characterized as negligible or non-existent [93]. SFN is widely regarded as a significant adjuvant to currently used chemotherapeutic drugs.

To summarize, the majority of the scientific reports demonstrate that SFN, alone or in combination with other isocyanates and with already available anti-cancer medications, can effectively suppress a wide range of cancers. Its activity as a cancer cell death inducer and a cancer preventer warrants further research. The findings presented here show that more animal and human studies with SFN are required to justify its inclusion in the list of “Green Chemopreventers.”

Author Contributions

The author did all the research work of this study.

Competing Interests

The author has no conflicts of interest to report.

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