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REVIEW

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The preventive mechanisms and research progress of sulforaphane in relation to prostate cancer

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Abstract: Prostate cancer is one of the most common tumors in urology. Dietary prophylaxis can effectively reduce prostate cancer incidence and progression. A growing body of research has shown that natural food ingredients such as Sulforaphane (SFN) can reduce the incidence of prostate cancer. It has a significant inhibitory effect on the progression from local prostate cancer to more aggressive prostate cancer. This article mainly expounds on the prevention mechanism and research progress of sulforaphane in various ways for prostate cancer and provides a reference for its future clinical application. In this review, 'SFN', 'Prostate Cancer', and 'PCa' were searched through PubMed, Embase, Web of Science, and other databases. SFN inhibits the occurrence and development of prostate cancer mainly through anti-oxidation, inhibition of fatty acid metabolism, inhibition of glycolysis, inhibition of pro-inflammatory factors, inhibition of cell proliferation and promotion of apoptosis, reduction of androgen receptors, and influence of epigenetics. Therefore, SFN is a natural compound with great potential for the prevention and treatment of prostate cancer, but the key factors such as effective chemoprevention dose, bioavailability, toxic dose, and response of sulforaphane in the human body need to be further studied in the future.

Abbreviations: Full Name of the Technical Term

SFN	Sulforaphane
PCa	Prostate cancer
CRPC	Castration-Resistant Prostate Cancer
ARTA	Androgen receptor-targeted drugs
PARP	Poly ADP-ribose polymerase
nmCRPC	Nonmetastatic castration-resistant disease
mCRPC	Metastatic castration-resistant disease
AR	Androgen receptor
ADT	Androgen Deprivation Therapy
MFS	Metastasis-free survival
OS	Overall survival
PFS	Progression Free Survival
ROS	Reactive oxygen species
GST	Glutathione S-transferase
NQO	NAD (P)H quinone oxidoreductase
Nrf2	Nuclear transcription factor-E2-related factor 2
Keap1	Kelpin-like ECH-associated protein 1
MtDNA	Mitochondrial DNA
HO-1	Heme oxygenase 1
UGT	UDP-glucuronosyltransferases
SOD	Superoxide dismutase Modifications completed
ARE	Antioxidant response element defense system
sMaf	Small molecule myofascial fibrosarcoma
TRAMP	Ttransgenic adenocarcinoma mouse prostate
FASN	Fatty acid synthase
PIN	Prostate intraepithelial neoplasia
ACC1A	Acetyl coenzyme A carboxylase 1
CPT1A	Carnitine palmitoyltransferase 1A
OXPHOS	Oxidative phosphorylation
HK	Hexokinase
PFK	Phosphofructokinase
PK	Pyruvate kinase
LDH	Lactate dehydrogenase
PKM2	Pyruvate kinase M2
LDHA	Lactate dehydrogenase A
VHL	Von Hippel-Lindau Disease Tumor Suppressor
HREs	Hypoxia response elements

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TME	Tumor microenvironment
IL-6	Interleukin-6
TNF-α	Tumor necrosis factor α
IL-1	Interleukin-1
LPS	Lipopolysaccharide
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
NO	Nitric oxide
PGE2	Prostaglandin E2
iNOS	Inducible NO synthase
COX-2	Cyclooxygenase 2
TLR	Toll-like receptors
HIF-1	Hypoxia-inducible factor-1
STAT-3	Signal transducer and activator of transcription 3
cdc25C	Cytokine cycle 25C
ChK2	Checkpoint kinase 2
PTEN	Phosphatase and tensin homolog
hTERC	Human telomerase RNA component
TEP1	Telomerase associated protein 1
DRs	Ddeath receptors
MEF	Mouse fibroblast
SFN-Cys	SFN-cysteine
SFN-NAC	SFN-N-acetylcysteine
HATs	Histone acetyltransferases
HDACs	Histone deacetyltransferases
CpG	Cytosine-phosphate-guanineCpG
LncRNAs	Long non-coding RNAs

Introduction

Prostate cancer (PCa) is a type of malignant tumor that develops within the prostate tissue, Its pathogenesis is very complex and related to many factors [1,2], For example, diet [3,4], genetic or epigenetic [5–7], microbiota [8,9], inflammation [10], obesity [11] and race [12]. As reported in the Global Cancer Statistics 2020, PCa ranks as the second most prevalent solid tumor among men. Each year, millions of men worldwide succumb to PCa, making it the fifth leading cause of cancer-related fatalities [13,14]. Prostate, lung, and colorectal cancers account for almost half (48%) of all male cancer cases in the US in 2023, and prostate cancer alone accounts for 29% of diagnosed cases [15]. The incidence of prostate cancer is mainly in Europe and the United States, and the incidence of prostate cancer in China is increasing year by year [16,17]. Prostate cancer that is localized may be managed through radical surgery or radiation therapy. The five-year survival rate is nearly 100%, while the recurrence rate is approximately 30% to 40% [18–20]. If prostate cancer (PCa) has already spread beyond its original site, the preferred treatment is drug therapy aimed at providing relief [21,22]. The advancement and progression of PCa heavily rely on androgen receptor (AR) signaling, with androgen deprivation therapy (ADT) being the gold standard for treating metastatic PCa. Although there is a favorable initial response from the tumor to ADT, progression typically resumes after approximately 2 to 3 years, leading to the emergence of incurable castration-resistant prostate cancer (CRPC). Nonetheless, the five-year survival rate for patients diagnosed with metastatic PCa and CRPC is only about 30% [18,19].

When the patient's disease develops into CRPC, the treatment mainly includes taxane chemotherapeutic drugs (such as docetaxel, and cabazitaxel); androgen receptor-targeted drugs (ARTA), such as enzalutamide and abiraterone acetate, and the recent poly ADP-ribose polymerase (PARP) inhibitor [23]. CRPC includes nonmetastatic castration-resistant disease (nmCRPC) and metastatic castration-resistant disease (mCRPC) [24]. In the past few years, Rosellini et al. showed that androgen receptor (AR) axis receptor inhibitors have significantly benefited from the results of nmCRPC. The administration of enzalutamide alongside androgen deprivation therapy (ADT) is linked to extended metastasis-free survival (MFS) and a favorable safety profile. The addition of apalutamide to the ongoing ADT significantly improved MFS and symptom progression time in patients with high-risk nmCRPC, showing an increased OS (25% lower risk of death compared to placebo). The addition of darolutamide to ADT ensures prolonged MFS and OS high-risk non-metastatic diseases. In addition, when darolutamide is analyzed alongside the previously mentioned enzalutamide and apalutamide, it appears to be associated with improved safety and a reduced incidence of adverse events [24]. In the early 2000s, mitoxantrone emerged as the initial cytotoxic chemotherapy for advanced diseases resistant to ADT. While overall survival did not show significant differences between men treated with mitoxantrone and those who were not, it enhanced palliative treatment for symptomatic cases of mCRPC [25]. Since 2004, taxane chemotherapy drugs have been widely studied to prolong the OS of mCRPC patients. Although prostate cancer is in a castration state, the AR axis continues to be a significant factor in the advancement of prostate cancer. In patients who have had prior treatment with docetaxel, abiraterone acetate has been shown to enhance OS and progression-free survival (PFS) when compared to treatment with prednisone alone. Recent studies have also validated the possible advantages of PARP inhibitors, like olaparib, in the context of prostate cancer [24,26].

In addition, antibody-drug conjugates of cytotoxic drugs (also known as payloads), are linked to specific antibodies that can recognize antigens expressed on the surface of cancer cells [24,27]. Regarding prostate cancer, scientists are exploring the possibility of applying this treatment to the condition [28–30]. Nevertheless, the existing mCRPC therapy has notably extended the lifespan of patients. Currently, there are several treatments available for metastatic castration-resistant prostate cancer (mCRPC), including PARP inhibitors (PARPi) [31–33], androgen receptor signaling inhibitors (ARSI) [33,34], taxane chemotherapeutic agents [35,36], and radium-223 [37,38]. These treatments have significantly improved the survival lifetime of prostate cancer patients [39–42]. The lasting survival advantages provided by these medications remain constrained, necessitating further investigation into more effective options.

Isothiocyanate represents one of the numerous investigations demonstrating that dietary choices may help mitigate both the onset and advancement of prostate cancer [43–45]. Sulforaphane (SFN, 1-isothiocyanato-4-(methanesulfinyl)butane) is a phytochemical belonging to the isothiocyanate family, and it is present in consumable cruciferous vegetables like broccoli, cauliflower, and cabbage [46–50], It exists in form of glucoraphanin (glucosinolate conjugate) and is produced in the catalytic reaction of thioglycosidase (myrosinase). There is no endogenous activity in mammalian cells and myrosinase enzymes are present in plants or intestinal biota, where it is physically separated through the plant cell wall and thioglucoside and is released after damage to the plant caused by cutting or chewing [51]. Talalay and Zhang were the first to isolate it from broccoli and prove its anticancer properties [52]. Its biological precursor glucoraphanin was subsequently found in large quantities in broccoli buds, and SFN was confirmed to be active in animal carcinogenic models [53]. Posner et al. evaluated the structural activity of more than 100 synthetic analogues and found no more effective phase II detoxification enzyme inducer than SFN. SFN is still one of the most effective natural inducers found so far [54]. Subsequently, studies have found that this molecule has a variety of pathways and metabolisms in mammalian cells, tissues, and humans, and has strong anticancer properties [55]. Preventing cancer can be achieved by hindering the proliferation of cancer cells, obstructing the cell cycle, and promoting apoptosis. SFN provides cancer protection by altering several epigenetic and non-epigenetic mechanisms. SFN can block the activity of histone deacetylase deacetylases are important in the prevention of cancer because they enhance multiple mechanisms such as apoptosis and cell cycle arrest. In addition, SFN also prevents histone phosphorylation by enhancing phosphatases [56]. The anticancer properties of SFN emphasize its potential as a versatile and potent agent against various malignant tumors. Its impact on the proliferation, migration, and drug resistance of cancer cells presents a potential avenue for developing innovative treatment strategies and enhancing patient prognosis. As early as 2000, studies have shown that SFN can reduce the risk of prostate cancer [57].

Studies have shown that SFN prevents prostate cancer mainly through antioxidants [58], inhibition of fatty acid metabolism [59], inhibition of glycolysis [60], inhibition of pro-inflammatory factors [61], inhibition of cell proliferation and induction of apoptosis [62,63], reduction of androgen receptors [64], and influence of epigenetics [49,65].

Prostate Cancer-Preventive Effects of SFN

Antioxidant effect

Oxidative stress plays a crucial role in the onset and development of prostate cancer [66–69]. It typically denotes the disruption between the production of reactive oxygen species and the antioxidant defenses, or the capability to oxidize beyond the existing antioxidant capacity. Reactive oxygen species (ROS) are characterized as unstable and highly reactive molecules, commonly existing as superoxide anion, hypochlorous acid, hydrogen peroxide, singlet oxygen, hypochlorite, hydroxyl radicals, and lipid peroxides, which are involved in cell processes such as growth, differentiation, and death [70]. Under physiological conditions, the human body has a solid antioxidant system, including antioxidant enzymes and some small molecules, the main antioxidant enzymes are phase II detoxifying enzymes: for example, glutathione S-transferase (GST), NAD (P)H quinone oxidoreductase(NQO), epoxide hydrolase, heme oxygenase 1 (HO-1), UDP-glucuronosyltransferases (UGT), superoxide dismutase (SOD), phase II detoxification enzymes are redox-sensitive stress-inducing proteins downstream of the Nrf2-Keap1 axis that reduces various oxidative stress and inflammation-derived cytotoxicity [71,72]. Numerous elements, both inherent to the cells (Nrf2 deficiency; DNA) and from the external environment (chronic; radiation), can result in elevated ROS generation in the prostate. Elevated levels of ROS can cause prostate dysfunction, which subsequently leads to even greater ROS production [73]. An antioxidant defense system, which can be enzymatic or non-enzymatic, helps to counteract and regulate the levels of reactive oxygen species (ROS) in order to sustain physiological homeostasis. Reducing ROS levels below the homeostatic threshold might disrupt both proliferation and the host defense mechanisms. Conversely, an accumulation of ROS in the prostate can disturb its normal functioning, resulting in a decreased antioxidant capacity by interfering with the Nrf2-antioxidant response element axis (ARE), increasing mitochondrial DNA (mtDNA) mutation and aggressive phenotypes, and causing DNA damage [73]. SFN is an antioxidant that, once in the cell from the blood, reacts spontaneously with glutathione and other thiols, enhancing the oxidative state of the cell and leading to a transient increase in reactive oxygen species. This change in oxidation status led to rapid activation of the Nrf2-antioxidant response element defense system (ARE), leading to increased transcription of many genes involved in restoring the redox state of cells and preventing ROS damage [74,75]. In homeostasis, Nrf2 is associated with cytoplasmic protein KEAP1, which is continuously ubiquitous by Cul3 E3 ubiquitin ligase and subsequently degraded by proteases. In the presence of oxidative stress, conformational changes KEAP1 can occur directly with Sulfhydryl KEAP1 or indirectly through changes in the cellular redox state, leading to Nrf2 separation from KEAP1, metastasis to the nucleus, heterogeneity with the small molecule myofascial fibrosarcoma (sMaf) protein, and binding to ARE, leading to a large number of gene transcription and antioxidant responses [76,77].

SFN activates Nrf2, leading to structural changes in KEAP1, disrupting the KEAP1-Nrf2 complex, blocking Nrf2 ubiquitination from being degraded, and promoting Nrf2 nuclear translocation [77], which enhances the expression of phase II detoxification enzymes GST, HO-1, and NQO-1, causing an enhanced antioxidant effect (Fig. 1). Excitingly, the effect of adding SFN to human prostate cells and the increased activity of phase II detoxification enzymes (GST, NQO1) after tube feeding of SFN in F-344 rats [72,78].

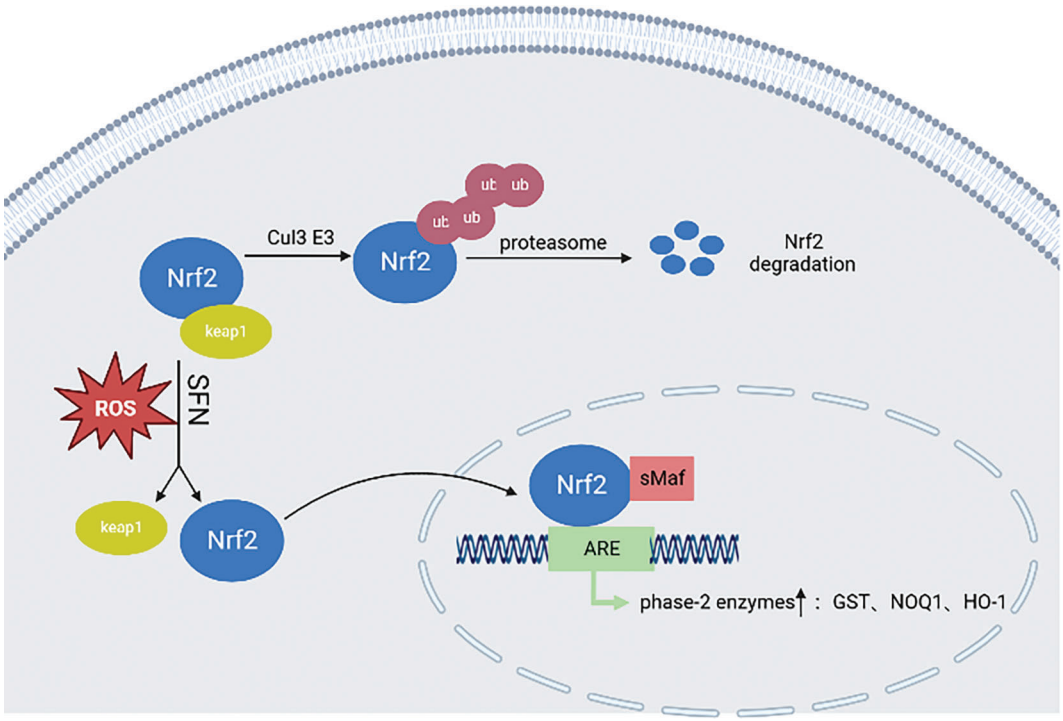

FIGURE 1. In the steady state, Nrf2 is linked to KEAP1, continuously ubiquitinated by Cul3 E3 ubiquitin ligase, and then degraded by proteasome. In the presence of oxidative stress, the conformational change of KEAP1 will be induced, which will lead to the separation of Nrf2 and KEAP1, translocation to the nucleus, and small molecule myofascial fibrosarcoma (sMaf) protein heterodimerization and binding to ARE, leading to the transcription and antioxidant response of a large number of genes. SFN can activate Nrf2, lead to the change of KEAP1 structure, destroy the KEAP1-Nrf2 complex, block the degradation of Nrf2 ubiquitination, and promote Nrf2 nuclear translocation, thereby enhancing the expression of phase II detoxification enzymes GST, HO-1, NQO-1, etc. This illustration was generated utilizing resources accessible on BioRender.com.

Significantly enhanced protein expression of Nrf2 and NOQ1 was similarly observed in transgenic adenocarcinoma mouse prostate (TRAMP)-C1 cell lines after SFN treatment [79].

Inhibition of fatty acid metabolism

It has been shown that *ab initio* synthesis of fatty acids is necessary for prostate cancer growth and that lipid metabolism and genes related to lipid metabolism can play an important role in the progression of prostate cancer through metabolic pathways and anti-apoptotic effects [80–83]. The key enzyme for fatty acid synthesis is fatty acid synthase (FASN), a 250–270 kDa cytoplasmic protein, and fatty acid synthase is involved in the final step in the *ab initio* synthesis of fatty acids (i.e., condensation of acetyl coenzyme-A and malonyl coenzyme-A to produce palmitate), which in turn generates more types of fatty acids, which undergo β-oxidation catalyzed by the key enzyme carnitine palmitoyltransferase 1A (CPT1A). It also plays an important function in energy homeostasis, converting excess carbon into fatty acid stores and supplying energy through β-oxidation when necessary. The mechanisms regulating the expression of fatty acid synthases are complex and not fully understood, and their expression and activity are regulated by growth factors, hormones, and dietary factors, among others [84]. The expression of FASN is low in most human tissues and high in liver and adipose tissue [85]. It has been shown that FASN gene expression is upregulated in approximately one-quarter of human prostate cancer patients [86]. Migita et al. showed that FASN overexpression leads to prostate intraepithelial neoplasia (PIN) progression [87]. However, the regulation of fatty acid synthase mechanisms is unknown, cytotoxicity can be produced on tumor cells through the use of FASN inhibitors [88], and because of this, FSAN is considered a potential new target for the treatment of many cancer cell line (22Rv1), Singh et al. found that SFN could reduce the protein and mRNA levels of acetyl-CoA carboxylase 1 (ACC1A), FASN and CPT1A, and the expression of FASN and ACC1A protein in TRAMP mouse model treated with SFN was also significantly reduced chemoprevention of prostate cancer is associated with the inhibition of fatty acid synthesis and its β-oxidation [59] (Fig. 2).

Inhibition of glycolysis

In normal cells, glucose undergoes initial metabolism to pyruvate within the cytoplasm; under aerobic circumstances, pyruvate is further converted to carbon dioxide through the process of oxidative phosphorylation (OXPHOS). In contrast, when oxygen is absent, pyruvate is transformed into lactate through glycolysis, thereby generating ATP [89]. In cancer cells, the energy supply comes mainly from aerobic glycolysis and tumor cells convert the major ATP pathway OXPHOS to aerobic glycolysis also known as the Warburg effect [89]. The conversion from glucose to lactate requires the involvement of several enzymes such as hexokinase (HK), phosphofructokinase (PFK), pyruvate kinase (PK), and lactate dehydrogenase (LDH) [90]. In Singh et al.'s study, it was found that SFN significantly

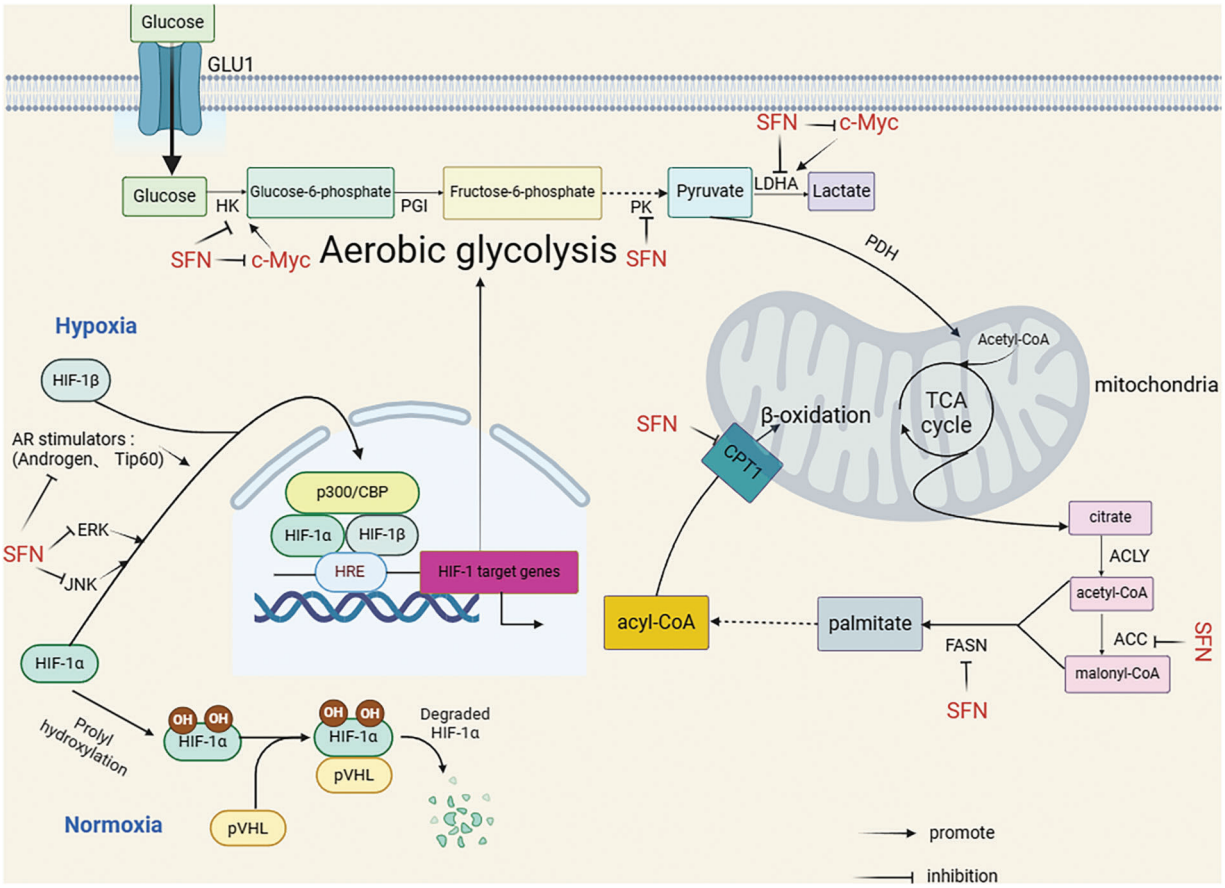

FIGURE 2. SFN indirectly inhibited HK and LDHA or directly inhibited HK and LDHA by inhibiting c-Myc, and also directly inhibited PK. SFN inhibits hypoxia-induced HIF-1α expression by inhibiting JNK, ERK pathways, and AR stimulators (Androgen, Tip60). In addition, SFN can inhibit ACC, FASN, and CPT1 to inhibit β-oxidation. This illustration was generated utilizing resources accessible on BioRender.com.

downregulated the expression of hexokinase 2 (HK2), pyruvate kinase M2 (PKM2) and/or lactate dehydrogenase A (LDHA) in mouse TRAMP model and prostate tumor lesions in Hi-Myc mice *in-vitro* and *in-vivo*, and significantly inhibited glycolysis in the prostate of Hi-Myc mice, reversing Warburg phenomenon in prostate cancer [60]. Warburg effect is considered to be a central component of tumor metabolic recoding and is mainly associated with overexpression of the transcription factor hypoxia-inducible factor HIF-1. HIF-1 is mainly composed of two subunits, HIF-1α and HIF-1β. Under normoxic conditions, HIF-1α is hydroxylated by proline and recognized with the Von Hippel-Lindau Disease Tumor Suppressor (pVHL) complex, which exhibits ubiquitin ligase activity that ubiquitinates HIF-1α, causing its degradation through the proteasomal pathway. Under hypoxic conditions, proline hydroxylation is inhibited, resulting in the accumulation of HIF-α translocated into the nucleus and HIF-1β forming a dimer with the hypoxia response elements (HREs) binding and recruitment of transcriptional co-activators (e.g., the histone acetyltransferases CBP/P300) thus obtaining complete transcriptional activity [91]. SFN can affect directly and/or indirectly affect glycolysis in prostate cancer (Fig. 2). Findings from a study conducted on the DU145 cell line related to human prostate cancer indicated that SFN may reduce the expression of HIF-1α induced by hypoxia by inhibiting the pathways of Jun N-terminal kinase (JNK) and extracellular regulated protein kinase (ERK) [92]. In addition, Carrasco et al. showed that SFN blocked androgen receptor agonist (androgen and Tip60)-induced glycolysis in human prostate cancer LNCaP cells, and that hexokinase and acetone kinase activities increased to reduce HIF-1α stability [93]. In addition, Myc genes can upregulate genes of the glycolytic pathway (HK2, LDHA) to enhance glucose metabolism [94], and one study reported SFN-mediated inhibition of c-Myc protein levels in human prostate cancer cell lines (LNCaP, PC-3, C4-2) and prostate adenocarcinoma of a Hi-Myc transgenic mouse (Myc-CaP cell line) [95].

Inhibition of pro-inflammatory factors

Inflammation has a role in cancer in regulating the tumor microenvironment (TME) and promoting tumor proliferation and migration [96–99]. For example, the cytokine interleukin-6 (IL-6) can promote prostate cancer cell proliferation and inhibit apoptosis through a variety of cellular signaling pathways [100]. Nuclear transcription factor-κB (NF-κB) is an inducible protein transcription factor, mainly formed as a heterodimer by p50 and p65 of the Rel protein family. NF-κB can be activated by a variety of stimuli, such as tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), lipopolysaccharide (LPS), ultraviolet (UV) and oxidative stress, etc. Activation of NF-κB by extracellular stimuli leads to phosphorylation, ubiquitination,

and protein degradation of IκB kinase, which exposes the nuclear localization signal on NF-κB, resulting in nuclear translocation of the NF-κB complex and phosphorylation of p65. NF-κB regulates different inflammatory responses and immune responses and can also promote tumor progression by controlling tumor angiogenesis through upregulation of vascular endothelial growth factor (VEGF) and receptors [101,102], and Huang et al. have also shown that transfection of the highly metastatic prostate cancer cell line PC-3M with mutated IκBα (blocking NF-κB activity) injected into the prostate of nude mice revealed significant inhibition of major pro-angiogenic molecules such as VEGF, IL-8, and Matrix metalloproteinase 9 (MMP-9), as well as downregulation of MMP-9 mRNA and collagenase activity, and in general, blocking NF-κB signaling inhibited tumor invasion, angiogenesis, and metastasis [103]. In conclusion, NF-κB activation is common in cancer and is thought to be a key link between inflammation and cancer, with inflammatory factors in the tumor microenvironment again being the most common factors that enable NF-κB activation. Interestingly, SFN is known for its anti-inflammatory effects. Following stress, bacterial, viral, and pro-inflammatory cytokine-related cellular stimulation, IκB kinase is phosphorylated and then the kinase is degraded, which allows free translocation of NF-κB dimers into the nucleus and induces transcription of pro-inflammatory cytokines (IL-6, IL-10, TNF-α) [104]. It was shown that SFN could reduce inflammation by inhibiting the binding of NF-κB to DNA [105]. In addition, it has also been shown that SFN inhibits IκB kinase complex (IKK) phosphorylation in human prostate cancer PC-3 cells, specifically inhibiting IKKβ, leading to IKKβ-mediated inhibition of IκBα phosphorylation. This in turn leads to reduced ubiquitination and protein degradation of IκBα, with subsequent retention of NF-κB in the cytoplasm and reduced nuclear translocation of p65 and consequent attenuation of NF-κB-regulated VEGF, cyclin D1, and B-cell lymphoma/leukemia-2 protein X-linked (Bcl-XL) gene expression [106]. The stimulation of tumor cell proliferation, apoptosis, or mutations in cancer cells can be prompted by the activation of NF-κB and the subsequent cascade of inflammatory cytokines or chemokines [107]. Consequently, blocking the activation of NF-κB plays a crucial role in mitigating detrimental effects. SFN notably reduces the levels of several inflammatory mediators, including IL-6, IL-1β, TNF-α, nitric oxide (NO), and prostaglandin E2 (PGE2), along with inflammatory enzymes such as inducible NO synthase (iNOS) and cyclooxygenase 2 (COX-2), through the suppression of the NF-κB signaling pathway [61,105].

In addition, Toll-like receptors (TLR) are key pattern recognition receptors (PRR) that induce innate or adaptive immune responses, whereas TLR-4 is a key signaling receptor that triggers inflammation. LPS recognizes CD14/TLR-4/MD-2 heterotrimers and activates myeloid differentiation factor 88 (MyD88)-dependent pathways and TRIF (MyD88-independent pathway) to trigger inflammation.TLR4 activation also increases the expression of VEGF and transforming growth factor-β1 (TGF-β1) in prostate cancer cells, thus promoting tumor development [108]. It has been shown that SFN inhibits the TLR4/MyD88 pathway and reduces TNF-α and IL-6 levels [109]. In macrophages, HIF-1 can upregulate TLR4 expression, while SFN can inhibit hypoxia and $CoCl_2$-induced TLR4 expression upregulation by inhibiting phosphatidylinositol 3 kinase/protein kinase B (PI3K/AKT) pathway and HIF-1α activation [110]. It has also been shown that the anti-inflammatory mechanism of action of SFN is closely related to the inhibition of TLR4 response by directly and indirectly targeting the TLR4-md2 receptor complex [111,112]. In addition, signal transducer and activator of transcription 3 (STAT-3) is closely associated with inflammation, and tumor promoters, lipopolysaccharide, and cigarette smoke can activate the STAT-3 signaling pathway, and STAT-3 binds competitively with NF-κB at overlapping DNA binding sites [113], and studies have shown that SFN reduces STAT-3 in the prostate cancer cell lines DU145 and LNCap expression [114]. In conclusion, SFN can inhibit pro-inflammatory factors through various targets to disrupt the tumor microenvironment in prostate cancer (Fig. 3).

Inhibition of cell proliferation and induction of apoptosis in cancer cells

Numerous experimental studies, both *in vivo* and *in vitro*, have demonstrated that SFN and its metabolites can inhibit cell proliferation and induce apoptosis in prostate cancer (Fig. 4). Induction of G2/M phase cell cycle arrest in SFN-treated human prostate cancer cell line (PC-3) involves checkpoint kinase 2 (ChK2) checkpoint activation leading to phosphorylation of cell division cycle 25C (cdc25C), resulting in its segregation in the cytoplasm [115]. SFN was also found to upregulate CD44 variants v4, v5, and v7 to slow down the proliferative activity of tumor cells in human prostate cancer cell lines (DU-145 and PC-3 cell lines) *in-vitro*, and also upregulate the tumor suppressor p19 in blocking cell cycle and apoptosis [116]. Administration of SFN in a PTEN gene-deficient mouse model reversed the effects of early prostate cancer development due to PTEN deficiency and served to inhibit cell proliferation [117].

Phosphorylated expression of AKT protein (cell cycle protein D1) was reduced after feeding high doses of broccoli sprouts in a TRAMP mouse model, thereby inhibiting cell proliferation [118]. SFN was also found to cause G2/M phase cell cycle arrest in wild-type LNCap cell lines, but not in its variant Rh-0 cells (mitochondrial DNA deletion), thus SFN causes G2/M phase cell cycle arrest in human prostate cancer cells due to mitochondria-derived ROS-mediated [119]. Moreover, telomerase consists of a complex of ribonucleoproteins in eukaryotes that includes six distinct subunits: heat shock protein 90, the human telomerase RNA component (hTERC), dyskerin, the telomerase-associated protein 1 (TEP1), p23, and the human telomerase reverse transcriptase (hTERT). The activity of the hTERT gene is absent in normal human cells; however, it is frequently expressed in different forms of cancers (such as:prostate cancer), signifying a necessary role in the unlimited proliferation of tumor cells [120]. It has been shown that SFN can inhibit hTERT expression in prostate cancer cells in two prostate cancer cell lines, LNCap and PC-3 [121].The apoptosis triggered by SFN is primarily facilitated through intrinsic mitochondrial pathways as well as extrinsic death receptors (DRs) mechanisms [122]. Intrinsic mitochondrial-

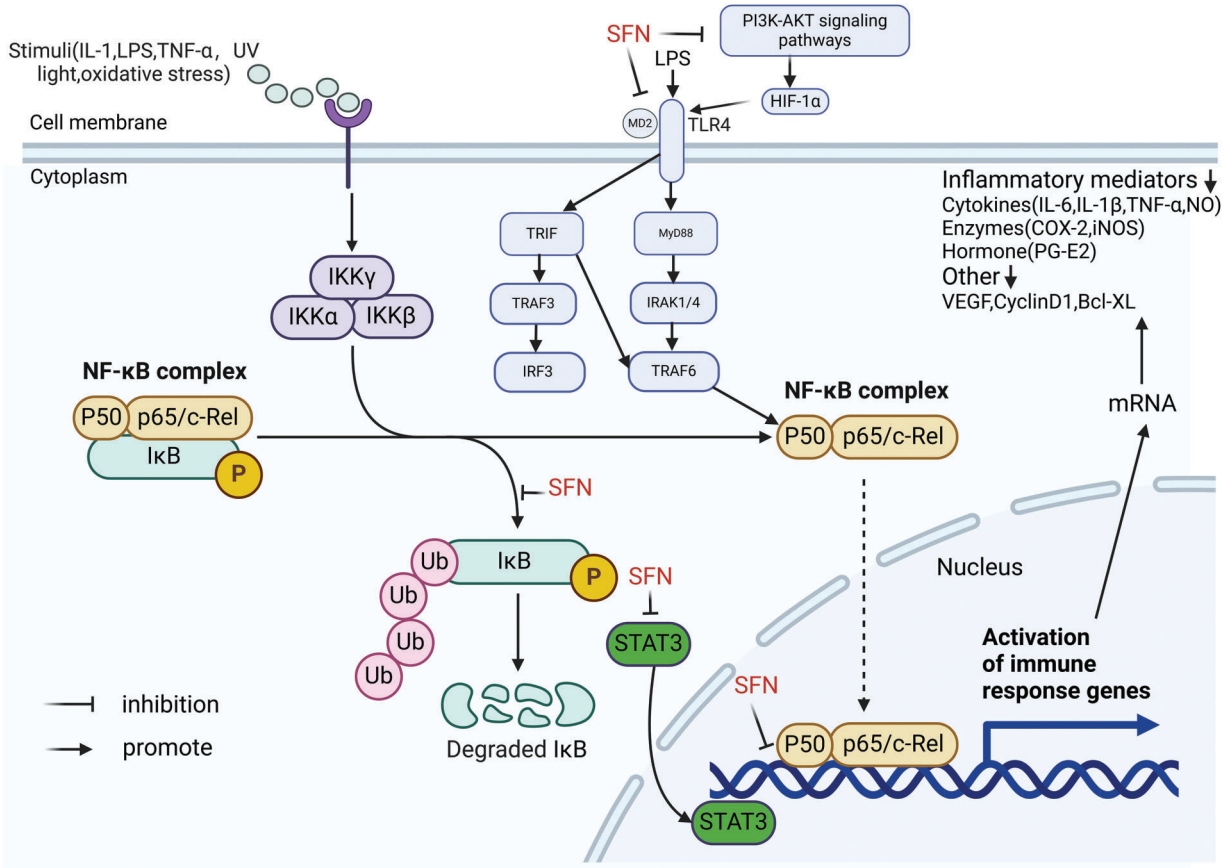

FIGURE 3. SFN can inhibit the phosphorylation of IκB kinase and the expression of STAT3; SFN inhibited hypoxia and $CoCl_2$-induced upregulation of TLR4 expression by inhibiting PI3K/AKT pathway and HIF-1α activation; SFN inhibits TLR4-md2 receptor complex by direct and indirect targeting. Inhibiting the activation of the NF-κB signaling pathway by the above three methods significantly attenuated various inflammatory mediators, such as IL-6, IL-1β, TNF-α, nitric oxide (NO), and prostaglandin E2 (PGE2), as well as inflammatory enzymes: inducible NO synthase (iNOS) and cyclooxygenase 2 (COX-2). This illustration was generated utilizing resources accessible on BioRender.com.

mediated apoptosis begs the question of mitochondrial autophagy, a catabolic process in which the autophagic system targets damaged mitochondria and delivers them to lysosomes for degradation. Mitochondrial autophagy helps control the quality and quantity of mitochondria [123]. Mitochondrial autophagy is one of the organelle-specific autophagic pathways that are used to maintain cell structure and function [124]. Mitochondria are believed to be the primary location for the production of ROS, primarily via the electron transport chain and various localized proteins, and overproduction of ROS occurs when mitochondrial dysfunction occurs, and overproduction of ROS further damages mitochondria, creating a vicious cycle [125]. Excessive intracellular ROS production and imbalance of antioxidant capacity cause oxidative stress, which not only leads to mitochondrial dysfunction, but excessive accumulation of damaged mitochondria may lead to apoptosis. In turn, mitochondrial autophagy and tumor cell suppression are closely related [126].

Extrinsic death receptors mainly include Tumor necrosis factor-related apoptosis-inducing ligand 1 (TNFR1), Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand 1 (TRAIL1) receptors (DR-4, DR-5), and Fas (Apo-1; CD95) mediated [122]. Research indicates that the cell death induced by SFN in human prostate cancer cells is attributed to the generation of ROS. This ROS production triggered by SFN is associated with a disruption of the mitochondrial membrane potential, which in turn facilitates the release of cytochrome C from the mitochondria into the cytoplasm. This process culminates in the activation of caspase 9, ultimately resulting in cell death [127]. It has also been reported that in human prostate cancer cell line PC-3, SFN-induced apoptosis is associated with upregulation of B-cell lymphoma-2 Associated X Protein (Bax), downregulation of B-cell lymphoma-2 Bcl-2) and activation of caspase-3, caspase-8 and caspase-9. SFN causes upregulation of the pro-apoptotic protein Bax and downregulation of the anti-apoptotic protein Bcl-2 in the Bcl-2 protein family will lead to an increase in the Bax to Bcl-2 ratio, making activation of the mitochondrial pathway for cytochrome c release, which activates caspase-9; and then caspase-8 and caspase-9 activate caspase 3 to shear the DNA repair enzyme PARP, leading to apoptosis [128]. In addition, research involving mouse embryonic fibroblasts (MEFs) revealed that SFN plays a role in triggering caspase activation, which in turn facilitates apoptosis by enhancing the expression of Apoptotic protease activating factor (Apaf) and decreasing levels of X-linked inhibitor of apoptosis protein (XIAP) [129].

In addition, in BPH1, PC3 and LNCap prostate cancer cells, SFN induced apoptosis by inhibiting HDAC activity,

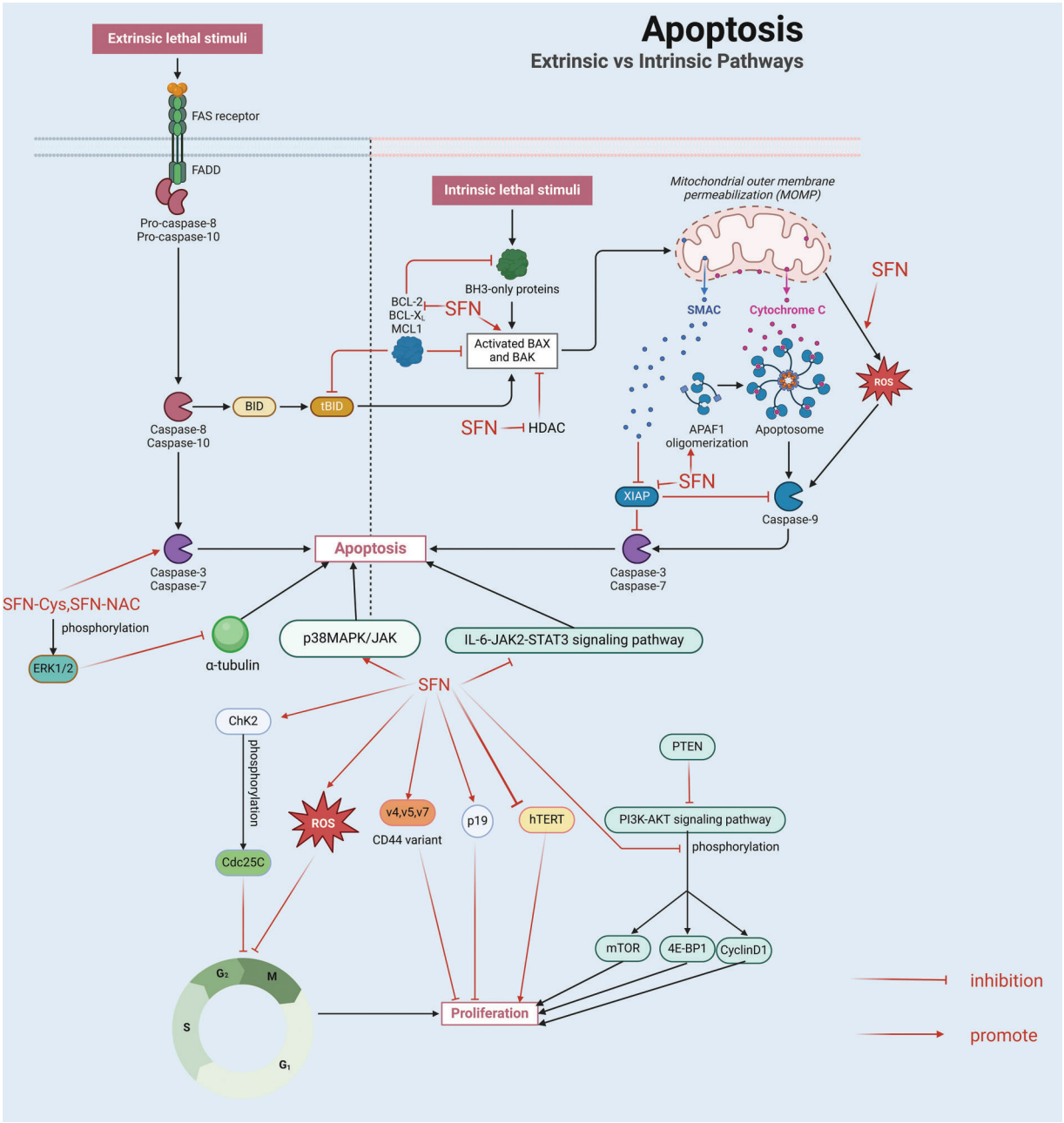

FIGURE 4. 1. Inhibition of cell proliferation: (1) SFN involves checkpoint kinase 2 (ChK2) checkpoint activation leading to phosphorylation of cell division cycle 25C (cdc25C), (2) SFN up-regulates CD44 variants v4, v5 and v7, (3) SFN inhibits the phosphorylation of AKT and its downstream kinases (mTOR, 4E-BP1) and target protein (cyclin D1), (4) SFN induces ROS production, (5) SFN inhibits hTERT expression. 2. Promoting apoptosis: (1) The production of ROS induced by SFN is associated with the disruption of mitochondrial membrane potential and the subsequent release of cytochrome C from the mitochondria into the cytoplasm, which results in the activation of caspase 9 and ultimately causes cell death; (2) SFN enhances the expression of the pro-apoptotic protein Bax while diminishing the levels of the anti-apoptotic protein Bcl-2 within the Bcl-2 protein family. This change results in a higher Bax to Bcl-2 ratio, which in turn triggers the activation of caspase-9. Additionally, SFN stimulates the activity of caspase-8 and caspase-9, leading to the activation of caspase-3, which subsequently cleaves the DNA repair enzyme PARP; (3) SFN can mediate the activation of caspase by inducing Apaf and down-regulating XIAP; (4) SFN promotes apoptosis by inhibiting the IL-6/JAK2/STAT3 signaling pathway; SFN metabolites SFN-cysteine (SFN-Cys) and SFN-N-acetylcysteine (SFN-NAC) activate caspase 3 and induce phosphorylation of protein kinase 1/2 (ERK1/2), which down-regulates α-tubulin; (5) SFN can activate p38 MAPK and JNK to induce apoptosis. This illustration was generated utilizing resources accessible on BioRender.com.

inducing cell cycle arrest through upregulation of mRNA and protein levels of p21 and Bax, and activating caspase [130]. Hahm et al. in DU145 and LNCap human prostate cancer cell lines found that SFN induced apoptosis by inhibiting IL-6/JAK2/STAT3 signaling pathway to promote apoptosis [114]. It has also been shown in DU-145 and PC-3 cells that the SFN metabolites SFN-cysteine (SFN-Cys) and SFN-N-acetylcysteine (SFN-NAC) cause apoptosis by activation of caspase 3 and induction of protein kinase 1/2 (ERK1/2) phosphorylation, resulting in downregulation of

α-microtubulin [131]. SFN was found to activate p38 Mitogen-activated protein kinase (p38MAPK), JNK leading to apoptosis in a PC-3 prostate cancer cell line [132]. In studies on androgen-independent prostate cancer cell lines (PC-3, DU145) and androgen-dependent prostate cancer cell lines (VcaP), SFN was found to have cytotoxic and pro-apoptotic effects on prostate cancer cell lines [62].

Reducing androgen receptors

Prostate cancer initially develops in a manner dependent on androgens, driven by the signaling pathway of the androgen receptor (AR), which is critical not only for normal prostate development and physiological function, but also for the proliferation, survival, invasion, and clonogenic capacity of PCa cells [133–135]. SFN has been shown to reduce AR protein in LNCap and C4-2 cell lines by inhibiting transcription of androgen receptor mRNA, leading to Ser210/213 phosphorylation and reduced total androgen receptor [64] and increasing proteasomal degradation of androgen receptor protein [136]. SFN was shown in LNCap cells and Vcap cells to increase HSP90 acetylation and lead to AR and HSP90 dissociation by inhibiting HDAC6 activity in cells, decreasing AR protein levels and reducing AR target gene expression [136]. In 22Rv1 cell line (a CRPC cell line expressing AR-FL and multiple AR splice variants), it was demonstrated that SFN can reduce AR-FL and AR-V7 levels, and this reduction in AR protein levels may result in diminished cell proliferation, migration and cloning capacity [137]. SFN was found to reduce AR protein levels through AR protein degradation and inhibition of AR gene expression in androgen-dependent cell lines (LNCap) and androgen-independent cell lines (C4-2B) [138]. Another interesting study in a TRAMP mouse model found that SFN treatment with Nrf2 levels similar to ADT treatment reduced ROS levels in prostate cancer cells and caused prostate cancer cells to show similar sensitivity to radiotherapy as with ADT treatment [139].

Influence on epigenetic inheritance

In epigenetics, histone modifications, DNA methylation, RNA regulation and nucleosome remodeling are considered to be important influential mechanisms that are dysregulated in cancer [140–142], as well as in prostate cancer [143–145]. Modifications of histones include acetylation, methylation, phosphorylation, and ubiquitination, among which histone acetylation plays the most prominent role. Histone acetyltransferases (HATs) and histone deacetyltransferases (HDACs) are in balance in normal cells, and when histone acetyltransferase expression is decreased and/or histone deacetyltransferase expression is increased is closely related to the process of tumorigenesis and progression, while SFN inhibits histone deacetylases (HDACs), histone deacetylase (HDAC) overexpression will lead to histone deacetylation, and deacetylation causes DNA to wrap around histones too tightly, thus inhibiting gene expression, which may lead to cancer development if the affected genes are oncogenes [146]. Zhang et al. treating TRAMP-C1 cell lines with 1.0, 2.5 μM SFN respectively found that SFN decreased HDAC1, HDAC4, HDAC5, HDAC7 proteins were reduced in a dose-dependent manner [79]. SFN inhibited the epigenetic regulator HDAC3 in PC-3 cells and decreased HDAC3 expression in TRAMP mice [147]. In prostate cancer cells PC3 and LnCap, as well as in BPH1, SFN similarly suppressed HDAC activity, which resulted in heightened global histone acetylation. This enhancement promoted the interaction between acetylated histone H4 and the P21 and Bax promoters, leading to an upregulation of both mRNA and protein levels of p21 and Bax [130].

DNA methylation occurs mainly at cytosine residues of cytosine-phosphate-guanine (CpG) dinucleotides and is regulated by DNA methylation transferase, and DNA hypermethylation leads to gene silencing. In prostate cancer, overall hypomethylation of tumor-associated genes and site-specific hypermethylation influence tumorigenesis and progression [148], with hypomethylation associated with genomic instability, transposons, and proto-oncogene activation, and hypermethylation can silence genes involved in cancer protection, with targets including those involved in DNA repair, detoxification, and apoptosis [148]. In previous studies treating TRAMP-C1 cell lines with 1.0 and 2.5 μM SFN respectively found that SFN reduced the protein levels of DNMT1 and DNMT3a in DNA methylation transferase (DNMT) in a dose-dependent manner [79]. It was also shown that SFN treatment of LNCap cell lines inhibited DNMT1 and DNMT3b expression, and SFN treatment of benign prostatic hyperplasia cells (BPH-1) and PC-3 cells significantly inhibited DNMT1 and DNMT3a mRNA expression, while protein expression only showed a downward trend. The expression of cell cycle protein D2 mRNA increased after SFN treatment in LNCap cell lines, which served to inhibit prostate cancer growth [149]. Furthermore, SFN in both LNCap and PC-3 prostate cancer cell lines by regulating and reversing aberrant promoter DNA methylation in chemokine-related gene targets in cancer cells [150].

Long non-coding RNAs (lncRNAs) are closely associated with prostate cancer development and progression [151,152]. Treatment with SFN in a study of LNCap and PC-3 cell lines was found to inhibit the expression of the long non-coding RNA (lncRNA) LINC01116 [65].

Other

In addition to the above pathways through which SFN inhibits prostate cancer, it has been found that the SFN metabolite SFN-Cys causes sustained phosphorylation of ERK1/2 and triggers downregulation of galectin-1 (an invasion-associated protein) in DU145 and PC-3 cells, which in turn inhibits invasion [153]. SFN inhibits invasion by regulating E-calcine mucin (an invasion inhibitor), CD44v6 (invasion promoter) and MMP-2 (invasion promoter) to inhibit invasion [154]. In the advancement of lung metastasis, by diminishing cell proliferation and boosting the lytic activity of NK cells [155].

Singh et al. found that SFN treatment of TRAMP mice led to increased IL-12 production by dendritic cells. This effect leads to increased cytotoxicity of NK cells to prostate cancer cell lines, and improves the activation efficiency of dendritic cells with cytotoxic function of NK cells after co-culture. Aside from the effects observed *in-vitro* regarding NK cells and dendritic cells due to SFN administration,

researchers noted a rise in T cell infiltration in the prostate tumors of TRAMP mice treated with SFN when contrasted with control mice. This research demonstrates that SFN has the potential to boost the immune response in prostate tumors by prompting dendritic cells to secrete IL-12, which leads to heightened NK cell cytotoxicity and, consequently, an increase in T cell presence within prostate tumors, ultimately contributing to a decrease in tumor burden and metastasis [155]. As we described earlier that the c-Myc gene is associated with cancer stem cells in addition to glycolysis [156], SFN also inhibits c-Myc protein levels to impair prostate cancer stem cell (pCSC) capacity in LNCaP, PC-3 and Myc-CaP cells [95]. It has also been observed in PC-3 cell lines that SFN inhibits protein synthesis and is accompanied by a reduction in mTOR substrate phosphorylation [157].

TABLE 1

Mechanism of prostate cancer preventive effect of SFN

	Cell lines/animal models	Mechanism/outcome	Reference
Antioxidant	LNCap, MDAPCa2A, MDAPCa2B, PC-3, TSU-Pr1	GST, NOQ1↑	[72]
	F-344 rat	GST, NOQ1↑	[78]
	TRAMP-C1, C2	Nrf2, NOQ1↑	[79]
Inhibition of fatty acid metabolism	LACap, 22Rv1	ACCA1↓FASN↓	[59]
	TRAMP rat	ACCA1↓FASN↓CPT1A↓	[59]
Inhibition of glycolysis	DU145	JNK↓ERK↓HIF-1α↓	[92]
	LNCaP	AR↓Tip60↓HK↓PK↓HIF-1α↓	[93]
	LNCaP/PC-3/Myc-CaP	c-Myc↓	[95]
Inhibition of inflammatory factors	RAW264.7	NO↓PG-E2↓TNFα↓NF-κB binding to DNA↓	[105]
	PC-3	IKK Phosphorylation↓p65 Nuclear translocation↓	[106]
	MDM	TNF↓IL-6↓	[109]
	RAW264.7	PI3K/AKT signaling pathway↓	[110]
	RAW264.7, 293T	TLR4-MD2 Complex↓	[111]
	Ba/F3	TLR4-MD2 Complex↓	[112]
Inhibition of cell proliferation	PC-3	ChK2↑cdc25C Phosphorylation↑	[115]
	PC-3, DU145	CD44v4↑CD44v5↑CD44v7↑p19↑	[116]
	TRAMP rat	mTOR↓4E-BP1↓CyclinD1↓	[118]
	LNCaP, PC-3	hTERT↓	[121]
Promotes apoptosis	PC-3, DU-145	ROS↑Fas↑Caspase 8↑bid Cleavage↑	[127]
	PC-3	Bax↑Bcl-2↓Caspase 3↑Caspase 8↑Caspase 9↑PARP↓	[128]
	MEF	Apaf↑XIAP↓	[129]
	BPH-1, PC-3, LNCap	HDAC↓p21↑Bax↑	[130]
	DU-145, LNCap	IL-6/JAK2/STAT3 signaling pathway↓	[114]
	DU-145, PC-3	Caspase 3↑ERK1/2 Phosphorylation↑α-tubulin↓	[131]
	PC-3	p38MAPK↑JNK↑	[132]
	PC-3, DU-145, VaP	G2/M Cell cycle arrest↑	[62]
Reduces androgen receptors	LNCaP, C4-2	AR mRNA Transcription↓	[64]
	LNCaP, VCap	HDAC6↓AR Protein degradation↑	[136]
	22Rv1	AR-FL↓AR-V7↓	[137]
	LNCaP, C4-2B	AR Protein degradation↑/ARGene expression↓	[138]
Influence epigenetic	TRAMP-C1	HDAC1↓HDAC4↓HDAC5↓HDAC7↓DNMT1↓DNMT3a↓	[79]
	PC-3, TRAMP rat	HDAC3↓	[147]
	LNCaP	DNMT1↓DNMT3b↓	[149]
	PrEC, LNCap	DNMT1↓DNMT3b↓	[150]
	PC-3	DNMT1↓DNMT3a↓DNMT3b↓	[150]
	LNCap, PC-3	lncRNA(LIN01116)↓	[65]

Table 1 (continued).

	Cell lines/animal models	Mechanism/outcome	Reference
Other	DU-145, PC-3	ERK1/2 Phosphorylation↑galectin-1↓	[153]
	DU-145	E-cadherin↑, CD44v6↓, MMP-2↓	[154]
	TRAMP rat	NK Cell lysis↑, Pulmonary metastasis↓	[155]
	LNCap, PC-3, C4-2, Myc-Cap	c-Myc↓Stem cell capacity↓	[95]
	PC-3	Protein synthesis↓	[157]

Discussion

The value of SFN in the prevention of prostate cancer is positive, but its dose, bioavailability and safety still need further study. A study showed that the average concentration of glucoraphanin in broccoli seeds was 0.38 μmol/g. In clinical trials, the dose of glucoraphanin supplementation was 25–800 μmol broccoli [158]. However, it is not realistic to eat such a large amount of broccoli every day. Other ways to supplement SFN can be considered, such as using dried broccoli buds and seed extracts to make capsules or beverage preparations.

Secondly, in terms of bioavailability, the rapid and unstable metabolism of SFN in the body requires cryopreservation, which poses a challenge for research use in animals and humans [159]. Its precursor glucoraphanin is relatively inert and water-soluble, which is converted into sulforaphane by intestinal bacteria and myrosinase of the plant itself. The results showed that the conversion rate of SFN was only 10% when broccoli sprout extract was given. When myrosinase and glucoraphanin were administered simultaneously, the bioavailability was up to 35%–40% [160]. Unfortunately, glucoraphanin seems to be absorbed and excreted faster in the human body than SFN, and its inter-individual variability is smaller. This means that the SFN supplement study may be easier to accurately assess the dose [158].

However, as a disease prevention substance, its safety is also a problem that we must consider. In another clinical study, BSE containing 200 μmol SFN was supplemented every day, and no adverse events above grade 3 were found in the subjects [49]. At present, the exact effective and toxic doses of SFN remain undetermined. Whether there will be safety problems when the daily supplemental dose is greater than the above dose needs more tests to explore.

Viewed through an economic lens, SFN, being a natural food item, is both safer and more affordable compared to other cancer-fighting medications. Future research on SFN certainly merits further investigation.

Conclusion and Perspectives

As the second largest solid tumor in men, the treatment cost and time of PCa have become a huge burden for patients and a major burden on the global economy. At present, the treatment of PCa is progressing very rapidly, but there are still many deficiencies, especially in the prognosis of patients with mPCa and CRPC, which is still a major problem in treatment. Therefore, there is an urgent need for a safe, environmentally friendly, and effective natural compound to treat PCa on multiple potential targets. In addition, as a natural compound, the prevention of PCa is particularly critical. More and more studies have shown that SFN can play a huge advantage in the prevention and treatment of Pca. We summarized the research mechanism of prostate cancer in SFN, as shown in Table 1.

SFN can enhance the expression of phase II detoxification enzymes GST, HO-1, NQO-1, etc., thus playing an antioxidant role. Lipid metabolism and its related genes can play an important role in the progression of PCa through metabolic pathways and anti-apoptotic effects. However, SFN can inhibit the metabolism of fatty acids, which is critical for the inhibition of PCa. More excitingly, SFN can significantly down-regulate a variety of key enzymes in aerobic glycolysis hypoxia-induced HIF-1α expression. SFN significantly attenuated various inflammatory mediators signaling pathways, thereby destroying the tumor microenvironment. SFN can inhibit cell proliferation by affecting the phosphorylation of cdc25C, and lead to apoptosis of tumor cells through PI3K-AKT-mTOR signaling pathway, IL-6/JAK2/STAT3 signaling pathway, p38MAPK and JNK pathways.

In cell and animal experiments, SFN has a significant effect on the prevention of PCa. In recent years, more and more clinical trials have explored the relationship between SFN and PCa, and many studies have confirmed its preventive mechanism. However, unfortunately, the current research on the key factors such as effective chemopreventive dose, bioavailability, toxic dose, and response of SFN in the human body is still insufficient. Whether as a natural substance for prevention or treatment, these factors are particularly important. Therefore, we look forward to more clinical trials to clarify these issues in order to achieve greater therapeutic effect.

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Availability of Data and Materials: The datasets generated during and/or analysed during the current study are available in the PubMed repository.

Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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