

# Sulforaphane in broccoli: The green chemoprevention!! Role in cancer prevention and therapy

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## Abstract

Isothiocyanates present in cruciferous vegetables are known to exhibit chemoprevention by various mechanisms. Presently, there is growing evidence that a phytochemical compound known as sulforaphane in these green leafy vegetables is found to be effective in preventing and treating various cancers such as prostate cancer, breast cancer, colon cancer, skin, urinary bladder and oral cancers. This component is naturally present in the broccoli sprouts, kale, cabbage, cauliflower and garden cress and is available as a commercial supplementary pill called Broccoli extract. Availability of many bioactive substances such as vitamins, polyphenols, sulfides, glucosinolates and antioxidants makes broccoli consumption important in daily diet regularly. Researchers have named it as “Green chemoprevention.” It is easily affordable and more cost-effective than the traditional chemopreventive drugs. Results from the epidemiological and experimental studies have emphasized the role of sulforaphane as a complementary or alternative chemopreventive agent.

**Keywords:** Adjuvant therapy, anticarcinogenic, antioxidant, antitumor, apoptosis, benefits, broccoli, cell cycle, chemoprevention, effects, glucosinolates, isothiocyanates, nutraceuticals myrosinase, sulforaphane

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## INTRODUCTION

The value of cruciferous vegetables in cancer prevention is being evaluated widely in the recent years. Fahey *et al.* in 1997 were the first to introduce the anticarcinogenic property of Broccoli sprouts (BSp).<sup>[1]</sup> Ever since, numerous studies have shown that young broccoli and its sprouts provide glucosinolates which have a preventive role in different primary cancers as well as second tumors which are usually fatal.<sup>[2]</sup>

Broccoli contains many active biochemical substances such as carotenoids, Vitamin C and glucosinolates.

One such compound is sulforaphane (SFN) (1-isothiocyanato-4-[methylsulfinyl] butane), which is derived from a precursor compound known as glucoraphanin (GPN).<sup>[3]</sup> Conversion of GPN to SFN occurs while cutting or chewing broccoli, which exposes the GPN to the action of the endogenous myrosinase enzyme. GPN is stable than SFN. GPN is several times more in sprouts compared to the mature whole heads. In order to exert physiologic activity, glucosinolates must be converted to their bioactive form, known as isothiocyanates, by the heat-labile enzyme myrosinase.<sup>[4]</sup> However, this enzyme is destroyed on cooking or even steaming or blanching for

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more than a minute. It is further believed that boiling the broccoli as well as thawing it below  $-85^{\circ}\text{C}$  will spoil its anticancer properties.<sup>[5]</sup>

SFN is one of the powerful anticarcinogenic substances which work by increasing the levels of enzymes in the liver, which counteract the carcinogenic effects of chemicals in the food and environment. SFN is linked to a sugar molecule through a sulfur band which needs to be broken to release it. Then, a sulfur-grabbing protein will remove the exposed sulfur on SFN and inactivate it. The myrosinase enzyme in the broccoli breaks this bond. When broccoli is cut or chopped, the myrosinase enzyme hydrolyzes SFN to form isothiocyanates.<sup>[6]</sup> SFN production may reduce due to inactivation of myrosinase enzyme. Isothiocyanate formation not only depends on myrosinase but also on epithiospecifier protein which helps in the conversion of hydrolysis products to nitriles at the expense of isothiocyanates. This protein is temperature dependent and is known to get destroyed when broccoli is heated at  $60^{\circ}\text{C}$ – $70^{\circ}\text{C}$  for 5–10 min. In such a condition, the formation of SFN increases by 3–7 times.<sup>[7]</sup>

Raw or freshly harvested broccoli should be used whenever possible. A delay of 10 days might result in loss of GPN by nearly 80%.<sup>[8]</sup> Glucosinolates leak out in water while boiling as they are water soluble. Hence, mild steaming and microwaving may retain maximum SFN rather than boiling.<sup>[6]</sup>

Unlike raw sprouts, many commercially available supplements do not contain myrosinase, and this cannot be encapsulated because it is active only when it is fresh.<sup>[5]</sup> Consumption of broccoli along with a food ingredient consisting of myrosinase enzyme provides more amount of SFN. Mustard seed powder, daikon radish, wasabis, arugula or coleslaws are some myrosinase-rich food. Some myrosinase enzyme is synthesized by the intestinal bacteria which may not be seen in persons with imbalanced flora. Myrosinase produced by the microorganisms in the intestine further acts on the ingested glucosinolates which have escaped the endogenous myrosinase in the plant. However, mammalian cells lack this enzyme.<sup>[9]</sup> Iberin and erucin are other compounds found in lesser amount in broccoli extracts, which show similar cancer-protective property as SFN.<sup>[10]</sup>

### BIOAVAILABILITY

Once SFN is ingested, it is primarily absorbed in jejunum and enters circulation by passive diffusion.<sup>[11]</sup> SFN binds to thiols of plasma proteins and crosses the plasma membrane

to enter the cells where it reacts with glutathione to form conjugates which are expelled by the transporter protein and metabolized to mercapturic acid. These metabolites are transported to kidney where they are eliminated through urine. It is observed that the urinary levels correlate with the dietary consumption and serve as biomarkers.<sup>[12,13]</sup> SFN is rapidly absorbed, reaching peak concentration after 1–3 h. Levels are back to baseline within 72 h. The bioavailability is said to be 74%. SFN tissue concentration varies depending on the end organ. For example, SFN concentration in the skin is less compared to those in plasma due to low perfusion. Thus, dosage required may be more. Three doses of 50–200  $\mu\text{mol}$  daily are well tolerated.<sup>[14,15]</sup>

The amount of SFN varies in different plants of same species and even in specific parts of the same plant. It also depends on the cultivation, climate and other agronomic factors.<sup>[11]</sup> Broccoli sprouts are said to be 20–50 times more effective in chemoprevention than the mature heads. First, sprouts contain more amount of GPN, a potent Phase 2 enzyme inducer and second, they cause less potential toxicity due to minimal content of indole and b-hydroxyalkenyl glucosinolates.<sup>[16]</sup> Sulforadex or broccomax is a commercially available synthetic form of SFN.<sup>[8]</sup>

Presence of myrosinase enzyme, epithiospecifier protein, and preparation of SFN are some other factors which alter the bioavailability and pharmacokinetics of SFN. The metabolites of SFN are removed through urine rapidly, thereby enhancing the elimination of harmful carcinogens. This process may, however, depend on individual genetic variation in metabolism and excretion. Cooking methods using less water such as steaming or microwaving also increase the bioavailability of SFN. However, boiling, microwaving at high power ( $>750\text{ W}$ ) and steaming at high temperature reduce the amount of SFN levels by inactivating myrosinase enzyme.<sup>[16,17]</sup>

### ROLE OF SULFORAPHANE IN VARIOUS CANCERS AND EPIGENETIC ALTERATIONS

SFN has numerous cancer-preventive properties [Table 1]. SFN role has been described in brief and requires a separate extensive review by itself as there are numerous studies. It promotes programmed cell death/apoptosis, induces cell cycle arrest, inhibits angiogenesis, reduces inflammation, alters susceptibility to carcinogens, reduces invasion and metastasis and exhibits antioxidant and anti-inflammatory properties.<sup>[18]</sup> Evidence also suggests that SFN may target the epigenetic alterations observed in specific cancers, reversing aberrant changes in gene transcription through mechanisms of histone deacetylase inhibition, global

**Table 1: Anticancer effects of sulforaphane**

Anticancer effects	Action of SFN
Induction of cell cycle arrest (S and G2/M)	Increases cyclin 2, chk 2, p21
Reduction in cell proliferation	Inhibits cyclin B1, cdk 1, cdc25B, cdc2 Inhibits Phase 1 enzymes such as the CYP p450 family Induces Phase 2 enzymes
Induction in apoptosis	SFN induces pro-apoptotic pathway and inhibits anti-apoptotic pathways, Induces mitochondrial apoptotic pathway Increases Bax, induces p21 and p53 Activates Caspases 3, 7, 8 and 9 Reduces Bcl-2 and Bcl-XL Inactivates PARP, decreases HIF 1A and $\beta$ -catenin Causes tubulin modulation, induces reactive oxygen species Causes autophagy in cancer cells
Inhibition of tumor invasion, angiogenesis and anti-inflammatory effect	Inhibits NF- $\kappa$ B pathway, activates Nrf-2 Regulates MAPK Inhibits TNF- $\alpha$ , NLRP3, IL-1 $\beta$ , IL-18, IFN- $\gamma$ , IL6, IL-17, IL-23 and IL-12, TGF- $\beta$ /Smad Increases IL-10, IL-4, Arg1 and YM-1 (R) Inhibits NO, iNOS and COX-2, silences Th 17/Th1 Inhibits MMP-9, LDH and PGE2 ROS, free radicals Inhibits VEGF, Akt, EGF, CSF
Epigenetic modulation and altered gene expression through histone deacetylase inhibition, global demethylation and microRNA modulation	The Keap1/Nrf2 antioxidant pathway modulation Histone acetyltransferase inhibition - HDAC 1, 2, 3 and 4 inhibition, decreases miR-21 and hTERT and inhibits DNMT 1 and 3A Challenges pro-oncogenic epigenetic pattern
Antimicrobial effects	Increases human $\beta$ defensins 2
Antioxidant effects	Induction of the Keap1/Nrf2/ARE pathway related with antioxidant genes and detoxifying enzymes, such as glutathione S-transferases
Reduction of susceptibility to carcinogens	Inhibits Phase 1 enzymes CYP1A1, A2, B1, CYP2B2, CYP3A4 Induces Phase 2 enzymes NQO1, GSTA1, HO-1, thereby reducing oxidative stress and DNA damage Clears DNA-damaging chemicals, reducing the toxicity on normal cells

SFN: Sulforaphane, PARP: Poly (ADP-ribose) polymerase, HIF 1A: Hypoxia-inducible factor 1A, NF- $\kappa$ B: Nuclear factor-kappa B, Nrf-2: Nuclear factor erythroid-2-related factor 2, MAPK: Mitogen-activated protein kinase, TNF- $\alpha$ : Tumor necrosis factor-alpha, IL: Interleukin, IFN- $\gamma$ : Interferon-gamma, TGF- $\beta$ : Transforming growth factor- $\beta$ , NO: Nitric oxide, iNOS: Inducible NO synthase, COX: Cyclooxygenase, MMP: Matrix metalloproteinase, LDH: Lactate dehydrogenase, PGE2: Prostaglandin E2, ROS: Reactive oxygen species, VEGF: Vascular endothelial growth factor, EGF: Epidermal growth factor, CSF: Colony stimulating factor, HDAC: Histone deacetylases, miR: MicroRNA, hTERT: Human telomerase reverse transcriptase, DNMT: DNA methyltransferases, CYP: Cytochrome P450, NQO: Nitroquinoline-1-oxide, GSTA: Glutathione-s-transferase, NLRP3: Nucleotide-binding domain (NOD)-like receptor protein 3, YM: A macrophage protein, a novel mammalian lectin

demethylation and microRNA modulation.<sup>[19]</sup> The role of cruciferous vegetables in altering genetic expressions via epigenetic modulation is being widely explored.

Carcinogenesis and cancer progression involve the genetic and epigenetic changes in genome leading to transcriptional dysregulation. Epigenetic alterations cause inhibition of the tumor suppressor genes and promotion of the oncogenes, leading to cancer development. Epigenetic mechanisms include posttranslational histone modifications, DNA global hypomethylation, noncoding RNAs and chromatin remodeling. Genetic mutations are not reversible, but epigenetic alterations are potentially reversible, making them attractive targets for cancer chemoprevention.<sup>[19-21]</sup>

The role of SFN in epigenetic modulation has been widely explored in various cancers. SFN may be involved directly or indirectly in effective upregulation of transcriptional activity of certain genes and restoring the epigenetic alterations. SFN and broccoli sprouts are considered as an “epigenetics diet” and have shown to modify the epigenetic

pathways by targeting the histone deacetylases (HDAC) and DNA methyltransferases (DNMT), thereby altering the gene transcription and expression in cancer. SFN and sprouts seem to alter the mitochondrial function and reduce the lipid peroxidation. SFN could reverse the aberrant epigenetic markers.<sup>[22]</sup>

Meeran *et al.* first observed the significant inhibition of DNMT1 and DNMT3a expression by SFN in a dose-dependent manner in human breast cancer cells (MCF-7 and MDA-MB-231 cell lines), and to a lesser extent in normal MCF10A cells. SFN caused significant downregulation of human telomerase reverse transcriptase (hTERT) in breast cancer cells, leading to apoptosis of cancer cells.<sup>[23]</sup>

Li *et al.* observed that SFN is a potent HDAC inhibitor, which suppresses the hTERT, thereby causing the reactivation of estrogen receptors (ERs) in the ER-negative breast cancer cells via epigenetic modulation. Maternal and early postnatal intake of SFN and broccoli sprouts was found to be beneficial in preventing breast cancer at a

later life by altering the tumor-related gene expressions of TERT, c-Myc, p16 and p53 as observed by the authors.<sup>[24,25]</sup>

Atwell *et al.* have reviewed various preclinical and clinical studies demonstrating the epigenetic alterations of SFN in breast and prostate cancer and the role of SFN in the regulation of cell cycle, apoptosis, inflammation, antioxidant defense and cancer cell signaling and their relationships with epigenetic mechanism.<sup>[20]</sup> Kaufman-Szymczyk *et al.* suggested that SFN downregulates histone deacetylase activity and subsequent alterations in gene promoter methylation indirectly.<sup>[21]</sup>

Inhibition of hTERT in MCF-7 and MDA-MB-231 breast cancer cells and reduction in DNMT1 and DNMT3a by SFN treatment were observed. SFN caused CpG demethylation of hTERT. SFN treatment showed chromatin remodeling with increase in chromatin markers such as H3K9ac and acetyl-H4 and decrease in H3K9me3 and H3K27me3 in hTERT promoter. These changes resulted in the death of breast cancer cells.<sup>[26]</sup> SFN caused downregulation of cyclin D1, CDK4 and pRB and alterations in the levels of DNMT and HDAC that resulted in the apoptosis of cancer cells. SFN reduced DNMT expression and repressed methylation silenced cyclin D2 expression in prostate cancer.<sup>[27]</sup>

Researchers found that SFN could affect a histone methylation and could alter gene expression. SUV39H1, an enzyme in prostate cancer cells, is affected by the exposure to SFN, thereby suggesting this enzyme as a therapeutic target. SFN has been proved effective in treating advanced cancers as well as preventing the metastasis in combination with the existing conventional therapies. It helps in re-expression of tumor suppressor genes, thereby causing selective killing of cancer cells and reducing cancer progression. Clinical human trials to prove the beneficiary effects of SFN are widely explored.<sup>[28]</sup>

SFN targets apoptosis at different steps, including downregulation of anti-apoptotic factors Bcl-2 and Bcl-XL, upregulation of proapoptotic Bax, proteolytic activation of caspase-3 and degradation and/or cleavage of poly(ADP-ribose) polymerase.<sup>[29]</sup>

SFN induced apoptosis of the human leukemic cells KG1a and K562 in a dose- and time-dependent manner through upregulation of Bax and Caspase-3 and downregulation of Bcl-2. SFN exhibited anticancer effects on acute myeloid leukemic cells as observed by Wang *et al.*<sup>[30]</sup>

SF was shown to modulate STAT3 in cancer cells and prevent ultraviolet (UV) light-induced skin cancer and

melanoma.<sup>[15]</sup> SFN causes epigenetic reactivation of Nrf2, thereby downstreaming target genes HO-1, NAD(P) H:Quinone oxidoreductase 1 (NQO1) and UGT1A1 in a mouse skin tumor model.<sup>[24]</sup>

SFN could increase mRNA and protein expressions of Nrf2, and it downstreams target gene NQO1 by reducing DNMT1 and DNMT3a. SFN also upregulates HDACs 1, 4, 5 and 7 and increases the level of active chromatin marker acetyl-histone 3(Ac-H3) during tumorigenesis *in vivo* (using TRAMP mice) and *in vitro* (using TRAMP C1 cells). SFN thus downstreams antioxidative stress pathway partly via epigenetic modifications, and via expression of the Nrf2 gene.<sup>[31]</sup>

SFN is a potent inducer of detoxification pathways by promoting antioxidant glutathione. It leads to the inhibition of Phase 1 enzymes such as cytochrome 450 that are responsible for cell proliferation and tumor growth. SFN induces Phase 2 enzymes by various mechanisms, thereby removing the DNA-damaging chemicals. Nuclear factor erythroid-2 (NF-E2)-related factor 2 (Nrf2) and mitogen-activated protein kinase (MAPK) are controlled by SFN. On the other hand, an overexpression of Nrf-2 makes cancer cells resistant to few chemotherapeutic drugs as observed by Xu *et al.*<sup>[32]</sup> The authors suggested that the time and the dose of SFN regulating this pathway during the cancer therapy need further research. This will eliminate the possible side effects while utilizing the anticancer effects of SFN. SFN enhances the effect of the chemotherapeutic agents by smaller doses and limits the toxicity to healthy normal cells.<sup>[32]</sup>

Researchers found that persons consuming broccoli regularly though not daily, expressed higher levels of tumor suppressor gene p16 than those who had no or few of these vegetables in their diet. This was surprising because SFN is cleared of the body within 24 h. This suggests that the SFN and its metabolites trigger epigenetic mechanisms in the body, which enhances protection from cancer even when the substance is eliminated from the body.<sup>[33]</sup> SFN is said to induce a protein called Nrf2 which in later stages of development of cancer is believed to support the tumor growth and cause plaque buildup in arteries. Thus, a further investigation on the role of Nrf2 in cancer and cardiovascular disease is needed.

SFN has shown to induce apoptosis in colon cancer, prostate cancer, breast cancer, liver cancer and lung cancer in mice. Although the benefits of SFN are proved in cell-based, animal and some human trials, recommendations are few. Hence, at present, SFN use is limited as an adjuvant

to the conventional chemotherapy and radiotherapy. It may be helpful in preventing recurrence among head-and-neck cancer survivors. Sulphoraphane helps in protecting against chronic exposure to environmental pollutants and carcinogens. Bauman *et al.* performed studies involving mice as well as humans and found some adverse effects on the use of this substance.<sup>[34]</sup> SFN is believed to cause autophagy in cancer cells. Treatment of prostate cancer cell lines, PC-3 and LNCap, with SFN resulted in the upregulation, processing and recruitment to autophagosomes of microtubule-associated protein light chain 3.<sup>[35]</sup>

The nuclear factor-kappa B (NF-κB) prevents tumor growth by inhibiting proliferation, angiogenesis and invasion. Inflammation is known to induce tumor proliferation and reduce apoptosis, thereby increasing the risk of tumor development. SFN is said to reduce the secretion of inflammatory cytokines from blood cells, thereby preventing the action of NF-κB on DNA.<sup>[36]</sup>

Unlike normal cells, cancer cells evade the DNA repair mechanisms and rapidly divide propagating the defective mutations, and they do not respond to the apoptotic cell signals. Broccoli extracts trigger the apoptosis of cancer cells activated by the mitochondria and also cause the arrest of cell division in S and M phases, which was not specific to any cell and tissue. This resulted in a decrease in cell division cycle 25C and breakdown of mitotic spindle assemblies. SFN is said to inhibit tubulin polymerization.<sup>[37]</sup>

The activation of the MAPK/ERK pathway has been reported after SFN treatment in a number of cell lines, including PC3 cells, through the activation of the activator protein-1 (AP-1) transcription factor which plays a role in apoptosis.<sup>[38]</sup>

Tang *et al.* also showed that broccoli extracts had the ability to prevent cancer cell proliferation, which was attributed to the presence of these isothiocyanates.<sup>[9]</sup> Further, SFN in broccoli induced the formation of Phase 2 enzymes. Broccoli extracts revealed antiproliferative properties similar to SFN, suggesting that they can be used as a replacement for SFN for potential clinical test and use. Thus, the naturally available SFN rather than the pharmaceutical agent would be easily available, and involves less complex procedures of preparation, thereby being much cheaper and cost-effective. However, loss of SFN while eating sprouts may result due to epithiospecifier protein. Further research to maintain the stability of these extracts is needed.<sup>[9]</sup>

Angiogenesis is an important step in carcinogenesis, which supports the rapidly dividing cancer cells. SFN is said to inhibit the development of new blood vessels, thereby depriving the tumor cells and limiting the tumor growth. In addition, SFN prevents tumor invasion and metastasis. SFN can prevent the development and growth of hormone-sensitive tumors such as breast and prostate cancers.<sup>[6]</sup> Glucosinolate hydrolysis promotes the apoptosis of cultured prostate cancer cell lines, thereby inhibiting the growth of tumor. An inverse association between intake of cruciferous vegetables and the risk of developing prostate cancer was suggested.<sup>[39]</sup>

Cancer stem cells (CSCs) initiate and maintain the cancer and are also responsible for recurrence and drug resistance, which is prevented by SFN.<sup>[40]</sup> Li *et al.*, 2017, observed that SFN reduced the proliferation rate of oral squamous cell carcinoma CSCs in a dose-dependent manner.<sup>[41]</sup> In addition, they noticed a limited effect on the normal oral mucosal cell proliferation. CSCs of oral cancer showed reduced migration, invasion, clonogenicity, *in vivo* tumorigenicity and a dose-dependent increase in the level of tumor-suppressive miR200c, suggesting that SFN suppressed initiation and stemness in cancer CSCs. This led to a decrease in tumor growth and prevented new tumor development as observed both in *in vitro* and *in vivo* animal experiments. SFN possibly targets the CSCs in various cancers via alteration of NF-κB, epithelial–mesenchymal transition and Wnt/β-catenin pathways.<sup>[40]</sup> Researchers believed that SFN when used as an adjuvant along with conventional chemotherapy yielded better results.<sup>[41]</sup>

The assessment of SFN in the regulation of miRNA expression is limited in the literature, and further investigation is required in order to complete understanding. The upregulation of miR-23b and miR-27b in colorectal cancer cells was significant by SFN.<sup>[42]</sup>

HPV-induced cervical cancer and *Helicobacter pylori*-induced gastric cancer are established facts. SFN was effective in preventing these cancers. SFN was found to be effective in reducing the conversion of intraepithelial neoplasia into cervical cancer in mice.<sup>[43]</sup> Further, SFN in purified form was found to be effective in the eradication of the strain in both mice and human trials.<sup>[44]</sup> The ability of SFN to modulate toll-like receptor (TLR) activation and signaling has been implicated as an additional chemopreventive property. Zhu *et al.* observed that SFN caused inhibition of TLR3, with the ability to modulate NF-κB signaling and downstream gene expression, including the downregulation of interleukin 8 and tumor necrosis factor-alpha.<sup>[45]</sup>

Studies on single urinary bladder cancer cell lines (UM-UC-3 cells) have revealed that isothionates in broccoli extracts along with SFN possess certain antiproliferative properties inhibiting the tumor growth. The authors believed that this may possibly be observed in other types of cancer as well. The risk of urothelial and bladder cancers was significantly more in individuals who carried genetic variants of glutathione S-transferase (GST) or NQO1 that yielded either a null or a suboptimal phenotype. This is not surprising, because both these Phase 2 enzymes are important cellular protectants against carcinogens and oxidants.<sup>[46]</sup> The ability of SFN to sensitize drug-resistant cancer cells to TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis has been demonstrated in multiple studies, with reports demonstrating SFN-enhanced TRAIL-induced apoptosis in human hepatoma cells.<sup>[47]</sup>

Thus, various studies have shown that SFN induces mitochondria-mediated cellular apoptosis, induces cell cycle arrest, acts as antioxidant reducing the oxidative stress, induces Nrf-2 preventing inflammation and cytokine secretion, inhibits histone deacetylase and DNA methylation thereby altering epigenetic mechanism and induces Phase 2 enzymes such as GST and quinone oxidoreductase 1, thereby protecting the cells from DNA damage caused by carcinogens and reactive oxygen species, disrupting the oncogenic signaling pathways.

#### OTHER HEALTH BENEFITS OF SULFORAPHANE

SFN has other beneficial effects in addition to cancer protection. SFN exhibits neuroprotective effects and is implemented in treating conditions such as traumatic brain injury, Alzheimer's disease and Parkinson's disease. Patients with autism have shown an improvement in social interaction, abnormal behavior and verbal communication after treatment with these compounds. SFN contains a flavonoid kaempferol which is effective in treating various allergies.<sup>[6]</sup> Broccoli has Vitamin A and higher amounts of fiber, which improves the digestion and gut health. It lowers cholesterol and combats ulcer-causing *H. pylori* bacteria in the digestive system. Broccoli extracts are said to prevent and repair the skin damage caused by UV light, however results on animal and human showed variation. High levels of carotenoids, lutein and zeaxanthin support eye health.<sup>[48]</sup> SFN supports detoxification because it has amino acids, Vitamin C and sulfur. Further, SFN shows anti-inflammatory effects, thus preventing many chronic diseases such as colitis, arthritis, airway-related problems such as asthma and chronic obstructive pulmonary disease. It provides important vitamins and minerals,

including magnesium, potassium, calcium, protein and Vitamin C, which improves the bone health, delays aging, boosts immunity and promotes hair growth. It prevents nonalcoholic fatty liver. It also helps in preventing the thickening of the arteries, thereby reducing the risk for heart disease. SFN is also said to reduce cholesterol levels.<sup>[34]</sup> Broccoli has a low glycemic index as it contains both soluble fiber and chromium, which is beneficial in diabetic patients when consumed in moderate quantity.<sup>[17,49,50]</sup>

#### ADVERSE EFFECTS

SFN acts as a double-edge sword. Eating broccoli in moderate quantity is beneficial, however excess consumption might lead to some side effects. Excess consumption in diabetic patients may give rise to hypoglycemia. Possible liver toxicity on intake of extreme doses has also been reported. Side effects such as gastric irritation, irritable bowel syndrome, diarrhea, abdominal pain and flatulence due to its high fiber content have also been reported. Isothiocyanates in broccoli are said to be goitrogens which alter the uptake of iodine, thereby altering the function of thyroid gland, resulting in hypothyroidism.<sup>[6]</sup> Broccoli has numerous traces of pesticides, of which formaldehyde is carcinogenic. It may cause allergic reactions such as skin rashes, itching, nasal congestion, wheezing and headache in some people. Smokers who consume excess broccoli may be at risk for developing lung cancer due to excess antioxidants. Risk of hemorrhagic stroke in persons with excess broccoli consumption is linked to Vitamin E in broccoli. Intake of too much potassium-rich broccoli can lead to the risk of hypotension. Vitamin K in broccoli might alter blood clotting and increase bleeding risk in patients having blood thinners if intake is excess. Thus, consumption in extreme doses has shown some side effects.<sup>[49]</sup> However, the health benefits outweigh the side effects when consumed in right amount.

#### CONCLUSION

Broccoli and its sprouts contain naturally occurring isothiocyanates such as SFN with potent cancer-fighting properties. *In vitro* and animal experiments have extensively studied the role of SFN in treating different types of cancers as well as other diseases. Although commercial supplements are available, they are not Food and Drug Administration approved as yet. In addition, the pharmacokinetics and side effects are widely being explored at present. Further clinical studies and human trials related to their safety, side effects, isolation and therapeutic dosage and frequency of intake would provide an insight into the beneficial effects of these isothiocyanates. They provide an easily available,

cost-effective alternative chemoprevention with little side effects compared to the conventional chemotherapeutic drugs. It is worthwhile to consume these vegetables in the right amount on a regular basis to promote general health and reduce the cancer risk.

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### Conflicts of interest

There are no conflicts of interest.

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