

## REVIEW

# Sulforaphane as a potential remedy against cancer: Comprehensive mechanistic review

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## Abstract

Sulforaphane belongs to the active class of isothiocyanates capable of delivering various biological benefits for health promotion and disease prevention. This compound is considered vital to curtail numerous metabolic disorders. Various studies have proven its beneficial effects against cancer prevention and its possible utilization as a therapeutic agent in cancer treatment. Understanding the mechanistic pathways and possible interactions at cellular and subcellular levels is key to design and develop cancer therapeutics for humans. In this respect, a number of mechanisms such as modulation of carcinogen metabolism & phase II enzymatic activities, cell cycle arrest, activation of Nrf2, cytotoxic, proapoptotic and apoptotic pathways have been reported to be involved in cancer prevention. This article provides sufficient information by critical analysis to understand the mechanisms involved in cancer prevention attributed to sulforaphane. Furthermore, various clinical studies have also been included for design and development of novel therapies for cancer prevention and cure.

## Practical applications

Diet and dietary components are potential tools to address various lifestyle-related disorders. Due to plenty of environmental and cellular toxicants, the chances of cancer prevalence are quite large which are worsen by adopting unhealthy lifestyles. Cancer can be treated with various therapies but those are acquiring side effects causing the patients to suffer the treatment regime. Nutraceuticals and functional foods provide safer options to prevent or delay the onset of cancer. In this regard, sulforaphane is a pivotal compound to be targeted as a potential agent for cancer treatment both in preventive and therapeutic regimes. This article provides sufficient evidence via discussing the underlying mechanisms of positive effects of sulforaphane to further the research for developing anticancer drugs that will help assuage this lethal morbidity.

## KEYWORDS

anticancer, cruciferous vegetables, glucosinolates, isothiocyanate, sulforaphane

## 1 | INTRODUCTION

Fruits and vegetables are rich sources of dietary antioxidants capable of scavenging free radicals and protecting the body from cellular damage (Naz et al., 2019). Furthermore, certain phytochemicals are bioactive compounds which can also be used for the treatment of various diseases when used as nutraceuticals in conjunction with routine therapies (Nalini et al., 2020; Nwanodi, 2017). In this respect, plant-based foods are considered an important part of a regular diet to ameliorate various lifestyle-related disorders (Haq et al., 2019). Furthermore, diet practitioners endorse the use of fresh fruits and vegetables in everyday meals to prevent from metabolic disparities (Haq et al., 2020; Imran et al., 2020). Several factors such as smoking, consumption of alcohol, sedentary lifestyle, unhealthy diet, and drug abuses are involved in escalating global burden of diseases especially cancer at alarming rate. Attributable to such lifestyle practices, it is being estimated that deaths due to cancer insurgence may rise 21.6 million new cases and 13 million deaths by the year 2030 (Fidler et al., 2018). According to World Health Organization, 9.6 million cancer-based deaths are reported worldwide (WHO, 2018). However, such rate of morbidity and mortality may be avoided by adopting healthy lifestyle practices like consumption of diets rich in bioactive compounds, regular exercise for active lifestyle, and avoiding tobacco and other drug abuses (Colditz et al., 2012; Mandrich & Caputo, 2020).

Numerous studies have revealed both preventive and curative effects of phytochemicals against oncogenesis (Chikara et al., 2018; Imran et al., 2020; Ruiz & Hernández, 2016). Pharmaceuticals may provide efficient results in disease treatment but there may be some side effects associated with them. However, natural bioactive compounds have been found to be safer in nature compared to synthetic pharmaceuticals (Nalini et al., 2020). Nevertheless, prevention from diseases as a proactive approach is always better than countering the medical conditions (Haq et al., 2020). Moreover, provision of bioactive moieties via diet is easier and non-corrosive in routine to prevent diseases than taking drug and radiation therapy (Minich & Bland, 2007). Further, dietary approaches are more practical, inexpensive, and tolerable for individuals to avoid onset of diseases and also may not involve discomforts (Calin & Croce, 2006; Haq et al., 2020; Minich & Bland, 2007; Nalini et al., 2020). It has been seen that phytochemicals with significant disease prevention perspectives can potentially reduce the overall burden of diseases in a community (Haq et al., 2020).

Sulforaphane (SFN), an isothiocyanate, is one such compound that holds a pivotal role in avoiding oncogenic events alongside providing enough safety to the normal cells. SFN is primarily obtained from cruciferous vegetables such as cabbage, broccoli, cauliflower, and brussels sprouts upon enzymatic hydrolysis of glucoraphanin (Yang et al., 2016). Generally, glucosinolates are hydrolyzed by the myrosinase enzyme (thioglucoside glycohydrolase) resulting in the production of organic aglycone moieties (Bartnik & Facey, 2017). Various epidemiological studies have identified a lower risk of cancer incidence among the individuals consuming cruciferous vegetables

which are the principal source of SFN (Abbaoui et al., 2018; Palliyaguru et al., 2018; Soundararajan & Kim, 2018; Vanduchova et al., 2019). One of the researches has endorsed the safe status of SFN where a dose of 3 g/kg b.w. day<sup>-1</sup> of broccoli seed extract (BSE) has not shown any adverse genotoxic effect and sperm abnormality during 30 days trial. Further, its LD50 was found to be >10 g/kg b.w. day<sup>-1</sup> for 30 days. Hence, routine use of broccoli or its extract in food items could be practiced considering its safe nature (Zhou et al., 2015).

Over the past few decades, SFN has grabbed the attention of researchers in clinical studies for cancer chemoprevention due to its natural ability as a potent inducer of phase II enzymes (Fuentes et al., 2016; Kwak et al., 2001; Yanaka et al., 2019). However, SFN is also recognized to possess biphasic behavior representing hormetic effects where it enhances certain metabolic functions at low doses while inhibiting them at higher doses (Bao et al., 2014). Nevertheless, for effective use of phytochemicals against cancer treatment, their mechanistic pathways should be understood with respect to bioavailability, metabolism, and nutraceutical effects at cellular and subcellular levels. In this way, an effective dietary regimen could be designed to prevent cancer onset and/or delay the already prevailing cancer cells in the body. Previous research studies have highlighted the cellular mechanisms of SFN with different types of cancers. Hence, this article substantially deals with understanding and elaborating the mechanisms underlying cancer prevention by SFN in order to depict a clear picture for future studies along with designing and developing therapeutic measures using this important anticancer agent.

## 2 | SULFORAPHANE: PHYTOCHEMISTRY, BIOAVAILABILITY, AND METABOLISM

SFN is a biologically active phytochemical belonging to a diverse class of isothiocyanates derived from glucosinolates. Chemically, SFN is 1-isothiocyanato-4-(methylsulfinyl)butane with a linear chemical expression of CH<sub>3</sub>-SO-(CH<sub>2</sub>)<sub>4</sub>-N=C=S (Vanduchova et al., 2019). In plant cells, SFN is stored in the form of glucoraphanin which is its stable precursor (Lucarini et al., 2018). It is highly concentrated in the reproductive organs like seeds & inflorescence, young leaves, roots, and mature leaves. Glucoraphanin is a glucosinolate and converted to SFN upon catalysis by myrosinase as detailed later. Glucosinolate-myrosinase system provides a defense mechanism to the plant, when it is attacked by pathogens or when a damage occurs to the cells via other means. When plant parts containing these are damaged, chopped, or chewed, the myrosin cells release myrosinase that catalyzes hydrolytic reaction with glucosinolates yielding SFN. Being highly reactive upon interaction, myrosinase and glucoraphanin are spatially separated by storing into different cellular compartments (Yang et al., 2016).

Metabolically, SFN is a hydrolytic product of its glucosinolate precursor, i.e., glucoraphanin found in plants of cruciferous family. A glycone molecule is cleaved from glucosinolate (glucoraphanin) via reaction catalyzed by  $\beta$ -thioglucosidase namely myrosinase

(Figure 1). This enzyme yields glucose, hydrogen sulfate, and aglycones upon cleavage of glucosinolate. The production of aglycones is dependent upon type of glucosinolate, availability of ion, and reaction pH. The stable isothiocyanates such as SFN are produced as hydrolysis products at high or neutral pH (Bones & Rossiter, 1996).

SFN is principally metabolized via the mercapturic acid pathway after absorption. A dithiocarbamate-glutathione (GSH) conjugate is formed when the sulfhydryl group of GSH reacts with electrophilic central carbon of  $-N=C=S$  group. Due to this electrophilic central carbon, SFN possesses high chemical reactivity making it readily react to sulfur, nitrogen, and oxygen-centered nucleophiles (Yagishita et al., 2019). Furthermore, with electrophilic central carbon and a lack of aromatic groups, SFN behaves as a water-soluble compound and possesses better pharmacological activity at neutral pH of the intestine (Mokhtari et al., 2018). Since the glutathione transferase (GST) enzymes are involved in catalyzing this conjugation reaction with SFN, the polymorphism may play a significant impact on isothiocyanate metabolism. Moreover, self-metabolism may also be induced by SFN via induction of glutathione-S-transferases. Finally, the SFN is converted to SFN-cysteine and ultimately to SFN-N-acetylcysteine by successive cleavage reactions catalyzed by  $\gamma$ -glutamyl transpeptidase, cysteinylglycine, and N-acetyltransferase, respectively, as depicted in Figure 2 (Vanduchova et al., 2019).

However, SFN is not the only hydrolysis product of glucosinolates but a sufficient amount of these precursors is converted to nitrile and its products. At higher pH or in presence of  $Fe^{2+}$  ions, this conversion is increased by epithiospecifier protein present in broccoli. Such nitrile products do not deliver major physiological benefits owing to their biologically inert nature. In this way, most of the studies designed to check the effects of SFN from vegetable having higher amounts of epithiospecifier protein may not observe physiological benefits. It has been reported that epithiospecifier protein may result in nine times higher production of inactive nitrile than isothiocyanates (Matusheski et al., 2004, 2006; Williams et al., 2008). The cleavage of glucosinolates to various components is demonstrated in Figure 3.

SFN can deliver cancer-preventive effects only when sufficiently absorbed and available in biologically active form in the body after consumption. In this respect, various factors affect the absorption and bioactivation of glucosinolates. The hydrolysis of glucoraphanin to produce SFN by the action of myrosinase plays a critical role as the mammalian biological system does not have this enzyme and it is only reported to be present in plant cells (Vanduchova et al., 2019). Furthermore, it is reported that apart from plant cells, gut microflora also has the ability to transform glucosinolates to SFN (Yang et al., 2016).

The type of isothiocyanates is also crucial as these are considered vital in delivering anticancer effects. As mentioned earlier, pH and presence of ions also affect the production of SFN. As far as the processing of foods is concerned, myrosinase present in different cruciferous vegetables is a heat-labile enzyme, thus cooking may reduce its activity. It has further been observed that epithiospecifier protein and myrosinase have different temperature tolerances. The myrosinase may work effectively when exposed to mild heat treatment (60–70°C) but epithiospecifier protein cannot withstand this temperature and hence higher production of isothiocyanates is expected instead of inactive nitrile products. However, much of the evidences are available showing a lack of SFN bioavailability from cooked broccoli. It has been noticed that optimum pH for SFN production ranged between 5 and 6 and at 14–25°C (Dosz & Jeffery, 2013). In a nutshell, SFN may not be biologically available when cruciferous vegetables are cooked at higher temperatures, but mild heat treatment may accelerate SFN production (Figure 4).

### 3 | SULFORAPHANE-ASSOCIATED MOLECULAR TARGETS FOR CANCER PREVENTION

Using SFN-enriched designer foods or nutraceuticals as a therapeutic measure against cancer may involve sufficient clinical evidences before being used in routine therapies. Researchers use various tools to identify anticancer perspectives of bioactive compounds

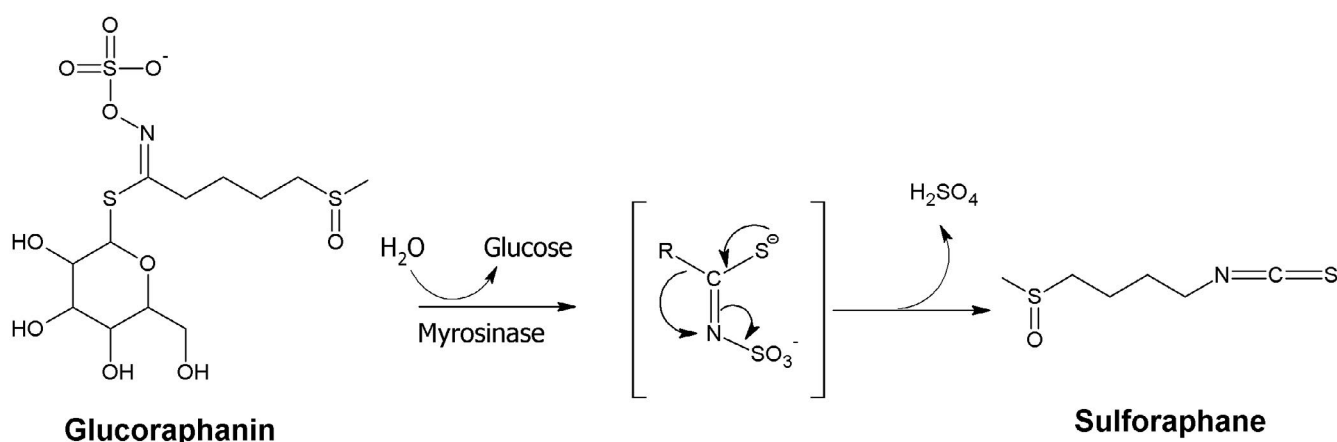


FIGURE 1 Conversion of glucoraphanin to sulforaphane

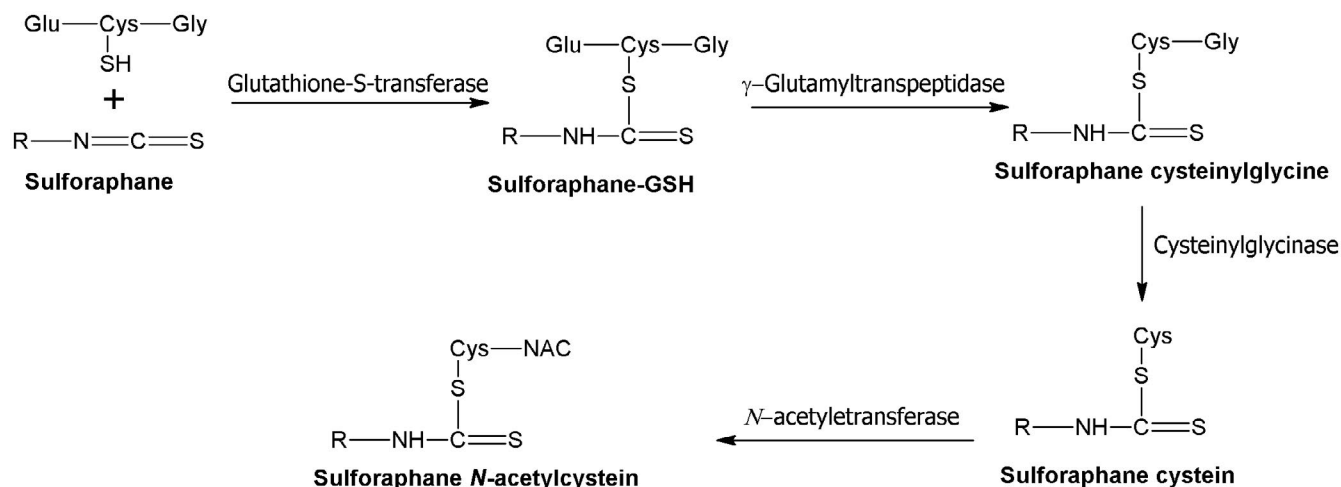


FIGURE 2 Metabolism of sulforaphane

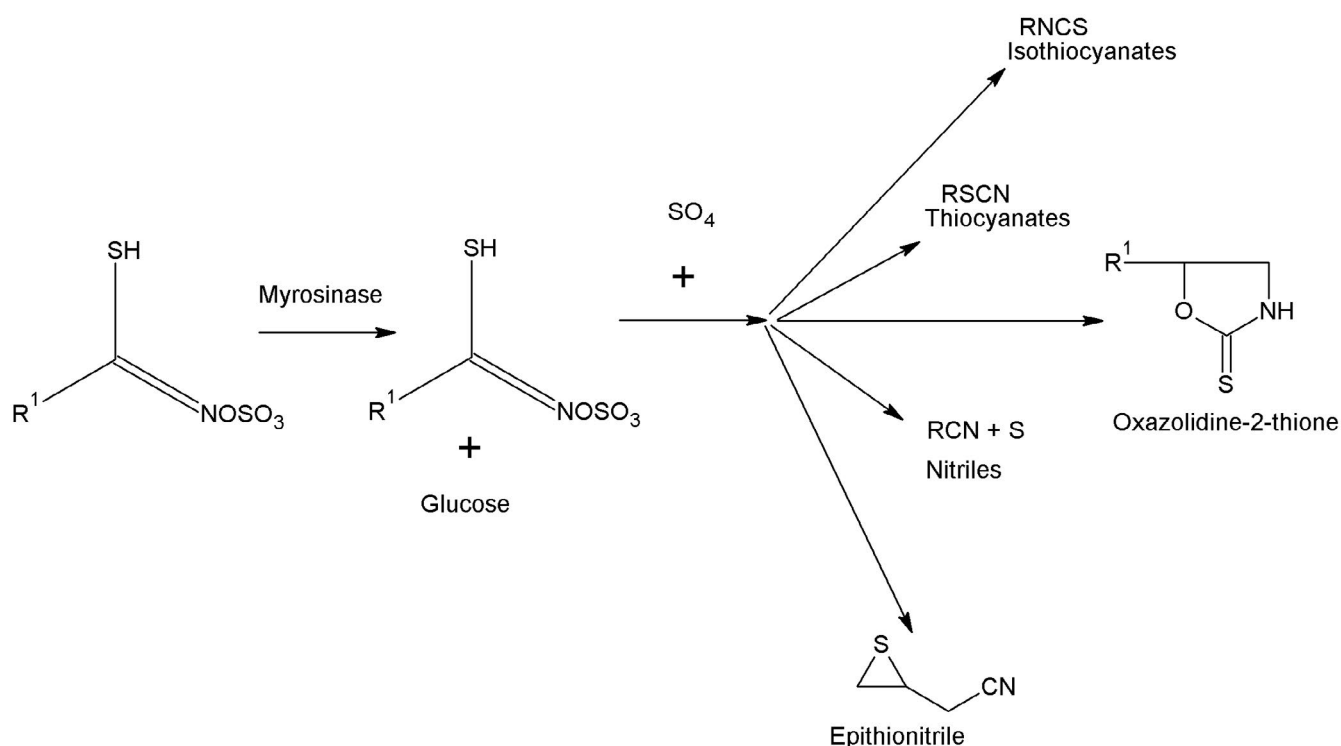
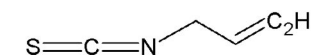


FIGURE 3 Break down of glucosinolates into different fractions

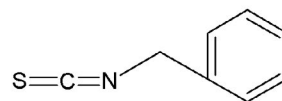
involving activation of nuclear factor erythroid 2-related factor 2 (Nrf2) cell signaling pathway, modulation of xenobiotic pathways and epigenetic regulation. Nrf2 signaling pathway is of critical importance in biological cells where it regulates and controls the detoxification mechanisms of the environmental stress inducers (Yang et al., 2016). In normal conditions, Nrf2 transcription factor is held by Keap1 in cytoplasm facilitating its successive degradation via ubiquitination followed by proteolysis by 26S proteasomal complex (Itoh et al., 1999; Zhang et al., 2004). Under stressed conditions, nascent Nrf2 is translocated to the nucleus due to interruption in proteolysis. Nrf2 then binds to antioxidant response element sequences present at the cytoprotective genes that encode for proteins and enzymes

for regulation of redox homeostasis. In this way, the oxidative stress and other toxicants are diminished (Osburn et al., 2008; Slocum & Kensler, 2011; Yates et al., 2009) (Figure 5).

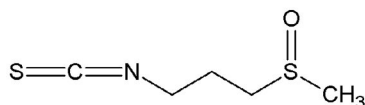
Hence, compounds capable of inducing Nrf2 signaling pathway may avoid mutagenic, carcinogenic, and toxic events at cellular scales. In this context, SFN has been recognized as one of the potential natural compounds capable of inducing Nrf2 signaling pathway (Dinkova-Kostova et al., 2002; Zhang, 2000). Although multiple domains of Keap1 are modified (Hong et al., 2005), SFN primarily targets cysteine 151 in Keap1 because the Keap1 is a cysteine-rich protein (Hu et al., 2011). This region is a major point for modification by SFN ultimately disturbing the association of Cul3 ubiquitin



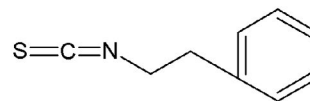
**Allyl Isothiocyanate**



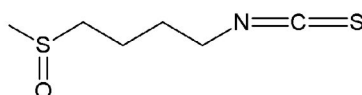
**Benzyl Isothiocyanate**



**Iberin**



**Penethyl Isothiocyanate**



**Sulforaphane**

**FIGURE 4** Some isothiocyanates possessing anticancer potential

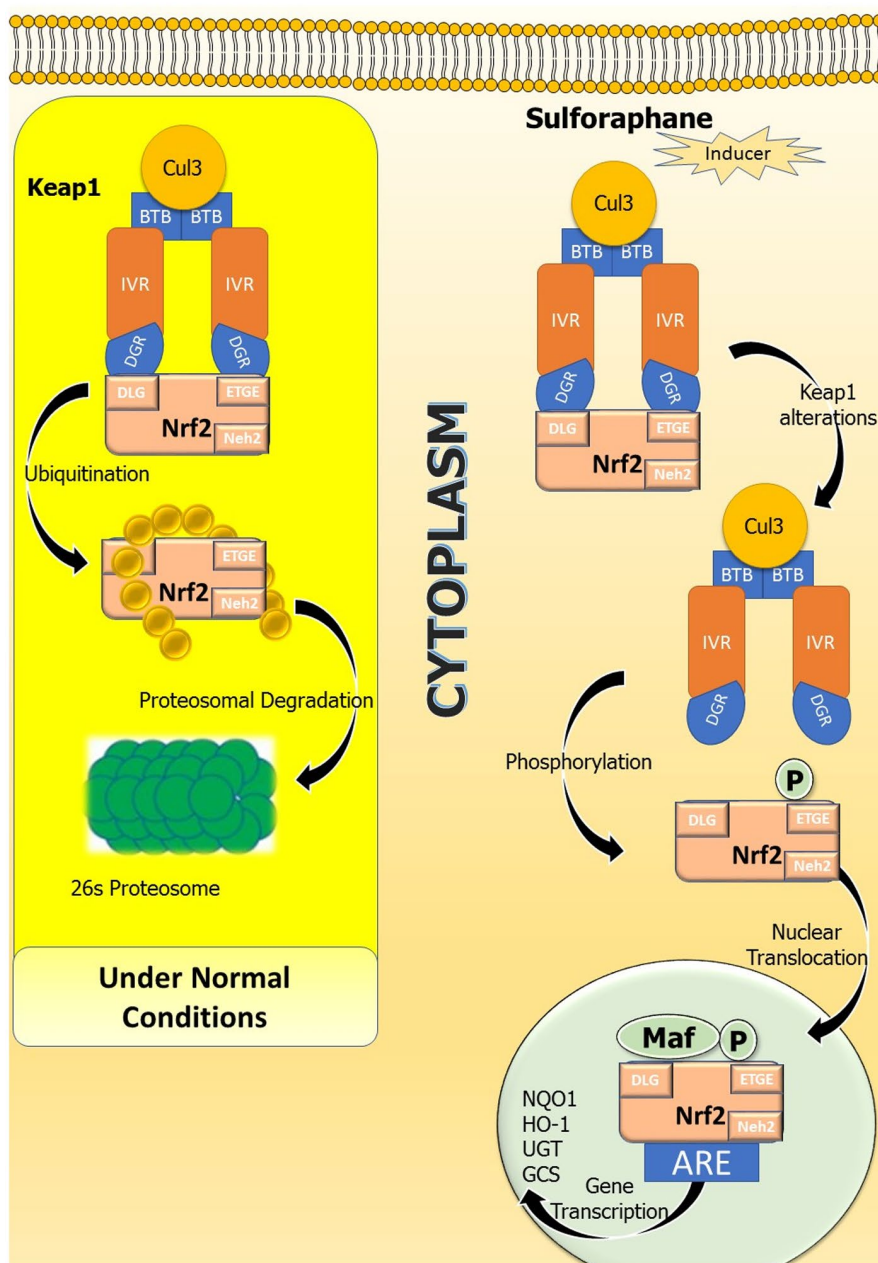
proteasome that stabilizes the Nrf2 which then translocated to the nucleus to induce transcription of target genes as mentioned earlier (Hu et al., 2006). It is worth mentioning that when the cysteine 151 in Keap1 is mutated with serine, the nuclear concentrations and subsequent induction of targeted genes are abrogated by the SFN (Takaya et al., 2012).

It has also been revealed that SFN affects the xenobiotic metabolism via modulating actions of cytochrome P450 (CYP) enzymes (Yang et al., 2016). The modulation of these enzyme may include inhibition or up-regulation of some enzymes like inhibition of CYP1A1 and CYP1A2 (Skupinska et al., 2009), CYP1B1 (Licznarska et al., 2015), CYP2B1/2 (Hu et al., 2006) & CYP3A4 (Mahéo et al., 1997), and up-regulation of CYP1A2 (Licznarska et al., 2015) in different cell models. The possible cross-talk between Nrf2 and aryl hydrocarbon (Ahr) receptor pathways is being considered as an underlying mechanism involved in the modification of CYP enzyme expressions; however, the actual mechanisms are still not clear (Wakabayashi et al., 2010). Accelerated apoptosis has also been induced by SFN in different types of cancers. This observation is majorly seen when high concentrations of SFN are used for treatment (Kanematsu et al., 2010; Misiewicz et al., 2005; Pledgie-Tracy et al., 2007). Different studies have reported various mechanisms for cancer prevention and/or delaying attributed to SFN such as inhibition of mitotic progression, tubulin polymerization (Jackson & Singletary, 2004), adipogenic differentiation, tumor formation, cancer cell migration (Li et al., 2013), cancer stem cells (Li et al., 2010), suppression of vascular adhesion molecule-1 expression (Kim et al., 2012), elimination of advanced cancer stem cells (Labsch et al., 2014), modulation of estrogen-DNA adducts (Yang et al., 2013), and epigenetic modifications (Su et al., 2014).

Recently, epigenetic regulation by the bioactive compound is being addressed as a major tool to target cancer prevention. The principle benefit of epigenetic regulation is that it does not affect the DNA sequence; however, the genetic expression is modified with additional heritable properties (Waddington, 2012). It has recently been reported that SFN increased the Nrf2 mRNA expression and reduced the methylation of 1st 15 CpGs of Nrf2 gene promoter. Furthermore, protein expression of histone deacetylase (HDAC) and DNA methyltransferases (DNMTs) was decreased when SFN was administered (Su et al., 2014). It has also been noticed that sulforaphane inhibits the human telomerase reverse transcriptase (hTERT) expression (Meeran et al., 2010). Other studies have also concluded that SFN regulates genetic expression via lowering the methylation & HDAC activities and induction of acetylated histones on promoters of P21 and bax genes (Myzak et al., 2006, 2007). Such diversity of actions attributed to SFN makes it a potent anticancer agent for clinical manifestations (Figure 6).

#### 4 | POTENTIAL EFFECTS OF SULFORAPHANE AGAINST DIFFERENT CANCERS

Various research works indicate beneficial impacts of SFN against wide-ranging forms of cancers (Ferreira et al., 2018; Mazarakis et al., 2019; Mokhtari et al., 2018). The *Brassicaceae* (*Cruciferae*) family among the cruciferous vegetables are known for high concentration of glucosinolates, which are later metabolized to isothiocyanate compounds. SFN is a highly potent variant of isothiocyanate, exhibiting anti-carcinogenic activity in cells with multiple targeted mechanisms as described earlier (Mokhtari et al., 2018). Different pathways



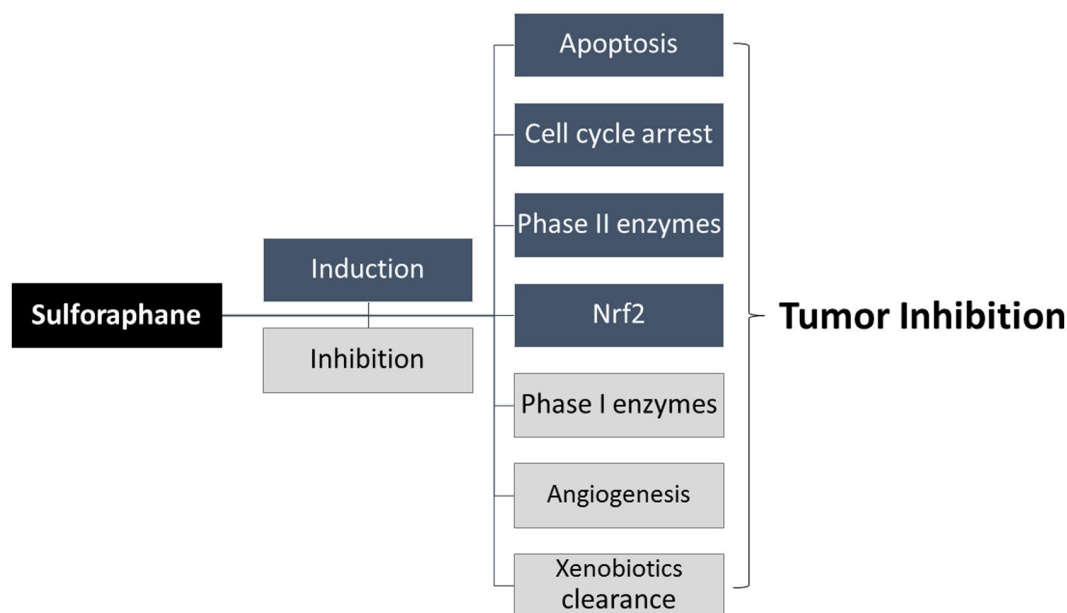
**FIGURE 5** Sulforaphane targets Keap1 and Nrf2 pathways (in normal conditions, Nrf2; transcription factor is held by Keap1 in cytoplasm facilitating its successive degradation via ubiquitination followed by proteolysis by 26S proteasomal complex whereas under stressed conditions, nascent Nrf2 is translocated to the nucleus due to interruption in proteolysis. Nrf2 then binds to antioxidant response element sequences present at the cytoprotective genes that encode for proteins and enzymes for regulation of redox homeostasis hence managing the oxidative stress)

are targeted by SFN to diminish, reverse, or to completely block the harmful effects of carcinogens. Epidemiological research indicates an inverse pattern of dietary intake of *Brassicaceae* family and cancer risks (López-García et al., 2020; Mandrich & Caputo, 2020; Ruiz & Hernández, 2016; Šamec & Salopek-Sondi, 2019). The epidemiological studies related to cruciferous vegetables consumption and their relations with risk of different types of cancers are outlined in Table 1. Most of these studies have shown an inverse association between consumption of cruciferous vegetables and onset of different types of cancers. However, in some studies no or weak

association between cancer prevention and consumption of cruciferous vegetables has also been reported which could possibly be due to different factors influencing the etiology of the disease. Hence, a meta-analysis of such studies may depict a wider and better picture for endorsing the inverse relation.

Recent research has demonstrated the affectivity of isothiocyanate SFN against different kinds of cancer, consisting mainly of cystic carcinomas, ovarian cancer, liver cancer, bladder cancer, and colorectal cancer (Kim et al., 2017; Leone et al., 2017; Mokhtari et al., 2018; Tsai et al., 2019). It is reported that SFN regulates the





**FIGURE 6** Summary of sulforaphane antitumor mechanisms

phase II detoxification enzymes, causes cell cycle arrest, and induces apoptosis (Lewinska et al., 2017). Its chemoprotective functions are delivered through both “blocking” and “suppressing” effects on carcinogens (Li et al., 2018). Furthermore, it also enhances the radio-sensitivity of the tumor cells and prevents the oxidative stress-induced injury (Nalini et al., 2020). Cytotoxic effects of SFN are delivered via complex mechanisms where ROS generation results in improving apoptosis and the autophagy of the targeted cell (Fimognari et al., 2012). Higher concentration of SFN is associated with extensive pancreatic cancer cell death. This ROS generation is also followed by mitochondrial membrane potential disruption that results in cytochrome c cytosolic release cleaving the poly-ADP-ribose polymerase and apoptosis (Singh et al., 2005). Some major isothiocyanates (ITCs) delivering anticancer effects are presented in Figure 4. The flavonoids present in *Brassicaceae* family (flavonoids, phenolic acids, and total polyphenol content (kaempferol, quercetin glycosides, and hydrocinnamic acid esters)) also provide protective effects against cancers (Abotaleb et al., 2019; Ibrahim et al., 2018). Table 2 summarizes various studies conducted on different types of cancers, their physiological effects along with mechanisms adopted and clinical trials. The effects of sulforaphane in different targeted cancerous cells are detailed as under.

#### 4.1 | Blood cancer/Leukemia

Leukemia is characterized by increased myeloid cells in bone marrow that lack maturation resulting in hematopoietic insufficiency. In heterogeneous hematopoietic malignancies, leukemia is one of the leading causes of cancer-associated deaths. Epidemiological researches suggest a reversed relationship between cancer incidence and the dietary consumption of sulforaphane obtained from cruciferous

vegetables (Bosetti et al., 2012). SFN is recognized as a potent anticancer agent that not only reduces the cancer risk but also results in weak metastasis of tumors (Lin et al., 2012). It demonstrates anticancer properties as well as neuro-protective (Tarozzi et al., 2013), cardio-protective (Guerrero-Beltrán et al., 2012), anti-inflammatory (Briones-Herrera et al., 2018), and exhibits pleiotropic potential as a nutraceuticals component (Prata et al., 2018).

Multiple mechanisms of SFN are being researched on to target different carcinogenetic cells. Some reports suggest that SFN tumor inhibition by preventing the phase I enzymes activation (Mokhtari et al., 2018) along with the provocation of detoxification enzymes (Mokhtari et al., 2017). Similarly, SFN also prevents cancerous cell proliferation by modification of genes that are involved in apoptotic mechanisms and arrest of cell cycle (Briones-Herrera et al., 2018; Mokhtari et al., 2017), in angiogenesis (Bertl et al., 2006; Kim et al., 2015), and in metastasis (Jee et al., 2011; Lee et al., 2015). SFN has also demonstrated the cytotoxic effects in the treatment of HL-60 and also in case of acute lymphoblastic leukemia cells, where it triggers apoptosis or cell cycle arrest (Jakubikova et al., 2005; Moon et al., 2009). Likewise, a study conducted on human erythromegakaryocytic cell line B1647 (acute myeloid leukemia) also demonstrated anticancer potential of SFN acting mainly on AQP8 functions, without deteriorating the normal cells (Prata et al., 2018).

A plethora of research have reported the importance of non-coding RNAs (microRNA/miRNA) which play a vital role in pathological pathways and regulate 30% of human protein-encoding genes (Tsuchiya et al., 2006). The disturbance in miRNA results in impairment of differentiation at cellular level, division, apoptosis, and therefore resulting into the formation of different cancerous cells (Deschler & Lübbert, 2006; Peng & Croce, 2016; Zhang et al., 2007). SFN is claimed to modulate the miRNA expression

**TABLE 1** Epidemiological studies regarding cruciferous vegetables consumption and risk of different cancers

Type of cancer	Participants	Findings	References
Lung cancer	Post-menopause women $N = \text{♀} 41,837$	Significant protection from lung cancer and diagnosis of large cell carcinoma due to consumption of cruciferous vegetables ( $p = .02$ ; OR = 0.72; 95% CI = 0.40–1.29).	Steinmetz et al. (1993)
	$N = \text{♀} 89,284$ (34–59 years)	Consumption of broccoli lowered the relative risk of lung cancer ( $p = .03$ ; RR = 0.9; 94% CI = 0.6–1.3).	Speizer et al. (1999)
	$N = \text{♀} 77,283$ (39–63 years) $N = \text{♂} 47,778$ (40–75 years)	Non-significant association was reported for both males and females.	Diane et al. (2000)
	$N = \text{♀} 14,254$ (50–69 years) $N = \text{♂} 4,060$ men (45–69 years)	Consumption of cruciferous vegetables more than 3.5 times a week lowered the relative risk of lung cancer ( $p = .01$ ; RR = 0.68; 95% CI = 0.45–1.04).	Marian et al. (2003)
	$N = \text{♀} 272,303$	No significant association was found for the reduction of lung cancer.	Smith-Warner et al. (2003)
	$N = \text{♀} 519,978$ (25–70 years)	No correlation was recorded with risk reduction.	Grundy et al. (2016)
	Systematic review of 30 studies	Association between cruciferous vegetables consumption and cancer reduction was observed (OR = 0.78; 95% CI = 0.70–0.88).	Lam et al. (2009)
Colorectal cancer	$N = \text{♂} 1997$ $N = \text{♀} 396$	Lower ( $p = .001$ ; RR = 2.49) or no ( $p = .0003$ ; RR = 2.98) consumption of cruciferous vegetables was related with increase colon cancer risk.	Graham et al. (1978)
	$N = 971$	Inverse correlation was observed between proximal & distal colon cancer risk and consumption of low fat high cruciferous vegetables diet (OR = 0.59; 95% CI = 0.35–0.97).	Young, and Wolf, (1988)
	$N = \text{♂} 112$ cases +185 controls $N = \text{♀} 119$ cases +206 controls	Reduced cancer risk was observed in men than women due to consumption of cruciferous vegetables (OR = 0.3; 90% CI = 0.1–0.8).	West et al. (1989)
	$N = 784$	Consumption of cruciferous vegetables protects from rectal (RR = 0.5) and colon (RR = 0.48) cancers.	Benito et al. (1990)
	$N = \text{♀} 41,837$	Insignificant associations with cancer risk reduction were observed.	Steinmetz et al. (1994)
	$N = \text{♀} 88,764$ $N = \text{♂} 47,325$	Insignificant associations with cancer risk reduction were observed.	Michels et al. (2000)
	$N = \text{♀} 62,573$ $N = \text{♂} 58,279$	Consumption of cruciferous vegetables two times a week lowered the relative risk of colon cancer ( $p = .004$ ; RR = 0.51; 95% CI = 0.33–0.80).	Voorrips et al. (2000)
	$N = \text{♂} 62,609$ $N = \text{♀} 70,554$	Significantly reduced colon cancer risk among men was observed ( $p = .03$ ; RR = 0.66; 95% CI = 0.46–0.95) but not for women.	McCullough et al. (2003)
	$N = 1773$ (40–79 years)	Colorectal cancer risk remained unaffected among surveyed patients.	Annema et al. (2011)
	Meta-analysis of 35 studies	Colorectal and colon cancer risks were reduced with cruciferous vegetables consumption ( $p = .03$ ; RR = 0.66; 95% CI = 0.46–0.95).	Wu et al. (2013)
Breast cancer	$N = \text{♀} 5,482$ (50–74 years)	Breast cancer risk reduction with cruciferous vegetables consumption ( $p = .01$ ; R = 0.84; 95% CI = 0.71–0.98).	Paul et al. (2001)
	$N = \text{♀} 351,825$	No association was observed with overall breast cancer risk.	Stephanie et al. (2001)
	$N = \text{♀} 3,015$ (25–64 years)	Glucosinolate intake was negatively related to breast cancer ( $p < .01$ ; OR = 0.5; 95% CI = 0.3–0.8).	Fowke et al. (2003)
	$N = \text{♀} 1,550$	Marginally inverse relation of broccoli consumption with breast cancer in premenopausal women was observed ( $p < .058$ ; OR = 0.6; 95% CI = 0.40–1.01).	Ambrosone et al. (2004)

(Continues)



TABLE 1 (Continued)

Type of cancer	Participants	Findings	References
	N = ♀1,491 cases N = ♀1,482 controls	Inverse relation between cruciferous vegetables consumption and breast cancer risk was found ( $p < .0006$ ; OR = 0.68; 95% CI = 0.55–0.86).	Lin et al. (2017)
	N = ♀2,150 (<65 years) N = ♀1,463 cases N = ♀1,500 controls	No coalition in breast cancer patients. An inverse association among postmenopausal (OR = 0.80; 95% CI = 0.60–1.05) but not premenopausal breast cancer and fruit and vegetable intake was noted.	Steck et al. (2007) Gaudet et al. (2004)
	N = ♀6,072	Higher Chinese cabbage consumption resulted in lower risk of postmenopausal breast cancer ( $p < .049$ ; OR = 0.76; 95% CI = 0.60–0.96).	Lee et al. (2008)
	Meta-analysis	Cruciferous vegetables consumption reduced breast cancer incidences ( $p = .047$ ; OR = 0.85; 95% CI = 0.77–0.94).	Liu and Kezhen (2013)
Prostate cancer	N = ♂17,633 (<35 years) N = ♂58,279 (55–69 years) N = ♂1,253 N = ♂1,230 (40–64 years) N = ♂3,237 (>84 years) Meta-analysis of 12 studies N = ♂47,365 N = ♂130,544 N = ♂965 (45–85 years) N = ♂29,361 (55–74 years) N = ♂11,405 Meta-analysis of 13 studies	No significant association could be concluded with respect to vegetable consumption and prostate cancer risk. No significant association was noticed with respect to vegetable consumption and prostate cancer risk. Protective effect was noticed by consumption of cruciferous vegetables and risk of prostate cancer (OR = 0.69; 95% CI = 0.52–0.91). Consumption of cruciferous vegetables was associated with reduced risk of prostate cancer ( $p = .02$ ; OR = 0.59; 95% CI = 0.39–0.90). Intake of cruciferous vegetables was inversely related to risk of prostate cancer ( $p = .006$ ; OR = 0.61; 95% CI = 0.42–0.88). High intake of <i>Brassica</i> vegetables modestly reduces the risk of prostate cancer ( $p = .06$ ; OR = 0.80; 95% CI = 0.58–1.10). Intake of cruciferous vegetables was inversely related to risk of prostate cancer in males aged below 65 years ( $p = .02$ ; RR = 0.81; 95% CI = 0.64–1.02) whilst no association was seen with aged >65 years. No association was observed in prostate cancer risk and consumption of cruciferous vegetables. Prostate cancer risk was reduced with cruciferous vegetables consumption ( $p = .002$ ; OR = 0.58; 95% CI = 0.38–0.89). High intake of cruciferous vegetables was associated with reduced risk of aggressive prostate cancer ( $p = .02$ ; RR = 0.60; 95% CI = 0.36–0.98). Prostate cancer risk decreased on glucosinolate consumption ( $p = .03$ ; HR = 0.68; 95% CI = 0.48–0.97). Cruciferous vegetables intake was related to decreased risk of prostate cancer (RR = 0.90; 95% CI = 0.85–0.96).	Hsing et al. (1990) Schuurman et al. (1998) Jain et al. (1999) Cohen et al. (2000) Kolonel et al. (2000) Kristal and Lampe (2002) Giovannucci et al. (2003) Key et al. (2004) Joseph et al. (2004) Kirsh et al. (2007) Steinbrecher et al. (2009) Liu et al. (2012)
Pancreatic cancer	N = ♀1753 N = ♀36,616 N = ♂45,306 N = ♀183,522	Decreased pancreatic cancer cells with increased cruciferous vegetables consumption for both males and females (OR = 0.50; 95% CI = 0.4–0.8). Cabbage consumption has significant inverse relation with pancreatic cancer risk reduction (HR = 0.62; 95% CI = 0.39–0.99). No significant association was found with cruciferous vegetable consumption and pancreatic cancer risk.	Silverman et al. (1998) Larsson et al. (2006) Nöthlings et al. (2007)

that may relate to its anticancer activities (Dacosta et al., 2017). A recent study has indicated that sulforaphane promotes the dendritic cell stimulatory capacity via modulation of miRNA and other regulatory molecules (Wang et al., 2020). Although, the role of SFN in modulating miRNA has been explored in various other cancer types (Dacosta et al., 2017; Huang et al., 2018; Lewinska et al., 2017) but further investigations are still needed to firmly confirm the mechanisms by which the SFN may influence the activities of miRNA in leukemia. It has been reported that SFN minimized the number of cancer cells and likewise improved the mortality rate in acute myeloid leukemia (AML) cells through apoptosis induction. This is however a dose-dependent treatment that may carry for different types of cancers (Koolivand et al., 2018).

Another study suggested that SFN treatment exhibited modulating effects on immune system through enhancing the T- and B-cell marker population, their proliferation & phagocytic activity among macrophages and an increase in natural killer (NK) cell cytotoxicity in WEHI-3-induced leukemia cell line of mice in vitro (Shih et al., 2016). The NK cells are innate immune cells which are of critical importance in controlling cancer. Mechanistically, the activating receptors recognize the cancer cells from the molecules which are expressed on their surfaces and then switch on the NK cells to kill these targeted cells. Alongside, NK cells also secrete the cytokines like  $\text{TNF}\alpha$  and  $\text{INF}\gamma$  which act on other immune cells like macrophages and dendritic cells to promote the immune response (Bald et al., 2020).

Recent research also highlights the increase in retinoid acid-induced superoxide-generating activity, cytotoxicity, and growth retardation in human monoblastic U937 cells by application of SFN resultantly assuaging leukemia (Akiyoshi et al., 2019). Recent research work supported the role of SFN in autophagy induction in leukemia with specific concentration and time-dependent factors observed in KG1a and K562 cell lines. SFN exhibited the anti-proliferation effect by modulation of Bax, caspase-3, and Bcl-2 in this apoptosis induction process (Wang, Chen, Zhu, et al., 2018). Another research conducted on chronic myelogenous Leukemia K562 cells also demonstrated the autophagy contribution of isothiocyanates and induction of mitotic arrest leading to cell death so the induction of autophagy may also be devised as a vital mechanism involved in protection from leukemia (Wu et al., 2019).

## 4.2 | Brain cancer

The cancers of central nervous system (CNS) include different tumors that are formed from cells present inside the brain including glioblastoma multiform (GBM). It is among the most malignant and aggressive forms of tumors reportedly present (Zhou et al., 2018). GBM emanating from glial cells is highly malignant with main cases in elderly patients (Aldape et al., 2015; Louis et al., 2016). For their treatment, established tumors are majorly removed surgically, and their subsequent growth may be inhibited by cancer cell inhibitors

like radiations and chemotherapy. The use of ITC and SFN may act as adjuvant to slower or inhibit the growth of cancer cells. However, the dose of the compound and frequency of the exposure should be considered in therapies. In a recent study, it has been shown that sulforaphane-N-acetylcysteine (SFN-NAC) is a potential agent against glioma that induces autophagy via ERK1/2 activation (Liu, Wang, Kang, et al., 2018). Sita and co-workers summarized that death due to glioblastoma in adults is most frequent and SFN may play an important role in its therapeutic treatment (Sita et al., 2018). Vigorous research is needed to unveil the potential utilization of SFN and its derivatives for effective treatment of brain tumors. Furthermore, the use of SFN as adjuvant to other drugs should also be explored to fully benefit from its therapeutic effects.

## 4.3 | Breast cancer

The second major cause of cancer-based deaths among women is considered as breast cancer. Among the risk factors, genetic background including fetal development in *utero* and embryogenesis are cardinal (Li et al., 2018). The data indicated that many cancer types are commenced and propagated by a trifling number of cancer stem cells (CSCs) (Lv et al., 2017). This small population via repeated self-renewal and differentiation mechanisms results in the progression of tumor cell's lump. This mass production of tumor bulk is regulated by a quite similar pathway exhibited by normal stem cells (Li et al., 2018). In a dive of unveiling hidden mechanisms, Wnt/ $\beta$ -catenin, Hedgehog, and Notch are identified as critical self-renewal mechanisms related to CSCs (Aster et al., 2017; Luo et al., 2019). Additionally, they also contribute to tumor reversion as they are not eradicated fully by chemotherapy and radiation therapy (Baumann et al., 2008; Ludwig & Kornblum, 2017). Therefore, it is suggested that the self-renewal pathways should be targeted to remove the CSCs for avoiding relapse and for overpowering tumor resistance (Nalini et al., 2020).

Wnt/ $\beta$ -catenin pathway is considered an imperative pathway for the CSCs self-renewal mechanism in breast. The Wnt-targeted genes are moderated by  $\beta$ -catenin, that moving into the nucleus, fasten itself to the transcription factors T-cell factor (TCF), or to the lymphoid enhancer factor (LEF). The modulation of  $\beta$ -catenin at the intracellular level is carried out by multi-protein complex. This complex contains glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ), adenomatous polyposis coli, casein kinase 1 $\alpha$ , and some concentration of axin (Steinhart & Angers, 2018). The proteasome deterioration of  $\beta$ -catenin is carried out by GSK3 $\beta$  via phosphorylation of three specified amino acids (Ser33/Ser37/Thr41) on  $\beta$ -catenin (Nusse & Clevers, 2017). SFN targets both the breast cancer xenografts and the cancer cell line via suppression of Wnt/ $\beta$ -catenin pathway. The SFN not only prevented proliferation but also encouraged apoptosis among breast cancer cells. The in vivo breast CSCs elimination reflected the prevention of tumor growth in tumor cell-inoculated in mice (Liu, Peng, et al., 2017). Different other techniques and methods have also been developed to detach and characterize the

**TABLE 2** Physiological effects of sulforaphane against different cancer types

Cancer type	Experimental material	Physiological effects/mechanisms	Reference
Blood cancer/ leukemia	Chronic leukemia cancer stem cells	Enhanced abrogation of Wnt/ $\beta$ -catenin function (0–30 $\mu$ M SFN)	Lin et al. (2012)
	Leukemia cells	Modulates AQP8-linked redox signaling (5–30 $\mu$ M SFN)	Prata et al. (2018)
	Acute myeloid leukemia	Controls miR-155 levels (15–60 $\mu$ M SFN)	Koolivand et al. (2018)
	WEHI-3-induced leukemia	Enhanced phagocytosis of macrophages and natural killer cell active killer cell activities (0, 285, 570, and 1,140 mg/kg) for 3 weeks)	Shih et al. (2016)
	Human monoblastic U937 cells	Growth inhibition, cytotoxicity and enhancement of retinoic acid-induced superoxide-generating activity (0–5 $\mu$ M SFN)	Akiyoshi et al. (2019)
Brain cancer	Glioblastoma	Apoptosis via microtubule disruption in cancer (0–70 $\mu$ M SFN)	Zhou et al. (2018)
	U87MG and U373MG cells	Induction of autophagy via activation of ERK1/2 (0–30 $\mu$ M SFN-NAC)	Liu, Wang, Kang, et al. (2018)
Breast cancer	Breast cancer cells	Modulation of epigenetic mechanisms (26% SFN-based broccoli sprout diet)	Li et al. (2018)
	Mammary glands	Lowering tumors incidence and their multiplication (75–150 $\mu$ M sulforaphane/day) (25 and 100 mM glucosinolates or 25–100 mM isothiocyanates/day)	Zhang et al. (1994) Fahey et al. (1997)
	Breast cancer cells	Induction of apoptosis and cell cycle arrest (30 $\mu$ M SFN)	Kanematsu et al. (2010)
	Breast cancer cells	Inhibits the growth KPL-1 human breast cancer cells Suppress the growth and mastitis (25 or 50 mg/kg SFN/week for 26 days)	Kanematsu et al. (2011)
	Breast cancer cells	Induction of cell cycle arrest DNA hypomethylation (5–50 $\mu$ M SFN)	Lewinska et al. (2017)
	Mammary adipose mesenchymal stem cells	Inhibits mammary adipogenesis (10 $\mu$ M SFN for 7 days)	Li et al. (2013)
	Breast cell lines	Modulation of expression of cytochrome P450 (5–80 $\mu$ M/L SFN)	Licznerska et al. (2015)
	Human breast cancer cells	Epigenetic repression of hTERT (5–20 $\mu$ M SFN)	Meeran et al. (2010)
	Human breast cancer cell lines	Induction of cell type-specific apoptosis (5–25 $\mu$ M SFN)	Pledgie-Tracy et al. (2007)
	Human breast cancer cell lines	Modulation of AhR, ER $\alpha$ , and Nrf2 (Cabbage juice containing glucosinolates 3.283 to 4.623 $\mu$ mol/g)	Szafer et al. (2015)
Lung cancer	Lung adenomas	Inhibit malignant progression (1.5–3 $\mu$ M SFN/g of diet)	Conaway et al. (2005)
	Lung tumor	Suppression of tumorigenesis via downregulation of HDAC activity (5–15 $\mu$ M SFN)	Jiang et al. (2016)
	human lung cancer cells	Reduces anoikis resistance and anchorage-independent growth (1–40 $\mu$ M SFN)	Tsai et al. (2019)
	Lung cancer cell	Potentiate anti-metastasis through JAK2/STAT3 pathway (0–100 $\mu$ M PEITC)	Wang, Wang, et al. (2018)

(Continues)

TABLE 2 (Continued)

Cancer type	Experimental material	Physiological effects/mechanisms	Reference
Gastric cancer	AGS Human gastric cancer cells	ROS-mediated AMPK activation, apoptosis, and mitotic arrest (1–20 $\mu$ M SFN)	Choi (2018)
	Gastric cancer stem cells	Suppression of sonic hedgehog pathway (1–10 $\mu$ M SFN)	Ge et al. (2019)
	Human gastric cancer cells	Alterations of CDX1 and CDX2 expression and changes in miR-9 and miR-326 levels (31.25–250 $\mu$ g/ml SFN)	Kiani et al. (2018)
Liver cancer	Liver of C57BL/6J mice and C57BL/6J/Nrf2 (–/–) mice	Modulation of genetic expression	Hu et al. (2006)
	Liver cancer cells	Inhibition of liver cancer cell growth and angiogenesis	Sato et al. (2018)
Pancreatic cancer	Pancreatic cancer cells	Activation of Nrf2, inhibition of progression via AMPK-dependent signaling (1–100 $\mu$ M SFN)	Chen et al. (2018)
	Pancreatic cancer cells	Inhibition of miR30a-3p (10 $\mu$ M SFN)	Georgikou et al. (2020)
	Cancer stem-like cells of pancreas	Enhances drug-mediated cytotoxicity (5 $\mu$ M SFN)	Kallifatidis et al. (2011)
	Pancreatic tumor-initiating cells	NF- $\kappa$ B-induced antiapoptotic signaling (5–20 $\mu$ M SFN)	Kallifatidis et al. (2009)
	Pancreatic cancer cells	Perturbs cell cycle progression and increased DNA damage (2–10 $\mu$ M SFN)	Naumann et al. (2017)
	Pancreatic cancer	Inhibits the cancer cell progression via inducing miR135b-5p (10 $\mu$ M SFN)	Yin et al. (2019)
Ovarian cancer	Epithelial ovarian cancer cells	induces cell cycle arrest via protection of RB-E2F-1 complex (5–20 $\mu$ M SFN)	Bryant et al. (2010)
	Human ovarian cancer cells	Induces cell cycle arrest in G2/M phase through blockade of cyclin B1/CDC2 (6.25–12.5 $\mu$ M SFN)	Chang et al. (2013)
	Ovarian cancer cells	Antiproliferative effects (1–40 $\mu$ M SFN)	Chaudhuri et al. (2007)
	Ovarian cancer cells	Inhibited growth of cancer cells (0–100 $\mu$ M SFN)	Kim et al. (2017)
Cervical cancer	Cervical cancer cells	Induces G2/M arrest via cyclinB1 downregulation and GADD45 $\beta$ /CDC2 association (0–25 $\mu$ M SFN)	Cheng et al. (2016)
	Human cervical cancer cells	Induces differential effects in apoptosis and cell cycle arrest (2.5–8 $\mu$ M SFN)	Hussain et al. (2012)
	Human cervical cancer cells	Induces apoptosis and anti-inflammatory effects (0–20 $\mu$ M SFN)	Sharma et al. (2011)
Bladder cancer	Bladder cancer	Inhibits histone deacetylase (HDAC) activity (5–20 $\mu$ M SFN)	Abbaoui et al. (2017)
	BIU87 bladder cancer cell line	Inhibition of proliferation via IGFBP-3 elevation (2.5–80 $\mu$ M SFN)	Dang et al. (2014)
	Human bladder cancer cell	Inhibits cancer cell invasion by reversal of epithelial-to-mesenchymal transition via directly targeting microRNA-200c/ZEB1 axis (2.5–80 $\mu$ M SFN)	Huang et al. (2018)

(Continues)

TABLE 2 (Continued)

Cancer type	Experimental material	Physiological effects/mechanisms	Reference
	Bladder tumor	Targets epithelial-to-mesenchymal transition, tumor growth, and survival (10–40 $\mu$ M SFN)	Islam et al. (2016)
Prostate cancer	Human prostate cancer cells	Suppresses prostate cancer via normalization of lncRNAs, up-regulates genes including GAPDH, MAP1LC3B2, and H2AFY which regulates glycolysis, autophagy, and chromatin structure, respectively (15 $\mu$ M SFN)	Beaver et al. (2017)
	Human prostate cancer cells	Causes autophagy to inhibit release of cytochrome C and apoptosis (40 $\mu$ M SFN)	Herman-Antosiewicz et al. (2006)
	Prostate stem-like cancer cells	Enhances drug-mediated cytotoxicity (5 $\mu$ M SFN)	Kallifatidis et al. (2011)
	AIPC cell lines DU145 and PC3	Inhibition of tumor growth, TRAIL-induced NF- $\kappa$ B binding; CXCR4, Jagged1, Notch 1, SOX 2, & Nanog expression, ALDH1 activity and elimination of differentiation and self-renewal potential (10 $\mu$ M SFN)	Labsch et al. (2014)
	LnCaP and PC-3 prostate epithelial cells	Inhibition of histone deacetylase activity in BPH-1 (15 $\mu$ M SFN)	Myzak, Hardin, et al. (2006)
	PC-3 human prostate cancer cells	Induces caspase-mediated apoptosis and retards growth of cancer cells (0–100 $\mu$ M SFN)	Singh et al. (2004)
	Prostate cancer cells	Causes transcriptional changes	Traka et al. (2019)
Colon and colorectal cancer	HT-29 and RKO human colon cancer cells lines	Concentration-dependent inhibition of inflammatory cytokine production by immune cells (1.25–5 $\mu$ M SFN)	Bessler, and Djaldetti, (2018)
	Colonic adenocarcinoma Caco-2	Modulates microRNA expression to regulate oncogenes CDC25A, HMGA2, and MYC (10 $\mu$ M SFN)	Dacosta et al. (2017)
	Colorectal cancer cells	Increases mRNA expression of apoptosis-regulatory genes, cyclooxygenase 2, and Bcl-2-associated X protein	Darkwa et al. (2019)
	HCT116 and AGS cells	Inhibited HIF-1 $\alpha$ expression, hypoxia-induced vascular endothelial growth factor (VEGF), and HIF-1 $\alpha$ expression inhibiting human colon cancer progression and cancer cell angiogenesis (12.5–50 $\mu$ M SFN)	Kim et al. (2015)
	HCT 116 human colon cancer cells	Cell death induction through G2/M phase arrest and triggers apoptosis (0–40 $\mu$ M SFN)	Liu et al. (2016)
	Colorectal cancer cells	Epigenetic modulation of microRNA-21 and human telomerase reverse transcriptase (hTERT) down-regulation (2.5–20 $\mu$ M SFN)	Martin et al. (2018)
	AOM-pretreated mice	Suppressed formation of microscopic ACF and macroscopic colonic tumors, inducing apoptosis of colonic tumor cells through inhibition of HDAC activity (2,200 ppm $\text{kg}^{-1} \text{ day}^{-1}$ SFN for 8 weeks)	Yanaka et al. (2019)
Bone cancer	Canine osteosarcoma	Pro-proliferation and cryoprotective characteristics (0.8–100 $\mu$ M SFN)	Rizzo et al. (2017)
	Murine osteosarcoma cells	Radio-sensitization (2.5–20 $\mu$ M SFN)	Sawai et al. (2013)
	Human osteosarcoma MG-63 cells	Induces DNA damage and mitotic abnormalities (5–20 $\mu$ M SFN)	Ferreira de Oliveira et al. (2014)

(Continues)

TABLE 2 (Continued)

Cancer type	Experimental material	Physiological effects/mechanisms	Reference
Skin cancer	Skin of mice	Antitumor activity via blocking of sulfatase-2 (40 $\mu$ M SFN)	Alyoussef, and Taha, (2019)
	SKH-1 high-risk mice	Protected against UV-induced carcinogenesis (0.1–1.5 $\mu$ M SFN)	Dinkova-Kostova et al. (2006)
	TPA-induced mouse skin cell	Suppression of tumor promoter via epigenetics reprogramming of Nrf2 (0–5 $\mu$ M SFN)	Su et al. (2014)

breast CSCs in vitro. Mammosphere culture generally involves using 0.5–5  $\mu$ mol/L of SFN for mammary cells suppression (SUM159 and MCF7 cells) (Charafe-Jauffret et al., 2008). Another technique is cell marker usage for example CD44+CD24<sup>-/low</sup> lin<sup>-</sup> and ALDH positive in the differentiation of mammary stem cells and the differentiated cancer cells. It has been found that SFN at a dose of approximately 1–5  $\mu$ mol/L inhibited the tumor commencing ALDH-positive cells (65%–80%) in vitro (Charafe-Jauffret et al., 2008; Visvader & Lindeman, 2008).

SFN has also been reported to induce autophagy response in the triple-negative breast cancer cells through the downregulation of HDAC6-mediated acetylation modification phenomena of phosphatase and tensin homolog (PTEN) activation mechanism. The experiments were conducted on nude mice to confirm this inhibitory potential of SFN on MDA-MB-231 xenografts growths (Yang et al., 2018). Similarly, another research investigation further supported the autophagy induction by SFN in the breast cancer cell line at 20  $\mu$ M while lower concentration promoted cell cycle arrest and p2, p27 cell senescence in breast cancer cell lines of MCF-7, MDA-MB-231, and SK-BR-3 (Lewinska et al., 2017). Furthermore, research conducted on triple-negative breast cancer cell line indicated combined treatment with SFN and 5-fluorouracil (5-flu) synergistically reduced the level of thymidylate synthetase inducing autophagic death of the cell and senescence prematurely (Milczarek et al., 2018).

#### 4.4 | Lung cancer

Lung cancer (LC) is considered responsible for the first cause of death among other types of cancers (Zhang et al., 2018). Exposure to airborne carcinogens, cigarette smoke (CS), exhaust from automobiles, and combustion from coal mining industry cause initial DNA rupture, later followed by mutation (Cohen et al., 2019; Zhu et al., 2017). Cigarette smoke contains polycyclic aromatic hydrocarbons (PHAs) along with nicotine-derived nitrosamine ketones (NNK) that are prominent carcinogens (Hecht, 2012; Smith et al., 2016; Zhang et al., 2018). However, the epidemiological reports suggest that air pollution is more responsible for increased rates of LC (Eckel et al., 2016; Li et al., 2019). The particulate matter (PM) is predominantly consistent with increased carcinogenic potential according to epidemiological research and experiments carried out on animals (Gharibvand et al., 2017; Huang et al., 2017).

Apart from extrinsic factors, some of the endogenous mechanisms are also responsible for LC including the change in estrogen [17 $\beta$ -estradiol (E2)] and estrogen receptors (ERs) or estrogenic activity by smoking (Peng et al., 2017). Alteration, denaturation, methylation, and mutation in DNA, inflammation, immune/oxidative stress response, changes in telomere length along with some epigenetic factors are reportedly due to environmental pollutants (DeMarini, 2013; Wong et al., 2016). A research study conducted from year 1991 to 2009 on 12,469 cases of different cancers and 11,493 controls indicated significant decrease in risk of cancer development in oral cavity, pharynx, esophagus, breast, kidney & colorectum, and odds ratio (OR) in case of stomach, liver, pancreas, ovary, and prostate cancers (Bosetti et al., 2012). Multiple researches and systemic reviews signify reversed correlation between cruciferous vegetables and LC (Brennan et al., 2005; Mori et al., 2017; Zhang et al., 2018). In a population-based prospective study conducted in Japan, five-year survey of 82,330 participants concluded that consumption of cruciferous vegetables reduces the LC risk among both the past-smokers and non-smokers. However, no association was observed in current smokers that is attributed to lack of statistical power due to fewer patients in the highest tertile (Tang et al., 2010). This phenomenon needs further study and meta-analysis to find out the actual relation between the smoking status and risk of LC in consumers of cruciferous vegetables.

Many studies have reported the effectivity of isothiocyanate on cellular level against cancer. It also inhibits the induction of apoptosis and is linked with the nuclear factor-kappa B (NF- $\kappa$ B) functioning; a transcription factor commonly found in the cancerous cells of humans. Phenethyl isothiocyanate (PEITC) is most effective against the cancers via cytogenetic damage, variations in transcriptome and lung tumorigenesis propagated by CS (Fimognari et al., 2012). PEITC also prevents the formation of xenoestrogen bisphenol A (BPA)-induced DNA adducts (Cohen et al., 2019). SFN also suppresses lung tumorigenesis via downregulation of HDAC activity (Jiang et al., 2016). Additionally, the 13C and the products of its condensation process including 3, 3'-diindolylmethane (DIM) also exhibit antitumor potential especially in LC, along with SFN inhibiting the LC through epigenetic impacts. Another projected mechanism of SFN as an anticancer agent is through the modulation of microRNA (miRNA) expression. These are small RNA molecules having diversified biological functions, enmeshed during LC. PEITC and 13C exhibited the baseline expression of miRNAs (Cohen et al., 2016; Izzotti et al., 2010). This



impact is also related to anti-estrogenic potential of PEITC and 13C (Cohen et al., 2017). Research has also been conducted on the novel effectivity of SFN-N-acetylcysteine (NAC)-induced autophagy in glioma cells. This autophagias process is indicated in U87MG and U373MG cells lines with dose-dependent cell cycle arrest observed in the G2/M phase (Liu, Wang, Kang, et al., 2018) (Figure 7).

#### 4.5 | Gastric cancer

This type of cancer is considered as the fifth common disease worldwide (Duckworth et al., 2015). Although, the gastric cancer treatments have been developed but the relative survival rate of 5 years remains low among gastric cancer patients (Ge et al., 2019). The CSCs in gastric cancer not only delineate in the form of solid tumor but are also responsible for heterogeneity, resistance against drugs, metastasis, and the repeated recurrence of cancers in the human body (Takebe et al., 2015). Sonic hedgehog (Shh) pathway in the maintenance of CSCs for prevention of gastric cancer. Shh is composed of hedgehog (Hh) ligand with Patched (Ptch) receptor and Smoother (Smo) transmembrane protein. When Hh ligand is not present, Ptch inhibits the activity of Smo through catalytic action by suppressing the transduction of signals. When Hh binds with Ptch, this alleviates the preventive impact on Smo, thereby initiating the Gli transcription factor (Gli1 and Gli2 both). This controls the targeted gene transcription by merging both the promoters (Akyala & Peppelenbosch, 2018; Chakrabarti et al., 2018; Hu et al., 2015; Katoh & Katoh, 2005). The dietary broccoli alters the microbiota that consequently affects the conversion of glucoraphanin (Liu, Wang et al., 2017; Zinoviadou & Galanakis, 2017). The suppressive effect of SFN on gastric CSCs by down-regulating Sonic Hh pathway and other chemoprotective applications of SFN for cancer elimination is reported in the literature (Ge et al., 2019).

Similarly, in another research SFN prevented the escalation of AGS gastric cancer cells by promoting apoptosis, resulting in the usage of cellular proportion of G2/M phase through cyclin B1 reserves and cyclin-dependent kinase p21 (WAF1/C1P1). After SFN treatment, higher concentration of phosphorylated histone H3 was apparently present. The apoptosis effects were delivered by SFN via AMPK-dependent pathway. Likewise, SFN also activates the mitochondrial apoptotic signaling pathway by decreasing the mitochondrial membrane potential and rapid dislocation of cytochrome c (Choi, 2018). This apoptotic induction with mitochondrial arrest is accompanied with ROS production and increased AMPK activation resulting in energy homeostasis (Avolio et al., 2020).

Along with epigenetic modification, genetic alterations also contribute to the propagation of gastric cancer. Many miRNAs including miRNA-9 & miRNA-326 target the 3'UTR of homeobox (caudal type) 1 and 2 mRNA, respectively. Dose-dependent antiproliferative impact of SFN has been observed on AGS and MKN45 cells. SFN especially SEBS impacted the cancer propagation negatively in CDX1, CDX2, miR-9, and miR-326 cancer cell lines (Kiani et al., 2018; Rafiei et al., 2020). Nevertheless, further research is required to identify

the antitumor mechanisms of SFN mediated via miRNA regulation and apoptosis.

#### 4.6 | Liver cancer

Hepatocellular carcinoma (HCC) is considered as an assertive form of solid malignancy (Mancuso & Perricone, 2014; Sato et al., 2018). The HCC incidences are rising excessively on global scale resulting in 5th common cancerous type among men and 7th common disease among women (Globocan, 2012; Venook et al., 2010). Research work indicates the role of SFN in arresting the cell cycle by reducing retinoblastoma (Rb) phosphorylation among different types of cancers (Bryant et al., 2010; Choi et al., 2012). Some clinical research has also highlighted the dose-dependent preventive impact of SFN in cancer cell lines (Myzak et al., 2006). It has an inhibitory effect on cellular escalation by induction of apoptosis (Jang et al., 2015). Previous studies have also highlighted the efficacy of SFN against HepG2 cell line for in vivo studies with xenograft models (Liu, Atkinson, et al., 2017; Liu, Wang, Zhou, et al., 2018; Zou et al., 2017). Another research study concluded that SFN inhibited the proliferation, migration, and invasion of hepatocellular carcinoma cells. It also prevents the multiplication of HepG2 cells at 40.05  $\mu$ M exhibiting both time and dose dependency (Wu et al., 2016).

Although Zou and his associates highlighted antitumor effects of SFN their exact mechanisms are still unknown (Zou et al., 2017). Furthermore, the role of Nrf2 signaling pathway is conflicting due to its different expressions in normal and HCC cells. It has been reported that Nrf2 delivers beneficial effects in normal cells, but it causes detrimental effects in HCC and favors proliferation and survival of HCC (Raghunath et al., 2018). In a study conducted in 2018, SFN was found to hinder the growth of human liver cancer cells both in vivo and in vitro. It activated the Nrf2 signaling cascade in the cancerous cells of liver resulting in their proliferation, along with restraining of CCND1, CCNB1, CDK1, and CDK2 mRNA gene expression levels (Sato et al., 2018; Yagishita et al., 2019). Similarly, cell angiogenesis of human liver cancer is also mediated partially by the Nrf2 cascade (Sato et al., 2018). This dysregulation of Nrf2 makes the use of Nrf2 inducer compounds like SFN suspicious although their beneficial effects have also been observed in cancer prevention. In this context, further research is necessitated to unveil the hidden mechanisms and their link to cancer prevention to effectively utilize the SFN in targeted cells.

#### 4.7 | Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDA) is considered as the principal cause of cancer-based death of 2017 in the USA with firm expectations of progressive second cause of mortality due to cancer worldwide in the next decade (Yin et al., 2019). Palliative chemotherapy is the only therapeutic treatment for PDA despite extensive research of last few decades. However, scientific evidences

elaborate the efficacy of SFN for cytotoxic therapy via involvement of nuclear factor kappa B (NF- $\kappa$ B), mainly effective against pancreatic (Kallifatidis et al., 2009), breast (Li et al., 2010), prostate (Kallifatidis et al., 2011), and other tumor moieties (Labsch et al., 2014).

Some research studies have indicated microRNA (miRNA) as a potential tool for the control of pancreatic cancer progression. These are small 19–25-nucleotide long, single-stranded, endogenous, and noncoding RNAs that bind to the 3'UTR of a target mRNA that induces suppression of translation or degradation of mRNA that results in inhibiting the protein expression (Calin & Croce, 2006; Georgiou et al., 2020; Ha & Kim, 2014; Zhu et al., 2013). Different types of miRNA exhibited both anti- and pro-oncogenic effects via both direct and indirect mechanisms (Iorio & Croce, 2012; Vasudevan, 2012). Some studies also demonstrate that role of miRNA135b-5p and RASAL2 is inconsistent in different types of cancers like pancreatic cancer cells as compared to normal or semi-malignant tissues (Zhou et al., 2019). However, Yin and colleagues reported that sulforaphane induces miR135b-5p and its target gene "RASAL2" upregulation. miR135b-5p has been identified as the most important candidate for SFN-induced tumor suppressor by upregulation of RASAL2 which inhibits ERK signaling and progression of pancreatic cancer. Furthermore, immunohistochemistry and in situ hybridization identified positive correlation of miRNA135b-5p and RASAL2 gene expression (Yin et al., 2019). The research may be extended in this target domain to confirm the mechanisms involved that may be targeted to effectively utilize the SFN as an anticancer agent.

Along with inhibiting the pancreatic cancer cell growth, SFN also escalates apoptosis and reduces the colony formation accompanied by inhibiting their migratory potential (Abotaleb et al., 2019; Chen et al., 2018). Due to AMPK signaling activated by SFN, high concentrations of ROS are produced. These ROS propagate the translocation of Nrf2 that consequently prevent the pancreatic cancer cell from progression. Hence, SFN triggers Nrf2-Keap1 pathway to restrict cancer growth and tumors (Chen et al., 2018). Another research demonstrated the different expression of histone deacetylase (HDAC) enzyme in case of pancreatic cell signals. Inhibitors of HDAC, SFN modulates both histone and non-histone proteins (Ahmad Ganai et al., 2017). Similarly, some research work also supports the combined treatment of SFN with irradiations that imparts a distinctive DNA damage and prevention from cell multiplication among cancerous cells. It has been evinced that SFN also enhances the affectivity of chemo radiation in pancreatic cancer (Naumann et al., 2017).

#### 4.8 | Ovarian cancer

Ovarian carcinomas are primarily a heterogeneous group of neoplasms; however, these are conventionally subclassified on the basis of type & degree of differentiation. Globally, ovarian cancer is the primary cause of gynecological cancer-related deaths and majority

of the patients suffer relapse as well due to drug resistance (Jiang et al., 2020). It is contemplated as the major type of cancer affecting female reproductive organs (Torre et al., 2015). Apparently, developed countries have more cases of ovarian cancer than developing countries. Due to limited symptoms, rapid progression, disease relapse, and drug resistance for the treatment of ovarian cancer is recognized to be quite complicated (Hansen et al., 2017; Kaye, 2008; Kwon et al., 2015). The majority of its histological types are due to genetic defects that deregulate the specific signaling pathways in tumor cells (Cho & Shih, 2009). Furthermore, other lifestyle factors have also been identified to be involved in the progression of ovarian cancers (Jayson et al., 2014).

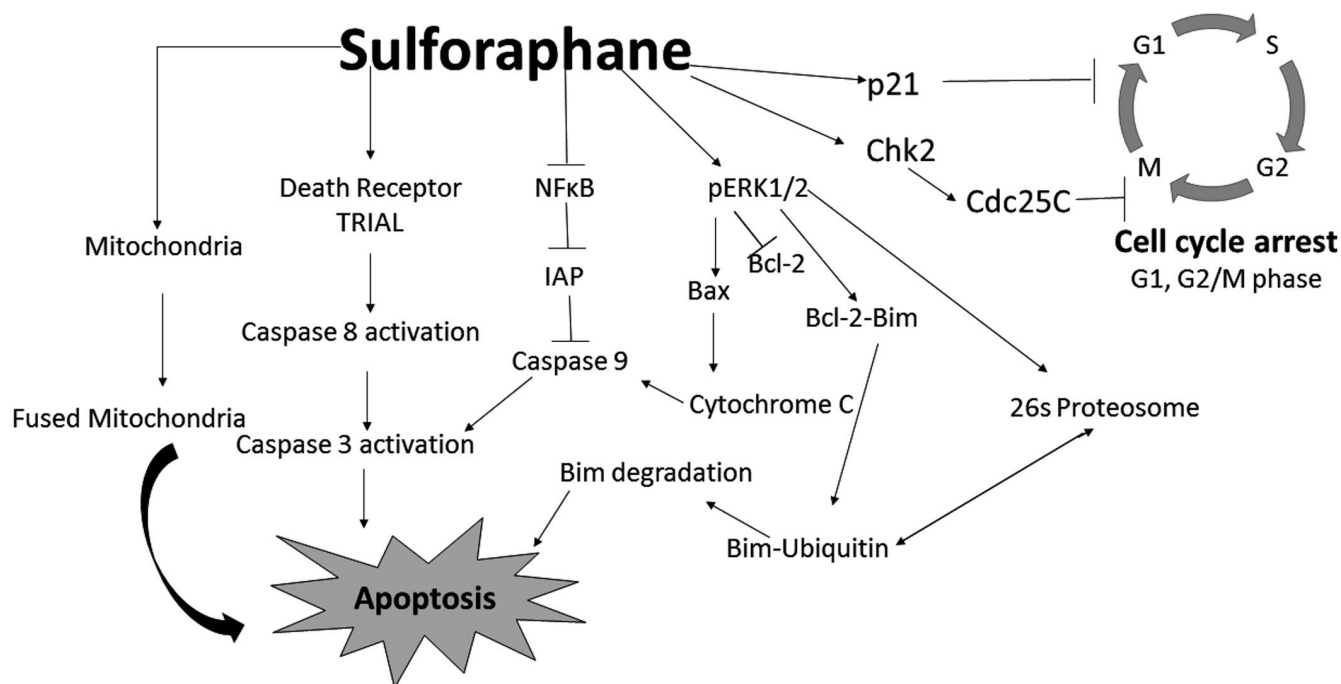
Various studies demonstrated the delineation effect of SFN on ROS and MAPK activation (Kim et al., 2017). The application of SFN (3.6–6.3  $\mu$ M) resulted in reducing the cell viability in ovarian cancer cells but not in non-cancer cells (fibroblasts). Even the application of 10  $\mu$ M induced only 30% restriction in growth among IHFNO-303 and IHFOT-208 fibroblasts. Similarly, antioxidant properties also contribute to this inhibition (Barrera, 2012). Another study demonstrated the effectiveness of SFN (12  $\mu$ M) in reduction of PA-1 ovarian cancer cell lines (Chang et al., 2013). Additionally, it was also effective against MDAH 2,774 and SKOV3 ovarian cancer cell lines resulting in 50% reduction of growth upon application of 8  $\mu$ M SFN (Bryant et al., 2010).

Previous research highlights the impact of SFN against ovarian cancer cells of mouse that overexpressed AKT (Chaudhuri et al., 2007). Its inhibitory role is visible among OVCAR4 and OVCAR5 cells also at low level of AKT along with OVCAR3 and SKOV3 cells with higher level of AKT (Kwon et al., 2015). Therefore, the effect of SFN seems to be independent of the levels of AKT. Furthermore, bioavailability of SFN is also high so it can effectively get absorbed and present anticancer source in the body (Hu et al., 2004; Ye et al., 2002).

#### 4.9 | Cervical cancer

Cervical cancer (CC) is the leading cause of death among women in the developing world (Bedell et al., 2020). Globally, it is considered as one of the lead causes of gynecological deaths (Islami et al., 2015). It is also regarded as the 6th regular malignancy among Taiwanese women (Cheng et al., 2012). Patients with cervical cancer exhibit disseminated disease resulting in low survival rates (Siegel et al., 2012). Genetic predisposition, environmental factors, and in some cases human papillomavirus (HPV) also resulted in the progression of cervical complications among the patients. Generally, the exposure by HPV is counteracted by human immune system but when survives it can lead to conversion of normal cells into precancerous cells, i.e., intraepithelial neoplasia. Nevertheless, in severe cases when virus stays for years it progresses to invasive cervical cancer (Hsu et al., 2010; Hung et al., 2014; Kasprzak et al., 2017).

The anti-tumor potential of SFN was reported in C<sub>x</sub>, C<sub>x</sub>WJ, and HeLa cell lines with dose specificity. On comparative evaluation



**FIGURE 7** Sulforaphane causes apoptosis and cell cycle arrest

with MTT method, significant reduction was observed in  $C_x$  survival rate and proliferation (Cheng et al., 2016). SFN is reported to delay the mitosis by down-regulating cyclin B1 and also dissociates the B1/CDC2 complex through GADD45 $\beta$  in the CC cell lines (Cheng et al., 2012). Similarly, it also reportedly inhibits the cell multiplication by apoptotic and chemo-preventive mechanisms (Cheng et al., 2016; Chinembiri et al., 2014; Sheth et al., 2015).

SFN primarily adopts Nrf2 signaling pathway and other mechanisms to deliver anticancer effects (Hussain et al., 2012). Among different mechanisms reactive oxygen species (ROS) production in the promotion of apoptosis is also involved in prevention from cervical cancer. It has been reported that SFN promotes the protective mechanism in healthy and normal cells while it blocks the factors responsible for tumors, their development and proliferation in cancerous cells (Briones-Herrera et al., 2018; Sharma et al., 2011).

#### 4.10 | Bladder cancer

Among the top ten types of cancers, bladder cancer contributes to the 550,000 cases globally (Richters et al., 2019). Developed countries contain higher burden of bladder cancer patients. Urinary bladder cancer (UBC) contributes to approximately 3.0% of all cases, while 2.1% of all cancer-based deaths (Bray et al., 2018). Majorly, imbalance in gut microbiota contributes to carcinogenicity. A research work involved induction of N-butyl-N-(4-Hydroxybutyl)-nitrosamine (BBN) in male C57BL/6 mice for UBC. SFN affects the histological changes in the UBC cells concluding in reduced submucosal capillaries (Leone et al., 2017). SFN normalized the gut microbiota in BBN-induced mice and increased the butyric acid level in the colon along

with repairing mucosal epithelium of both colon and cecum by tight junction protein and GLP2. The level of cytokines (IL-6) and secretory immunoglobulin A in the bladder of mice also reduced significantly on SFN consumption (Saif et al., 1988; Su et al., 2018).

Cigarette smoke (aromatic amines) contributes to 50% of UBCs. Non-tobacco users' exposure to amines, 4-aminobiphenyl, and anilines lead to 10% of all cases in UBCs death. Similarly, phenacetin-derived analgesics/medication in case of oral pains also lead to UBCs (Witjes et al., 2014). Epidemiological studies indicate that broccoli consumption reduced the UBC risk up to 39% with 2 servings of broccoli per week (Michaud et al., 1999, 2000, 2001). Similarly, in a meta-analysis of ten different clinical experiments concluding in the reduction of overall UBC with cruciferous vegetables consumption (Liu et al., 2013). In vitro studies also support the reduction in BC with the SFN consumption (Singh & Singh, 2012; Zhang, 2010; Zhang et al., 2003).

Further research studies indicate the toxicity of SFN toward malignant urothelial cells among humans as compared to normal urothelium. With BIU87 bladder cancer cells SFN down-regulated NF-KB levels along with up-regulation of insulin-like growth factor-binding protein-3 (IGFBP-3) that increased incidences of apoptosis (Dang et al., 2014). Additionally, a research carried out in animal model once concluded toxic results of SFN on overdosing in case of bladder hyperplasia. However, many other models using significantly higher doses in clinical trials did not result in any toxicity in the bladder of animal models (Akagi et al., 2003). Likewise, SFN also reportedly inhibited the UBC by reversing the epithelial-to-mesenchyme transition (EMT) through mRNA-200c/ZEB1 axis (Islam et al., 2016). SFN in a dose-dependent manner induced the EMT (E-cadherin) along with down-regulation of vimentin (Huang et al., 2018). Current

research also supports the impact of SFN in modulating the HDAC and HATs resulting in increased phosphoric activity, reduced histone H1 phosphorylation in bladder cancer cells (Abbaoui et al., 2017).

#### 4.11 | Prostate cancer

Globally, prostate cancer is reportedly the second most abundant type of cancer among men (Mohler et al., 2016). Even with intensive multimodal therapy, the metastatic prostate cancer remains largely incurable (Wang, Zhao, et al., 2018). Incorporation of SFN in prostate cancer cell lines (PC-3) and LNCaP showed induction of autophagy leading to lowered progression of cancer cells. It was also associated with up-regulating mechanism of autophagosomes of microtubule-associated protein 1 light chain (LC3). The cytoplasmic histone-associated DNA fragmentation indicates that not only apoptosis but also the release of cytochrome c was prevented (Clarke et al., 2008; Herman-Antosiewicz et al., 2006).

The consumption of SFN results in ROS generation along with mitochondrial membrane disruption that is later followed by apoptosis and cytosolic release of cytochrome c. Similarly, SFN-induced ROS generation also results in depletion of GSH levels. This was confirmed for both intrinsic and extrinsic caspase cascades that is conducive of SFN role as a promising chemoprotective compound (Mokhtari et al., 2018; Singh et al., 2004; Yang et al., 2016). Some research also highlighted the role of long noncoding RNAs (lncRNAs) in the management of prostate cancerous cells. SFN induced eight lncRNAs in reducing the prostate cancer cells linked with dysregulation of the expressions including RP11-57A19.2, LINC01351, LINC00883, RP11-700H6.1, MIR22HG, KB-1732A1.1, LINC01059, and LINC01116. LINC00883, and MIR22HG were significantly altered in all cells used in research with SFN incorporation in diet (Petryszak et al., 2016). The research also highlights the Nrf2 factor associated with MIR22HG in different immunoprecipitation studies (Beaver et al., 2017; Thimmulappa et al., 2002, 2016).

Recent investigations were carried out to observe the transcriptional changes in men suffering from prostate cancer were actively monitored. After 12 months of glucoraphanin-rich broccoli intervention, a randomized controlled trial Effect of SFN on prostate Cancer PrEvention (ESCAPE) indicates the decrease in cancer progression on effective consumption of glucoraphanin (Traka et al., 2019).

#### 4.12 | Colon and colorectal cancer

Colon cancer is reportedly highest in developed countries. The global burden of colon-rectal cancer (CRC) is expected to rise by 60% more till 2030 (Arnold et al., 2017). At present, colon cancer is treated by surgery, radiation, chemotherapy, and through the combination of radio- and chemotherapy. However, results still lead to unsatisfactory improvement among patients (Bessler & Djaldetti, 2018; Nautiyal et al., 2011). Epidemiological studies have indicated that cruciferous vegetable consumption was associated with lower risk

of CRC (Pan et al., 2018; Thanikachalam & Khan, 2019; Watanabe et al., 2018). SFN contributes to the anti-oxidant potential through Nrf2-Keap1 systems contributing to cytoprotective phenomena (Yang et al., 2016; Zhang et al., 2003).

Along with other functions discussed previously, SFN also contributes to antibacterial activity preventing the activity of gastric *H. pylori* along with known gastric carcinogens (Fahey et al., 2019; Yagishita et al., 2019). Research indicates its role in maintaining healthy population of intestinal micro-flora thereby preventing colon cancers in mice and humans (Yanaka, 2017; Yanaka et al., 2019). Similarly, SFN also prevented colon cancer cells via epigenetic modulation of mRNA-21 and down-regulation of human telomerase reverse transcriptase (hTERT). Regulation of HDAC, hTERT, and mRNAs are considered effective against colon cancer cells as it reduced the cell density, cell viability and caused apoptosis (Martin et al., 2018). SFN exerted a dose-dependent anti-tumor effect on the CCS in vitro HCT 116 through G2/M phase arrest and also be apoptosis of cell through caspase and mitochondrial-dependent signal mechanism (Liu et al., 2016).

Although SFN is well characterized for anti-tumor potential, in vitro elucidation of all biological mechanisms behind the apoptosis needs better research (Darkwa et al., 2019). Another study explored the effect of SFN on mRNA expression in case of Caco-2 and non-cancer cells lines CCD-481 through small RNA clone and sequencing mechanism. It was later followed by Northern Blot validation experiments that conclude its role in up-regulation of let-7f-5p and let-7g-5p expression after 24 hr in Caco-2 cells. However, this effect was not reported for CCD-481. The process also down-regulated the miR-29b-3p in Caco cells. Two-way luciferase assays allowed let-7f-5p mimic and bound the miRNA to mRNA transcript 3'-UTR of 25A cell cycle division. Therefore, it was hypothetically concluded that let-7f-5p suppressed CDC25A, HMGA, and MYC (Dacosta et al., 2017). Scientific investigations have confirmed the proapoptotic role of SFN in colon cancer cell resulting in reducing the viability of HT29 and Caco-2 cells (Lan et al., 2017; Lenzi et al., 2014). SFN is not only chemoprotective but also prevents the DNA adduct formation along with decreased mutation rate. Similarly, it also activates proapoptotic pathway and regulates epigenetic gene control of CDKs, p21, Bax, and Nrf2 responsible for the cancer instigation and its progression hence arresting the cell cycle progression (Juengel et al., 2017; Royston et al., 2017; Xu et al., 2006).

#### 4.13 | Bone cancer

Among bone cancers, osteosarcoma is the primary malignant form. It is considered as the eighth common type of cancer that leads to morbidity among youngsters (Broadhead et al., 2011; Gill et al., 2013). The mortality rate is also linked to late diagnosis resulting in a 5-year survival rate with ongoing chemotherapy and surgical treatments (Osborne & Khanna, 2012). The impact of SFN was recorded for pro-proliferation and cryoprotective characteristics were observed for canine osteosarcoma cell line in D17, OS 2.4, and HMPOS (Rizzo

et al., 2017). The combination of SFN with radiation treatment was reportedly researched in LM8 murine osteosarcoma cells (Sawai et al., 2013). It induced apoptosis by G2/M phase arrest by suppressing ERK and AKT. Another study reported the ability of SFN in creating instability in the genomic structure of MG63 osteosarcoma by DNA breakage, mitotic abnormalities, nuclear alterations, and clastogenicity. This consequently reduced the viability of micronuclei and enhances the formation of apoptotic bodies (Ferreira de Oliveira et al., 2014).

#### 4.14 | Skin cancer

Radiations from the sunlight, chemical exposure, vulnerable genetic profile, and some virus including papillomavirus are among the factors responsible for skin cancers (Penta et al., 2018; Prasad & Katiyar, 2017). Two main types of cancers have been identified as melanoma and non-melanoma cancer cells. Non-melanoma are further divided into basal cell carcinoma and squamous cell carcinoma (Penta et al., 2018). Melanoma is the most common type of cancer in the USA, with highest frequency reported to be in Caucasians (Chinembiri et al., 2014). Apoptosis induction, preventing the proliferation of cell, and the metastasis inhibition are among basic anticancer functions of SFN observed. Many studies have reported the effective activities of SFN on melanoma cells (Arcidiacono et al., 2018; Fisher et al., 2016; Ramirez et al., 2018; Tahata et al., 2018).

Previous researches also support the role of SFN in the induction of apoptosis. It supported the up-regulation of caspase 3 and 9, p53 protein, and Bax gene. Similarly, SFN also reportedly down-regulated Bcl-2, Bid, and caspase 8 (Hamsa et al., 2011; Rudolf et al., 2014). The anti-metastatic potential of SFN in murine melanoma cancer therapy is also reported where it promotes metastasis by activating cell-mediated immune response by up-regulating IL-2 and interferon gamma (IFN- $\gamma$ ) along with down-regulating IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Thejass & Kuttan, 2007; Van Eylen et al., 2007). SFN is unstable at temperatures between 60 and 90°C, with short half-life and reduced bioavailability. Albumin microspheres are reportedly effective as drug delivery models in mice injected with B16 melanoma tumor. It has been found that SFN inhibited the tumor growth (Do et al., 2010). Moreover, another experimental research indicated higher therapeutic efficiency of SFN (approximately 10%) when delivered via magnetic microspheres (Enriquez et al., 2013). Additionally, SFN is associated with the prevention of UV-induced inflammation. It reacts mainly with the thiol group to produce dithiocarbamate that consequently blocks redox-sensitive DNA binding process and the transactivation of NF- $\kappa$ B. It also inactivates NF- $\kappa$ B by binding it with cysteine (Dinkova-Kostova et al., 2006; de Figueiredo et al., 2015). Similarly, it also regulates the glutathione, thioredoxin, and Ref-1- proteins considered important for NF- $\kappa$ B functionality (Alyoussef & Taha, 2019; Shibata et al., 2010).

## 5 | DIETARY REGIME USING CRUCIFEROUS VEGETABLES

Epidemiologically, provision of natural bioactive moieties via consumption of indigenous plant-based foods has been found to lower the oxidative stress-mediated diseases (Câmara et al., 2021). In this regard, cruciferous vegetables including broccoli, cabbage, cauliflower, etc., are highly acknowledged for their prophylactic health effects (Table 1) due to the presence of a variety of bioactive compounds (Houghton et al., 2013). Different glucosinolate molecules are reported in dietary crucifers; primarily, 3-butenyl and 4-pentenyl glucosinolate with hydroxylated forms are present in Chinese cabbage (*B. rapa* and *B. oleracea*) while 3-methylthiopropyl, 3-methylsulfinylpropyl, 2-propenyl, and 4-methylsulfinylbutyl are found abundantly in red and white cabbage, cauliflowers, and broccoli. Watercress (*Rorippa* spp.) is considered as a major source of phenylethyl glucosinolate while rockets (*Diplotaxis* and *Eruca* spp.) contain 4-methylthiobutyl glucosinolate (Juge et al., 2007).

Brassica vegetables provide an array of functional compounds, but SFN has grabbed significant attention due to its reported effectiveness against different types of cancers. It has been discussed earlier that the SFN is made from glucoraphanin and the myrosinase enzyme is responsible for this conversion. The activity of the enzyme is highly vulnerable to processing conditions like temperature. Domestic processing methods damage and expose the phytochemicals to different modifications impacting the quality and effectiveness. For instance, extensive cooking processes involving high temperature result in damaging SFN and other glucosinolates ultimately lowering their effectiveness (Jones et al., 2010; Tabart et al., 2018; Wachtel-Galor et al., 2008; Zhang & Hamazu, 2004; Zhong et al., 2015). Furthermore, glucosinolates are water-soluble entities, so boiling the vegetables may leach these active compounds in boiling water. Recent studies are focusing more on the methods that increase the bioavailability of such beneficial compounds using appropriate cooking methods. In case of broccoli and red cabbage, steaming seems to be most effective in preserving the nutritional profile of the vegetables (Murador et al., 2016; Tabart et al., 2018). Steaming and microwaving have shown to preserve SFN and in some cases enhance the SFN content attributed to conversion of glucosinolates to SFN (Ghawi et al., 2013; Tabart et al., 2018). In this regard, only mild heat treatments are recommended for cruciferous vegetables.

The broccoli can be consumed raw or freshly harvested alongside mildly processed. Heating decreases epithiospecifier protein resulting in higher production of SFN in broccoli (Matusheski et al., 2004). Chopping the broccoli releases myrosinase that converts the glucoraphanin to SFN. The same effect may also be obtained by thoroughly chewing the vegetables during consumption. It has also been observed that long-term storage (10 days) reduces glucoraphanin (80%) content in broccoli. Other than broccoli, mustard seed powder, daikon radish, wasabis, arugula, or coleslaw are also known for their myrosinase-rich constituents (Higdon et al., 2007; Matusheski et al., 2004; Nandini et al., 2020).



Alongside processing methods, the frequency and composition of a diet with vegetables are important to consider for obtaining maximum benefit from their beneficial compounds. Studies conducted previously indicate that 3–5 servings of cruciferous vegetables are associated with strongest inverse relationship with the cancer cell formation in the body (Jeffery & Keck, 2008; Mokhtari et al., 2018). Likewise, women consuming more than 5 servings of cruciferous vegetables per week showed lower incidence of non-Hodgkin's lymphoma (Zhang et al., 2000). Furthermore, a case-control study indicated inverse relation between consumption of cruciferous vegetables and prostate cancer (Kolonel et al., 2000). Similarly, other types of cancers have also been found negatively correlated with consumption of cruciferous vegetables (Mokhtari et al., 2018). Large populations-based systematic studies are required to establish minimum dietary frequency of cruciferous vegetables to avoid any adverse effects. Based on available data, at least 5 servings of cruciferous vegetables per week may be recommended in routine as a prophylactic measure to prevent onset of metabolic disorders alongside maintain active and healthy lifestyle practices.

In our opinion, sulforaphane possesses significant potential to ameliorate risk of cancer onset and in particular cases may be considered as a potent therapeutic agent. However, the limiting factors such as conversion of glucoraphanin by the action of myrosinase to sulforaphane and losses during cooking can significantly influence its biological availability and effectivity. Furthermore, the epidemiological studies have mostly been conducted in relation to overall consumption patterns of the cruciferous vegetables where the actual content of sulforaphane may vary in different meals and various confounders have not yet been explored like ethnicity, regional variations, seasonal and agricultural practices adopted to produce cruciferous vegetables, etc. Alongside, the synergistic or antagonistic effectivity of sulforaphane is yet to be investigated and needs extensive studies before finally designing a cancer therapeutic drug. Moreover, a comprehensive qualitative and quantitative metanalysis is needed to establish the effective meal frequencies and clinical doses to obtain positive outcomes from this bioactive agent.

## 6 | CONCLUSIONS

Sulforaphane is a potential bioactive compound with significant anticancer activities. Numerous studies confirmed its preventive role in different types of cancer. However, the biological availability and site-specific bioactivity are necessary to deliver such anticancer properties. Myrosinase is degraded when cruciferous vegetables containing glucoraphanin are heated at higher temperatures, only the gut microbiota are the remaining choice to convert it to sulforaphane. Moreover, bioavailability may possibly be enhanced using different delivery models, so a comprehensive research is desired in designing such models. Also, great interest exists in developing synthetic analog of this compound and testing its comparative bio-efficacies. Nutrigenomic studies linking the role of genetic basis

of an individual with the consumption of cruciferous vegetables can also be explored to advise personalized diet-plans for which novel research models are required. Furthermore, unveiling and correlating the hidden mechanisms involved in delivering anticancer effects with consumption of sulforaphane-precursor and/or sulforaphane-rich diets may direct future research in developing safer diet-based regimen in prevention of cancer insurgence.

## CONFLICT OF INTEREST

There is no conflict of interest to declare.

## AUTHOR CONTRIBUTIONS

**Iahtisham UI Haq:** Conceptualization; Data curation; Supervision; Visualization; Writing-original draft; Writing-review & editing. **Sipper Khan:** Data curation; Resources; Writing-original draft; Writing-review & editing. **Kanza Aziz Awan:** Data curation; Software; Validation; Writing-review & editing. **Muhammad Jawad Iqbal:** Data curation; Resources; Visualization; Writing-review & editing.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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