Review Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: www.ijrpns.com

https://doi.org/10.36673/IJRPNS.2025.v14.i05.A18

SULFORAPHANE: A BIOACTIVE PHYTOCHEMICAL IN DISEASE PREVENTION AND HEALTH PROMOTION

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ABSTRACT

The phytochemical sulforaphane (SF) has anticarcinogenic and anticancer properties. A number of cancer-related processes are regulated by SF. These include sensitivity to carcinogens, cell cycle, angiogenesis, invasion, and metastasis. In order to promote additional study on this significant chemical and to aid in the identification and development of new phytochemicals for cancer prevention, we summarise its history of discovery and development as a cancer chemopreventive agent. Sulforaphane, which is already present in plants as glucoraphanin, is converted into it by the β-thioglucosidase enzyme myrosinase, which can be found in either plant tissue or the microbiome of mammals. More than three thousand articles have detailed its effectiveness in rodent disease models, underlying mechanisms of action, or fifty clinical trials investigating pharmacokinetics, pharmacodynamics, or disease mitigation since it was initially isolated from broccoli and shown to have cancer chemoprotective characteristics in rats in the early 1990s. Research on the relationships between formulation (e.g., plants, sprouts, beverages, supplements), bioavailability and efficacy, as well as the doses of glucoraphanin and/or sulforaphane utilised in pre-clinical and clinical studies, is summarised in this review. Concerning the selection of dosage and manner of administration in particular, we highlight the difficulties associated with better integrating animal model and clinical investigations. Human biomarkers of pharmacodynamic activity need to be developed and validated and the underlying mechanisms of action need to be better understood.

KEYWORDS

Sulforaphane, Anticarcinogenic and Anticancer properties.

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INTRODUCTION

In addition to genetic predisposition, the modern way of life has a greater influence on the rising incidence of chronic noncommunicable diseases such as diabetes, obesity, cardiovascular, neurodegenerative disorders, cancer and others[1]. The global burden of liver illnesses, such as metabolic-associated fatty liver disease and

hepatocellular carcinoma, has risen dramatically in recent decades. Cancer development is a complex process including genetic abnormalities that lead to unlimited cell growth, inflicting several negative effects on the body due to malignant cell invasion and metastasis to distant places, resulting in broad organ dysfunction. As a result, cancer is the leading cause of morbidity and mortality around the world. This is a big strain for our society. However, pharmaceutical treatments for these liver illnesses, cancer, and other conditions are insufficient. A sedentary lifestyle, poor nutrition, alcohol consumption, smoking, constant exposure to environmental chemicals (toxic metals, phthalates, bisphenol A, flame retardants, pesticides and so on), many other factors can all contribute to health deterioration and the development of the aforementioned diseases[2]. Changing lifestyle behaviors, such as stopping smoking, maintaining a healthy weight, being physically active, limiting alcohol consumption and eating fruits and vegetables, can reduce the risk of disease. Furthermore, greater consumption of fruits and vegetables can lower the overall risk of acquiring cancer and cardiovascular disease. Recently, a number of natural products have been found to be beneficial in the treatment of liver illnesses, such as fatty liver disease and drug-induced liver injury, paving the way for the creation of pharmaceuticals to treat liver diseases[3,4]. Because cancer is so common, scientists are particularly interested in using naturally occurring substances to prevent, halt, or reverse tumor formation. Cancer chemoprevention is the use of various medicines, including natural food ingredients, with the primary purpose of delaying the start and/or suppressing cancer progression. This brings up an important notion known as "green chemoprevention", which is defined as the ingestion of whole plant meals or their extracts for cancer prevention. Numerous studies have found that eating cruciferous vegetables (plants from the Cruciferae family) may reduce overall cancer risk, particularly for breast, colorectal, bladder, lung, and prostate cancer[5]. This is especially true for crops from the Brassica genus, which includes broccoli (*Brassica oleracea*), Brussels sprouts, cabbage, cauliflower, and Bok Choy. Sulfur-containing organic compounds, particularly isothiocyanates (ITCs) found in these vegetables, are an important class of phytochemicals that have been linked to a variety of health benefits.

Sulforaphane (SFN) is an aliphatic isothiocyanate generated from the hydrolysis of glucoraphanin catalyzed by myokinase in plants. It is prevalent in cruciferous vegetables such as broccoli, cabbage and Brussels sprouts[6]. Since its discovery, SFN has been widely reported to have favorable effects on health, including antioxidative, anti-inflammatory, antidiabetic, anticancer, neuroprotective and cardiovascular protective properties, as well as minimal toxicity to the human body[7-11]. Clinical trials have recently been conducted to examine the therapeutic efficacy of SFN in the treatment of a variety of disorders, including cancer, neurodegenerative diseases, autism spectrum disorder and non-alcoholic fatty liver disease (NAFLD)[12-14]. SFN's effects on chronic and acute liver disorders have been studied for over a decade utilizing *in vitro* or *in vivo* models[15,16]. Previous research has shown that the antioxidative activity and biological functions of SFN are partially dependent on the activation of nuclear factor-erythroid 2-related factor 2 (Nrf2), a master regulator of cellular homeostasis that is ubiquitously expressed in many organs[17]. Previous research has examined the positive effects of SFN on lipid metabolism and NAFLD via Nrf2 activation. However, as the number of research concentrating on the role of SFN in liver disorders grows, more SFN-mediated pathways and targets are being found[18]. The goal of this study is to assess the potential of sulforaphane, a bioactive chemical found in cruciferous vegetables, for the prevention of chronic diseases and the improvement of human health. Sulforaphane protects against cancer, cardiovascular diseases, diabetes, obesity, liver disease and neurological illnesses by lowering oxidative stress, inflammation and metabolic dysfunction. This study seeks to emphasize

sulforaphane as a promising nutraceutical agent that can help with long-term health and illness prevention.

CHEMICAL NATURE AND SOURCES OF SULFORAPHANE

Sulforaphane (SFN) is a sulfur-containing molecule from the isothiocyanate family, a group of bioactive compounds found in cruciferous vegetables. Chemically, it is produced by the hydrolysis of glucoraphanin, a naturally occurring glucosinolate. Myokinase, an enzyme found in plant tissues, is critical to this process. When veggies are sliced, chewed, or digested, myrosinase is activated, converting glucoraphanin into sulforaphane[19]. Sulforaphane is a unique phytochemical that plants manufacture as a defense mechanism after tissue damage, rather than being kept in active form. Sulforaphane's strong reactivity is attributed to its isothiocyanate group (-N=C=S). This functional group enables sulforaphane to easily interact with human proteins and enzymes, particularly those implicated in antioxidant and detoxification pathways. The sulfur atom in its structure adds to its efficacy as a natural electrophile, allowing it to influence redox-sensitive signaling systems in cells[20]. Cruciferous vegetables are the primary sources of sulforaphane. Among these, broccoli and broccoli sprouts are regarded as the most abundant natural reservoirs. In fact, broccoli sprouts may contain 20-50 times more glucoraphanin than mature broccoli heads, making them an especially potent nutritional supply[19]. Other important sources are Brussels sprouts, kale, cauliflower, cabbage, kohlrabi, radish, and mustard greens. These vegetables are widely consumed in various cultures, increasing sulforaphane intake as part of a regular diet.

The concentrations of glucoraphanin and sulforaphane change greatly amongst plant species, cultivars, and even different portions of the same plant. For example, broccoli seeds and young sprouts contain far more glucoraphanin than mature plant florets and stems. Soil quality, climate, and agricultural techniques all have an impact on glucosinolate concentration and by extension, sulforaphane yield[19]. Food preparation methods have a significant impact on sulforaphane availability. Steaming vegetables for a brief time has been shown to maintain both glucoraphanin and the enzyme myrosinase, enhancing sulforaphane production. However, boiling and microwaving at high temperatures can inactivate myrosinase, resulting in less sulforaphane synthesis. Interestingly, even when plant myrosinase is damaged during cooking, the human gut microbiota can partially convert glucoraphanin to sulforaphane. However, this microbial conversion is very varied between individuals and frequently less efficient than direct enzymatic conversion in fresh or gently cooked veggies[21]. Aside from natural sources, sulforaphane has been studied through supplementation and extraction methods. Commercial treatments commonly contain broccoli sprout extracts with standardized glucoraphanin concentrations. However, the effectiveness of these supplements is greatly dependent on whether they contain active myrosinase. According to studies, myrosinase-free supplements have significantly lower sulforaphane bioavailability than fresh or minimally processed broccoli sprouts[22]. As a result, sulforaphane is a beneficial molecule derived from the diet and created by the enzymatic breakdown of glucoraphanin. Its biological activity is enhanced by its distinct chemical structure, which includes the reactive isothiocyanate group. Broccoli and its sprouts are the most abundant dietary sources, but a range of cruciferous vegetables contribute to its consumption. The amount of sulforaphane acquired through diet is determined not only by the type of vegetable ingested, but also by agricultural conditions, processing methods and individual gut microbiota composition. Understanding these elements is critical to appreciating the role of sulforaphane in nutrition and health promotion.

Pharmacological Properties of Sulforaphane

Cancer-Protective Properties

Sulforaphane (SFN) is one of the most thoroughly studied compounds for its anticancer properties. It has been shown to regulate a variety of biological

mechanisms, including apoptosis, cell cycle arrest, and angiogenesis. Experimental data suggests that SFN causes apoptosis by upregulating pro-apoptotic proteins like Bax and downregulating anti-apoptotic proteins like Bcl-xL, hence increasing programmed cell death in cancer cells[23]. Furthermore, SFN disrupts carcinogen metabolism and inhibits histone deacetylase (HDAC) activity, altering the epigenetic control of tumor suppressor genes. Such multiple activities confirm SFN as an effective chemopreventive drug.

Cardiovascular Protective Effects

Clinical and preclinical research indicate the cardiovascular benefits of SFN. A phase I clinical research found that one week of SFN supplementation resulted in a considerable reduction in total and LDL cholesterol, as well as an increase in HDL cholesterol. Simultaneously, oxidative stress indicators including 8-isoprostane and 8-OHdG were significantly reduced. These benefits are linked to SFN-mediated stimulation of the Nrf2 pathway, which increases antioxidant enzyme expression. Furthermore, SFN has been shown to diminish vascular inflammation and endothelial dysfunction, potentially lowering the risk of atherosclerosis and hypertension[24].

Metabolic Regulation

Sulforaphane has a dramatic effect on energy metabolism and obesity-related illnesses. SFN treatment significantly reduced body fat and improved glucose homeostasis in obese mice produced by a high-fat diet. These effects were primarily mediated by browning of white adipose tissue and increased mitochondrial biogenesis[25]. SFN improves metabolic-associated fatty liver disease (MAFLD) via modulating bile acid production and lipid metabolism through the FXR/LXRα signaling pathways[26]. These findings emphasize SFN's therapeutic potential in treating obesity, insulin resistance, and fatty liver disease.

Neuroprotective Effects

Oxidative stress and inflammation are important pathogenic aspects of neurodegenerative disorders, and SFN has demonstrated promising results in moderating these processes. SFN activates the Nrf2/ARE pathway, which boosts antioxidant defense systems in neuronal cells. Preclinical investigations have shown that it has neuroprotective properties in Alzheimer's and Parkinson's disease models, reducing neuroinflammation while improving mitochondrial function[27]. Furthermore, SFN treatment in human lung epithelial cells inhibited pro-inflammatory cytokine production while activating Nrf2, indicating a broader protective role against neuroinflammation[28].

Anti-Inflammatory Properties

Chronic inflammation is a hallmark of many metabolic and degenerative disorders, and SFN has been extensively researched for its anti-inflammatory properties. In obese (ob/ob) mice challenged with lipopolysaccharide (LPS), SFN dramatically reduced inflammatory gene expression and cytokine secretion, demonstrating immunomodulatory potential[29]. The anti-inflammatory effects are mediated by inhibiting MAPK signaling and modulating NF-κB activation. SFN, via such mechanisms, can lower low-grade systemic inflammation linked to obesity, type 2 diabetes and cardiovascular disease.

Hepatoprotective Actions

Aside from its metabolic benefits, SFN has hepatoprotective effects. In experimental hepatic injury models, SFN administration reduced oxidative damage and increased antioxidant enzyme activity. Furthermore, its involvement in lipid metabolism helps protect the liver from steatosis and fibrosis[30]. These actions highlight its potential as a natural medicinal agent for avoiding liver-related illnesses.

MECHENISM OF ACTION OF SULFORAPHANE

Anti-cancer mechanisms

Sulforaphane's anticancer activity has been extensively studied in a wide range of cancers, including cervical, breast, bladder, renal, lung, colon and prostate tumors[31]. The isothiocyanate functional group (-NCS) on the SFN molecule is the most important pharmacophore[30]. The core carbon

atom inside the -NCS group in the majority of isothiocyanates (ITCs) is strongly electrophilic, allowing interactions with nucleophiles centered on oxygen, sulfur, or nitrogen. This reactivity results in the creation of thiocarbamates, Di thiocarbamates, or thiourea derivatives, depending on the specific nucleophile involved and compounds having this central carbon atom in their structure are easily reversible with thiols under physiological conditions. Several potential mechanisms for SFN's anticancerogenic actions have been proposed. SFN Several efficiently suppresses cell cycle progression in both the G2/M and G1/S phases[32]. SFN has been reported to interact with both intrinsic and extrinsic apoptotic pathways, indicating that apoptosis induction is an essential mechanism[33]. It has also been proposed to interfere with cancer initiation by altering metabolic enzymes, leading to the inhibition of carcinogen-activating phase I enzymes (e.g., decreasing CYP1A1 and CYP3A4 activity) and the activation of carcinogen-detoxifying phase II enzymes[34]. Furthermore, SFN is recognized for its potent free radical scavenging characteristics, binding numerous oxidants, including superoxide, peroxide, and hydroxyl radicals[35]. Detoxification of electrophiles and oxidants as a result can protect against carcinogens, oxidative stress and inflammation. It has been demonstrated that SFN regulates balance in the body at the molecular level by activating the transcription factor, nuclear erythroid 2-related factor-2 (Nrf2). This isothiocyanate was found to induce Nrf2 accumulation due to an inhibition of proteasomal degradation of the basic region-leucine zipper (bZIP) protein. SFN can react with protein thiol groups to create thionoacyl adducts, which influences the key Keap1 cysteine residues and prevents Nrf2 polyubiquitination and breakdown, culminating in Nrf2-Keap1-ARE signaling and Nrf2 nucleocytoplasmic redistribution[36]. Nrf2 performs an important anti-inflammatory function in numerous tissues by activating phase II enzymes and subsequently, by suppressing the nuclear factor-kappa beta (NF-B) signaling pathway[37]. SFN stimulation of Nrf2 results in the production of a number of cytoprotective genes with anticarcinogenic properties. Some of these include NAD(P)H quinone oxidoreductase-1 (NQO1), heme oxygenase 1 (HO-1), catalase, glutamate-cysteine ligase (GCL), glutathione-S-transferase (GST), UDP-glucuronosyltransferase (UGT), epoxide hydrolase and superoxide dismutase (SOD). Activations of mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K) and protein kinase C (PKC) pathways and epigenetic changes are also suggested as potential SFN anticarcinogenic mechanisms[38]. SFN has also been shown to suppress histone deacetylases (HDACs) as well as topoisomerases I and II, all of which play critical roles in DNA replication.

Cardiovascular system related mechanisms

In addition to the prevention of carcinogenesis, SFN has also been linked with beneficial properties against cardiovascular system-related disorders, such as hypertension, atherosclerosis, and ischemia-reperfusion (I/R) injury[39]. It has been suggested to have cardiovascular-protective effects through activating the Nrf2 signaling pathway, suppressing inflammatory pathways and modulating lipid metabolism.

Anti- inflammatory Mechanisms

This isothiocyanate has also been demonstrated to increase lipolysis and prevent adipocyte differentiation, while this said effect has been connected with decreased expressions of the transcription factors PPARγ and C/EBPα, involved in the regulation of adipocyte differentiation and fat accumulation. Anti-obesogenic SFN effects include the increment of apoptosis, activation of AMPK and fatty acid oxidation pathway, triacylglyceride synthesis pathway activation, increased glucose uptake and reduced oxidative stress[40]. Additionally, SFN has been found to promote ribosome biogenesis, reduce ROS accumulation and decrease inflammation in fatty tissue, therefore leading to protection from obesity. SFN's contribution to lipolysis has also been suggested, through the activation of hormone-sensitive lipase and the browning of white adipocytes. Results suggest that SFN may provoke lipophagy through AMPK–

mTOR–ULK1 pathway signaling, resulting in partial lipolysis of adipocytes.

Antidiabetic Mechanisms

Regarding its antidiabetic effects, SFN was found to reduce insulin resistance via the PI3K/Akt and JNK/IKK, AMPK/mTOR pathways, enhance glucose transport via the IRS-1/Akt/GLUT4 and PPAR/GLUT4 pathways and improve blood glucose levels via the PPAR/GSK/GS pathway[41].

Other disorders related mechanism

main mechanisms behind SFN's beneficial effects against neurotoxicity, particularly against neurodegenerative On the other hand, SFN's effects through the Nrf2 pathway, such as the activation of genes and molecules with antioxidant, anti-inflammatory and anti-apoptotic properties, have been suggested as the diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and multiple sclerosis (MS).

The Potential of SFN in Disease Prevention and Treatment

Sulforaphane (SFN) has emerged as a key dietary compound with the potential to reduce the risk of multiple chronic diseases. Its multifaceted mechanisms-including antioxidant defense, anti-inflammatory activity, detoxification and metabolic regulation-make it effective for preventive health. Regular intake of SFN through cruciferous vegetables has been associated with lower incidence of cancer, cardiovascular diseases, metabolic disorders, neurodegenerative conditions and liver dysfunction. Below is a detailed disease-wise discussion of SFN's preventive roles.

Cancer Prevention

Cancer remains one of the leading causes of mortality globally, often driven by DNA damage, oxidative stress and chronic inflammation. SFN prevents cancer initiation by upregulating phase II detoxification enzymes, including glutathione S-transferases and NAD(P)H:quinone oxidoreductase. These enzymes neutralize carcinogens before they can damage DNA. In addition, SFN modulates apoptosis by increasing pro-apoptotic proteins such as Bax and caspase-3, while reducing anti-apoptotic proteins like Bcl-2, thus selectively inducing cell death in malignant cells.

Furthermore, SFN inhibits histone deacetylases (HDACs), restoring tumor suppressor gene activity and interferes with signaling pathways like PI3K/Akt and MAPK, which are commonly overactive in tumors. Human clinical studies with broccoli sprout extracts have demonstrated reduced biomarkers of carcinogen exposure and DNA adduct formation, confirming SFN's preventive role in cancer development. Regular dietary intake may, therefore, lower the risk of prostate, breast, lung and colorectal cancers, making SFN a potent chemopreventive agent[42].

Antidiabetic/Anti-Obesogenic Effects

Furthermore, SFN has shown positive effects by effectively increasing glucose uptake and improving insulin signaling in palmitic acid (PA)-induced HepG2 cells. SFN has also led to increased expression of antioxidant genes downstream of Nrf2 and decreased accumulation of lipid peroxides MDA and 4-HNE. In PA-induced HepG2 cells and flies, the alleviation of insulin resistance by SFN was diminished by the GPx4 inhibitor. Taken together, SFN ameliorated HFD-induced insulin resistance by activating the AMPK–Nrf2–GPx4 pathway, providing new insights into SFN as a therapeutic compound for the alleviation of insulin resistance[43]. Due to the increasing need to utilize substances of plant origin and the biological activity of SFN in the prevention and treatment of diseases, numerous studies have been conducted on their importance in the treatment of diabetes. Axelsson *et al,* (2017) demonstrated the antidiabetic activity of SFN in mice and rats and subsequently confirmed it in a human study. Treatment of these mice and rats with different doses of SFN resulted in a decrease in glucose production due to the translocation of Nrf2 and the reduction in enzymes important for gluconeogenesis. In addition, the effect of SFN was compared with the effect of metformin, the first-line agent for the treatment of diabetes mellitus type II, showing no significant difference, but demonstrating that they achieve their effect through a different mechanism[44]. In addition to the potential

of SFN in the treatment of diabetes, its contribution to the prevention of the development of macrovascular complications in diabetes is also well known. The protective effect on the development of retinopathy, nephropathy, and cardiovascular disease is evident in the activation of Nrf2, which contributes to the increase in the antioxidant capacity of somatic cells[45-47]. Li *et al*, (2019) showed that increased activity of the Nrf2 pathway leads to increased gene expression for heme oxygenase 1 (HO-1) and NAD (P)H oxidoreductase (NQO1) and the induction of gene expression for antioxidant enzymes (GSH, SOD, CAT). In addition, SFN decreases the level of inflammatory cytokines (TNFalpha, IL1beta, IL6) and the expression of inflammatory components (NLRP3, cleaved caspase 1 p20, IL1beta p17, and ASC), which contributes to the prevention of diabetic retinopathy[48]. In addition, activation of the Nrf2 pathway induces apoptosis and ferroptosis, preventing the progression of diabetic cardiomyopathy, as shown in a study by Wang *et al*, (2022). Ferroptosis was shown to be critical in the development of cardiomyopathy even 6 months after the development of diabetes in mice, whereas apoptosis was important for the early stages of cardiomyopathy development[49]. Khaleel *et al*, (2019) demonstrated that SFN has a protective effect on the kidneys and prevents the development of nephropathy through the activation of Nrf2 and HO-1, and suppression of the expression of IL6 and caspase 3[50].

Type II diabetes is usually associated with obesity, which together present a growing global problem causing numerous health, economic and social problems in the world[51]. Because SFN is able to affect lipid metabolism, animal studies have investigated whether it can help to reduce obesity. Liu *et al*, (2021) showed that SFN suppressed body weight gain and reduced adipocyte size and the accumulation of lipids in obese female mice, through its effect on the expression of genes involved in lipid metabolism and mitochondrial oxidative stress. This suggests the possibility of SFN as a potential anti-obesity drug[52]. SFN may also reduce oxidative and inflammatory damage caused by obesity-related glomerulopathy by activating Nrf2 and promoting autophagy, as shown by Lu *et al*, (2020) in a study of mice[53].

Cardiovascular-Protective Effects

The use of phytochemicals such as SFN could play an important role in the prevention of cardiovascular diseases, as numerous *in vitro* and *in vivo* studies have demonstrated. Poletto Bonetto *et al*, (2022) showed that SFN exerts a cardioprotective effect by reducing the expression of the ryanodine receptor (Ryr), leading to modulation of myocardial contraction and Ca handling in rats with cardiac ischemia[54]. Jayakumar *et al*, (2013) indicated the potential of SFN for use as a dietary supplement in the prophylaxis of acute pulmonary thromboembolism. SFN acted protectively by activating adenylate cyclase, resulting in an increase in cAMP levels and subsequent inhibition of signaling pathways, which, in turn, resulted in an inhibition of platelet aggregation[55]. In a study conducted by Zhang *et al*, (2022), SFN increased cardiac function and cardiomyocyte survival in mice with induced cardiac ischemia. This cardioprotective effect was achieved by inhibiting the expression of the CAMK2D gene (which encodes the structure of the protein CaMKIIδ, whose reduced activity protects the heart from ischemic damage) and inducing gene expression for the CaMKIIN2 protein, which inhibits CaMKIIδ[56]. Bai *et al*, (2017) indicated that SFN may have a protective effect on cardiac function through activation of Nrf2, inhibiting myocardial hypertrophy and fibrosis, inflammation and oxidative stress[57].

Metabolic Disorder Prevention

Obesity, insulin resistance, and type 2 diabetes mellitus are rising worldwide due to sedentary lifestyles and high-calorie diets. SFN plays a key role in preventing these metabolic disorders. It promotes the browning of white adipose tissue, increasing mitochondrial activity and energy expenditure. SFN also improves insulin sensitivity and glucose uptake, partly by regulating hepatic gluconeogenesis enzymes such as PEPCK and

glucose-6-phosphatase, thereby reducing fasting blood glucose levels. Clinical trials in obese individuals have shown that broccoli sprout supplementation rich in SFN reduces HbA1c levels and systemic inflammatory markers, supporting its preventive potential against diabetes progression[58]. Moreover, by decreasing adipose tissue inflammation, SFN mitigates the risk of associated cardiovascular complications, highlighting its multi-system preventive role.

Neurodegenerative Disease Prevention

Neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) are strongly influenced by oxidative stress, mitochondrial dysfunction and chronic neuro-inflammation. SFN enhances neuronal antioxidant defense by activating the Nrf2 pathway, reducing reactive oxygen species and preserving mitochondrial function. Additionally, SFN modulates epigenetic mechanisms, including histone acetylation and DNA methylation, which regulate the expression of genes responsible for neuronal survival and synaptic plasticity. Animal studies demonstrate that SFN reduces amyloid-beta accumulation in AD models and protects dopaminergic neurons in PD models, improving cognitive and motor functions. These effects suggest that regular dietary intake of SFN may delay onset or progression of neurodegenerative diseases[59].

Clinical and Preclinical Studies of Sulforaphane

Sulforaphane (SFN), a bioactive isothiocyanate derived from cruciferous vegetables, has been widely studied in preclinical models and clinical settings for its preventive and therapeutic effects across multiple diseases. Preclinical investigations, both *in vitro* and *in vivo*, have consistently highlighted its multi-targeted biological activities, while clinical studies have begun to confirm its efficacy and safety in human populations.

Preclinical Evidence

In cancer research, SFN has been shown to modulate cellular pathways that regulate proliferation, apoptosis and metastasis. In human prostate and breast cancer cell lines, SFN treatment resulted in activation of pro-apoptotic proteins such as Bax and caspase-3, coupled with inhibition of anti-apoptotic factors. Additionally, SFN inhibited histone deacetylase (HDAC) activity, thereby restoring the expression of tumor suppressor genes. *In vivo*, oral administration of SFN to tumor-bearing mice significantly reduced tumor volume and vascularization, with concurrent suppression of proliferative markers, indicating its chemopreventive potential[60]. These findings collectively suggest that SFN may interfere with cancer progression through epigenetic modulation and apoptosis induction. Cardiovascular protective effects have also been demonstrated in animal models. In spontaneously hypertensive rats, SFN administration improved endothelium-dependent vasodilation and reduced systolic blood pressure. These effects were associated with upregulation of endothelial nitric oxide synthase (eNOS) and suppression of pro-inflammatory cytokines including TNF-α and IL-6. Similarly, in ApoE-deficient mice fed a high-fat diet, SFN reduced aortic lipid peroxidation and limited vascular smooth muscle proliferation, which contributed to attenuation of early atherosclerotic lesions[61]. Metabolic benefits of SFN have been well-characterized in preclinical models of obesity and diabetes. In obese C57BL/6 mice, SFN supplementation improved glucose tolerance, enhanced insulin sensitivity and promoted the browning of white adipose tissue through upregulation of UCP1 and PGC1α. Hepatic gluconeogenesis was also suppressed via downregulation of enzymes such as PEPCK and glucose-6-phosphatase, leading to improved blood glucose control. Additionally, SFN reduced systemic inflammatory markers and oxidative stress, underscoring its potential role in preventing metabolic syndrome and obesity-related complications[62]. Neuroprotective effects of SFN have been explored in models of neurodegenerative diseases. In Alzheimer's transgenic mice, SFN administration resulted in reduced amyloid-beta plaque deposition, improved synaptic protein expression and enhanced cognitive performance.

Similarly, in MPTP-induced Parkinson's disease models, SFN preserved dopaminergic neurons in the substantia nigra and mitigated motor deficits. These findings suggest that SFN may protect neuronal integrity through antioxidant, anti-inflammatory and mitochondrial-protective mechanisms[63]. SFN also demonstrates hepatoprotective activity. In murine models of non-alcoholic fatty liver disease, SFN reduced hepatic lipid accumulation, suppressed NF-κB-mediated inflammatory pathways, and improved antioxidant enzyme activity. Interestingly, SFN influenced gut microbiota composition, which indirectly decreased endotoxin-mediated liver injury, highlighting its systemic protective effects[64].

Clinical Evidence

Clinical studies have provided supportive evidence for the preventive and therapeutic effects of SFN observed in preclinical models. In healthy adult volunteers, daily consumption of SFN-rich broccoli sprouts over several weeks led to decreased urinary biomarkers of carcinogen metabolism and reduced DNA adduct formation, demonstrating chemopreventive potential[65]. In the context of cardiovascular health, supplementation with SFN improved flow-mediated dilation and lowered circulating C-reactive protein, suggesting a reduction in vascular inflammation[66]. Among patients with type 2 diabetes, SFN-rich broccoli sprout extracts improved glycemic control, enhanced insulin sensitivity and reduced systemic inflammatory markers, indicating potential metabolic benefits[67]. Neuroprotective clinical studies, although limited in scale, demonstrated that SFN supplementation enhanced working memory and decreased oxidative stress markers in older adults[68]. Across these studies, SFN was generally well-tolerated, with minimal adverse effects reported, supporting its potential use as a safe dietary intervention. The cumulative evidence from preclinical and clinical studies underscores SFN as a multi-functional bioactive compound with promising applications in disease prevention and health promotion. Its ability to target diverse molecular pathways while maintaining a favorable safety profile highlights its potential for future clinical development and broader dietary recommendations.

Bioavailability and Metabolism of Sulforaphane

No mammalian digestive enzymes were able to hydrolyze GRP *in vitro*, according to the simulation model of gastrointestinal enzymatic digestion of GRP. GRP's indestructibility by gastrointestinal enzymes was demonstrated by the fact that its concentration remained constant after intestinal/pancreatin-bile, gastric/HCl-pepsin and oral/amylase digestion. Nevertheless, GRP becomes accessible as a substrate for gut microbiota in the intestine. A dynamic community known as the gut microbiota is made up of a large number of different bacteria that live in the human gastrointestinal tract (GIT) and interact with the host. About 1014 bacteria, primarily belonging to the phyles Firmicutes (renamed Bacillota), Bacteroidetes (Bacteroidota), Actinobacteria (Actinomycetota) and Proteobacteria (Pseudomonadota), are found in the colon, which has the highest microbial burden in the body. Ninety percent of gut microbes that continuously interact with the host and impact its health belong to the first two phyla. In summary, 95% of the phylum Firmicutes is made up of more than 200 genera, including Enterococcus, Lactobacillus, Ruminicoccus, Bacillus and Clostridium. The genera Bacteroides and Prevotella are the principal representatives of the second dominating phylum Bacteroidetes.

The microbial community offers the host many advantages, including aiding in the digestion of foods, medications, xenobiotics, intestinal immunological homeostasis, and gut barrier function. Furthermore, the gut microbiota contains a substantial amount of genetic material that enhances the human genome and fosters a productive symbiosis. Specifically, a number of investigations have demonstrated that gut bacteria support host gastrointestinal enzymes in these processes by converting GRP to ITCs and/or ITC-nitriles. In general, we have only located four published experimental investigations about GRP hydrolysis

linked to the gut flora. Information about the experimental setup and the detected GRP metabolites generated by the microbiota is summarized in Table No.1.

GRP hydrolysis *ex vivo* is demonstrated by Lai *et al*, (2010) using cecal microbiota from rats given GRP (150μmol/kg body weight) by gavage. Specifically, the MRS medium (which promotes the development of lactobacilli and other microorganisms) containing 0.5mM GRP showed a reduction in GRP levels over time. Following 12 and 24 hours of the experiment, there was a considerable increase in microbiota-mediated GRP hydrolysis. When 0.5mM GRP was added to RCM media (which promotes the development of clostridium, bifidobacteria and other microorganisms), a similar pattern was observed in the microbial hydrolysis of GRP, but only after 12 hours. Erucin nitrile was found to form under all conditions, but SFN was found to form solely in MRS medium. Additionally, Liu and colleagues (2017) showed that rats fed a 10% cooked broccoli diet for 0-14 days have myrosinase-like activity in their cecal microbiota. Specifically, the content of ITCs like SFN and erucin increased over time when the cecal microbiota was incubated with an excess of GRP. Rats fed broccoli for longer periods of time showed an increase in the microbial GRP hydrolyzing activity. This suggests that GRP's microbial hydrolysis rates are increased when it is present in the diet. Nevertheless, some research has shown that GRP is significantly converted to glucoerucin. For instance, a considerable conversion of GRP to glucoerucin and to a lesser amount, SFN, SFN-nitrile and SFN-conjugates was observed in an experimental model in which human fecal bacteria were subjected to a recurrent dose of GRP for seven 12-hour cycles. Another study by Li and colleagues (2011) found that the fecal microbiota of healthy people who were given a standardized meal that contained 200g of cooked broccoli had myrosinase-like activity. *Ex vivo* cultivation of fecal microbiota from specific human excretions with high or low ITC content using 50μM GRP produced varying degrees of GRP breakdown. More GRP could be broken down by bacteria from specific human excretions with high ITC content than by bacteria from excretions with low ITC level. However, the ultimate concentration of ITCs, like SFN, created by bacteria during incubation was negligible because they were unstable in the culture medium.

There was no proof that certain bacterial species and GRP hydrolysis to ITCs were directly related. However, microbial metabolism of GRP is adequate to increase SFN levels in the feces when plant myrosinase is not present. Zhang *et al*, (2023) shown, in example, that mice's ingestion of steamed broccoli sprouts containing inactivated plant myrosinase enhanced the presence of SFN in their stools. Furthermore, it was discovered that eating steamed broccoli raised the amount of SFN in the GIT, with the largest levels occurring in the colon, which also had the lowest GRP levels. The three types of GRP metabolites that the microbiota produces are as follows: These include (i) GLs like glucoerucin, (ii) ITCs like erucin and SFN, and (iii) ITC-nitriles like erucin-nitrile and SFN-nitrile. The structural formulae of GRP and the aforementioned GRP metabolites generated by the microbiota are displayed in Figure No.1. However, there is still a lack of knowledge on the metabolism of GRP linked to the microbiota. For instance, it is unclear if human cells manufacture the discovered chemicals or if the microbiota Human cells may make SFN-conjugates such glutathione SFN-conjugate (SFN-GSH) and SFN-N-acetylcysteine conjugate (SFN-NAC), as well as other known chemicals.

When GRP (172mg/kg body weight) was administered intragastrically to both germ-free and human microbiota-associated (HMA) mice, the mice's urine contained about 30% of the same amount of GRP. This suggests that a portion of GRP is not broken down and eliminated whole. When rats were given 150μmol/kg of GRP that was isolated from broccoli seed, Q and Jeffrey (2007) discovered that 5% of the GRP was intact. 20% of the oral dosage was excreted in urine, which included 0.65% free SFN, 2% SFN-nitrile, 12.5%

SFN-NAC, and 0.1% erucin. GRP and its metabolites, on the other hand, were not found in feces. These findings unequivocally demonstrate that a variety of factors influence the gut's ability to catabolize GRP, and the kind of food that humans and animals eat may be a significant element in this process. The GIT's metabolism of GRP and its physiologically active product SFN is shown schematically in Figure No.2. As previously stated, when cruciferous vegetables like broccoli are chewed, GRP becomes accessible to plant myrosinase, which causes GRP to be converted in the oral cavity to SFN and/or SFN-nitrile. The gut microbiota in the intestines either hydrolyzes GRP to erucin and/or erucin-nitrile, or converts it to SFN and/or SFN-nitrile, most likely via bacterial myrosinase. Furthermore, it is possible to interconvert SFN and erucin, GRP and glucoerucin, SFN-nitrile, and erucin-nitrile.

The intestine absorbs GRP metabolites created by the microbiota, which are then carried by blood to the liver and other organs before being partially expelled with feces. They are typically broken down via the mercapturic acid pathway. Because the electrophilic carbon in the SFN molecule and the nucleophilic thiol group of GSH spontaneously engage to produce the SFN-GSH conjugate, the first stage can already take place in the gut. The same reaction can also be catalyzed by intestinal glutathione-S-transferase (GST). The γ-glutamyltranspeptidase enzyme catalyzes the reaction in the liver where the generated SFN-GSH conjugates enter the mercapturic acid pathway, resulting in SFN-cysteinglycine (SFN-Cys-Gly). The SFN-Cys is created when cysteineglycinase separates the glycine from the SFN-Cys-Gly combination. N-acetyltransferase transforms the latter into SFN-NAC, which is then carried to the kidneys along with the blood and eliminated in the urine. The γ-glutamyltranspeptidase enzyme catalyzes the reaction in the liver where the generated SFN-GSH conjugates enter the mercapturic acid pathway, resulting in SFN-cysteinglycine (SFN-Cys-Gly). The SFN-Cys is created when cysteineglycinase separates the glycine from the SFN-Cys-Gly combination. N-acetyltransferase transforms the latter into SFN-NAC, which is then carried to the kidneys along with the blood and eliminated in the urine. Figure No.2 illustrates how erucin generated by the gut flora is processed similarly to SFN. Nevertheless, nothing is known about the detoxification processes of SFN-nitrile and erucin-nitrile (see the question marks in Figure No.2). Furthermore, to the best of our knowledge, erucin and erucin-nitrile were not reported if free SFN, SFN-nitrile, and SFN-NAC were found in the stool. This may have something to do with the excretion of trace amounts of erucin and its nitrile, which are hard to detect. Following a single serving of broccoli, the distribution of SFN metabolites in plasma, urine, and stool at various time points (24, 48 and 72 hours) revealed that: (i) SFN-nitrile was the only metabolite detected in plasma and as such, dominant at all time points; (ii) SFN-NAC was the main metabolite in urine between 0 and 3, 3-6 and 6-24 hours, while SFN-nitrile was the dominant metabolite between 24-48 and 48-72 hours; (iii) free SFN accounted for over 95% of detected metabolites in the stool after 48 and 72 hours, while free SFN was the major metabolite after 24 hours, followed by SFN-NAC and SFN-nitrile. A comparable urinary excretion pattern of SFN metabolites was shown in a study by Bouranis *et al*, (2021a). Specifically, six hours after individuals ingested a single dosage of broccoli sprouts containing 200μmol of SFN equivalents, SFN-NAC peaked and then steadily declined over the course of twelve to forty-eight hours.

However, the excretion of SFN-nitrile rose, peaking in six out of ten participants at six hours and in four others between twenty-four and forty-eight hours. It is evident that the amounts and qualitative makeup of GRP metabolites can fluctuate from person to person, most likely as a result of variations in the gut microbiota's makeup and metabolic activity.

Thus far, there has been evidence of a favorable correlation between SFN metabolism and gut microbiota representation. For instance, Bouranis *et al*, (2024) discovered that whilst members of the genus Blautia and Alistipes have a negative

association with SFN metabolite excretion, members of the genus Dorea, Bifidobacterium, and Ruminococcus torques have a positive association. Indeed, in the GIT, certain bacterial strains exhibit myrosinase-like activity.

Specifically, 309 bacterial sequence variants from genera including Lactococcus, Bifidobacterium, Lactobacillus, Bacteroides, Pseudomonas, Staphylococcus, Enterococcus and Streptomyces were found by Holman and colleagues (2023) to be linked to the expression of myrosinase-like enzymatic activity.

However, the makeup and functionality of the gut microbiota can also be impacted by GRP and SFN. For instance, the intestinal bacteria of people who ingest more GLs may be able to hydrolyze more GRP since the availability of GRP in the diet improved its microbial hydrolysis rates. The impact of SFN and GRP on the gut flora will be discussed in more detail in the following section.

The impact on the gut microbiota of glucoraphanin and sulforaphane, its bioactive derivative the function of gut microbiota and its qualitative and quantitative makeup are significantly influenced by diet. A particular microbial pattern may be beneficial or harmful. For instance, metabolic syndrome, cardiovascular disease, inflammatory bowel disease and neurological illnesses are linked to dysbiosis, also known as dysbacteriosis, an imbalance of the gut microbiota. We are thus what we consume.

Eating cruciferous vegetables high in GLs and ITCs alters the composition of the gut microbiota, which has an impact on the host's health. The impact of GRP and SFN on the gut microbiota in a number of recent research is displayed in Table No.2. For instance, C57BL/6 mice fed a high-fat diet (HFD) showed an increase in the richness and variety of bacterial species after taking 150μmol/kg body weight of GRP for six weeks.

In example, compared to the HFD group that did not eat GRP, GRP drastically changed the gut microbiota's community structure, increasing the abundance of Bacteroidetes and decreasing Firmicutes. Similar results were seen in C57BL/6 mice fed a high-fat diet (HFD) that included 1% broccoli seed extracts with 0.13% GRP and 0.322% mustard powder with plant myrosinase (Bankole *et al*, 2024). The proportions of Firmicutes and Bacteroidetes that consumed GRP were 80.4% and 15.9%, respectively, compared to 87.2% and 11.4% in the HFD group. Furthermore, mice treated with GRP showed a considerable increase in the phyla Actinobacteriota and Deferribacterota but a significant drop in the phylum Verrucomicrobiota.

Firmicutes/Bacteroidetes (F/B), the ratio between the two main phyla, is frequently described as a possible biomarker for a number of illnesses. Consuming GRP can, as previously shown, cause the quantity of Firmicutes to decline and Bacteroidetes to grow, which will cause their ratio to change downward. Conversely, an elevated F/B ratio may be regarded as a risk factor for the emergence of obesity. Koliada and colleagues (2017) demonstrated, for instance, that obese people had a much larger amount of Firmicutes and a lower number of Bacteroidetes than lean or normal-weight adults.

In fact, the F/B ratio rose as body mass index rose, supporting the link between gut microbiota and obesity. Therefore, eating cruciferous vegetables or preparations high in GRP/SFN may help prevent obesity and altering the gut flora may be the mechanism at play. It is significant to remember that the composition of the microbiota varies with the seasons.

For instance, samples taken in the summer had higher levels of Actinobacteria and lower levels of Bacteroidetes than samples taken in other seasons, while the content of Firmicutes was not affected by the season. Seasonal variation was thought to be linked to summertime consumption of a lot of fruits and vegetables.

The impact of SFN on the growth of forty-three common human commensals and diseases was investigated by Marshall *et al*, in 2023. Specifically, under aerobic conditions with 21% O2, SFN showed antibacterial capabilities by inhibiting the development of enteropathogenic *E. coli* EPEC ECE2348/69. SFN, however, had the opposite

effect at 0.01% O2 in anaerobic conditions. It promoted the growth of Escherichia coli EPEC ECE2348/69 by increasing its anaerobic respiration. This suggests that a large portion of the findings from aerobic studies should not be extrapolated to the anticipated *in vivo* outcomes, since they may differ entirely in the anaerobic environment of the GIT. We previously showed that the activity of antioxidant enzymes was linked to the varying oxygen sensitivity of different strains of *Escherichia coli*.

Therefore, it is reasonable to anticipate that the antioxidant potential and experimental settings, specifically the oxygen level, may affect the bacterium's susceptibility to SFN. It's interesting to note that SFN's effects on E. coli might be related to inhibiting the bacterial response to ROS at the level of OxyR, a master regulator that has active thiol groups that SFN may target.

In hyperuricemic rats, Wang *et al*, (2023) discovered that SFN administration reversed the increases in Clostridium bolteae, Clostridium innocuum, and Clostridium symbiosum abundance. Hyperuricemia was positively correlated with the latter bacterial species.

Furthermore, it changed the function of microorganisms and greatly expanded their diversity, which helped treat hyperuricemic rats. Chinese children and rats with autism spectrum disorders (ASD) showed promising therapeutic outcomes linked to the alteration of gut microbiota after receiving SFN for 12 weeks.

Specifically, network analysis revealed 25 taxa linked to rat social behavior, eight of which were linked to SFN therapy of rats that resembled ASD. Furthermore, 35 alterations in gut microbiota abundance were discovered to be associated with SFN treatment of ASD symptoms. Furthermore, in ulcerative colitis-affected mice, sulforaphane corrected intestinal dysbiosis. After seven days, the makeup of intestinal bacteria was not substantially changed by intragastric injection of 20mg/kg SFN.

But after 14 days, SFN dramatically raised the amount of Bacteroidetes and lowered the amount of Firmicutes in ulcerative colitis-affected mice that were treated with dextran sodium sulfate. Consuming SFN and its physiologically inactive precursor GRP may therefore help avoid dysbiosis and aid in the prevention or treatment of a number of physical and mental health conditions. The molecular process by which dietary glucoraphanin and sulforaphane preserve a balanced gut microbiota. Although the majority of intestinal bacteria are prokaryotic, the molecular mechanism of action of SFN in eukaryotes is well understood. Since gut health is unquestionably linked to a healthy gut microbiota, we will concentrate on examining the impacts of SFN on their home, which is the gut. The molecular mechanism of action of dietary SFN, which successfully supports intestinal homeostasis by preventing inflammation and oxidative stress, is schematically depicted in Figure No.6.

A temporary or permanent rise in the steady-state concentration of reactive oxygen species (ROS) causes oxidative alterations of biomolecules and cell death through necrosis or apoptosis. This phenomenon is known as oxidative stress. Increased intestinal barrier permeability and related gut dysbiosis may result from the latter. On the other hand, the Nrf2 (nuclear factor erythroid 2-related factor 2) signaling pathway, which regulates the cellular response to oxidative stress, is thought to be strongly activated by SFN.

In order to activate Nrf2 signaling, the electrophilic carbon of the isothiocyanate group of SFN interacts with the nucleophilic thiol group of Cys151 of the Keap1 protein. The latter causes antioxidant enzymes like SOD1, CAT, GST, GPx and NQO1 to have higher transcription levels. Thus, oxidative stress in the gut is reduced and the antioxidant defense system's capacity is increased. Furthermore, elevated Nrf2 signaling suppresses the inflammatory transcription factor NF-κB.

Importantly, GST enzyme is also a phase II detoxification enzyme, which helps to eliminate potentially toxic/toxic chemicals for both the gut microbiota and the host in general. All of the aforementioned factors contribute to intestinal homeostasis, which prevents gut dysbiosis. See the

text for further information. Abbreviations: Cul3, cullin 3; Keap1, Kelch-like ECH-associated protein 1; Cys 151, SFN-sensitive cysteine residue; Nrf2, nuclear factor erythroid 2-related factor 2; DLG, ETGE, Nrf2 motifs for Keap1 recognition/binding; Ub, ubiquitin; sMaf, small musculoaponeurotic fibrosarcoma; EpRE, electrophile responsive element; NF-κB, nuclear factor κB; SOD1, superoxide dismutase 1; CAT, catalase; GPx, glutathi.

Under homeostatic settings, transcription factor Nrf2 is produced but constantly susceptible to proteasomal degradation via Keap1 (Kelch-like ECH associated protein 1). In the cytoplasm, the Keap1 homodimer forms a ubiquitin E3 ligase complex with cullin 3 (Cul3), polyubiquitinating the Nrf2 protein and causing it to be continuously degraded by proteasomes. Keap1 is the primary negative regulator of Nrf2. It detects and binds the ETGE and DLG motifs in the structure of Nrf2 proteins, producing the Keap1-Nrf2 complex.

The first, ETGE, has a high affinity but slow rates of association/dissociation, whereas the second, DLG, binds rapidly but with a 100-fold lower affinity. The high-affinity ETGE, in particular, is thought to behave as a hinge, anchoring Nrf2 to Keap1, whereas DLG functions as a latch. Exposure to electrophiles such as SFN promotes alteration of numerous reactive cysteine residues of Keap1, resulting in instability of the binding of Keap1-DLG.

Takaya *et al*, (2012) discovered that the point Cys151 mutation dramatically lowered SFN-induced responsiveness to oxidative stress in mutant cells. In example, the expression of some Nrf2 target genes was dramatically reduced. These findings support the hypothesis that Cys151 alteration is critical for SFN-mediated Nrf2 signaling activation. Thus, SFN interacts with Cys151's thiol group, resulting in a partial loss of the Keap1-Nrf2 connection (Figure 3, right). As a result, polyubiquitination and proteasomal destruction of the Nrf2 protein are prevented, allowing its levels to remain stable. Furthermore, Nrf2 translocates into the nucleus, heterodimerizes with one of the small musculo-aponeurotic fibrosarcoma (sMaf) proteins, binds to the antioxidant responsive element (ARE) or electrophile responsive element (EpRE), and increases the transcription of genes that encode defense proteins/enzymes.

Antioxidant enzymes include superoxide dismutase 1 (SOD1), catalase (CAT), glutathione peroxidase (GP), GST, NAD(P)H quinone oxidoreductase 1 (NQO1) and others. They work together to eliminate ROS and its metabolites, thereby lowering oxidative stress.

Furthermore, as shown in Figure No.4, SFN has the potential to attenuate or disrupt the vicious cycle of oxidative stress and gut dysbiosis. Intestinal oxidative stress generated by high ROS levels changes tight junction proteins, leading to increased intestinal permeability, luminal bacteria invasion and dysbiosis.

The latter can activate the inflammatory process by identifying bacterial pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors (PRRs) on the host's immune cells. This activates the NF-κB pathway, which promotes the transcription of pro-inflammatory cytokines like IL-6 and IL-8. Furthermore, active immune cells produce considerable amounts of ROS, which increases oxidative stress (22) and completes the vicious cycle seen in the figure. SFN suppresses oxidative stress, inflammation, and increased intestinal permeability, so breaking the vicious cycle. Indeed, multiple studies have demonstrated the usefulness of SFN in increasing antioxidant status and avoiding oxidative stress in the gut, primarily by activating Nrf2 signaling.

Ma *et al*, (2023) demonstrated that SFN protects Cyprinus carpio haematopterus from oxidative stress caused by triphenyltin. SFN, in particular, increased antioxidant enzyme activity, including SOD, CAT and GPx, while also reducing inflammatory factor alterations. Furthermore, SFN treatment significantly reduced five inflammation-associated bacteria and restored normal gut microbiota composition after triphenyltin treatment. In another study, SFN reduced pro-inflammatory

cytokine levels while increasing tight junction protein expression in mice with dextran sulfate sodium (DSS)-induced ulcerative colitis. It also partially repaired the altered gut microbiota composition produced by DSS administration, including alterations in the relative abundance of Firmicutes, Bacteroidota and Verrucomicrobiota.

Furthermore, SFN treatment reduced colon and caecal mucosal epithelium damage in mice with N-butyl-N-(4-hydroxybutyl)-nitrosamine-induced bladder cancer by increasing tight junction protein expression, decreasing IL-6 release and preventing gut dysbiosis. Thus, the findings suggest that dietary SFN contributes to a healthy gut microbiota by avoiding the development of oxidative stress and inflammation in the intestines. However, the selectivity of SFN effects on the GIT microbiota remains an unanswered question[69].

THERAPEUTIC APPLICATIONS AND LIMITATIONS OF SULFORAPHANE

THERAPEUTIC APPLICATIONS

Cancer Chemoprevention and Therapy

One of the most extensively studied areas for sulforaphane is its anticancer activity. Research indicates that sulforaphane modifies multiple carcinogenesis pathways simultaneously, making it distinct from many single-target chemotherapeutic agents. A clinical trial by Li *et al*, (2011) in women with breast cancer demonstrated that daily consumption of broccoli sprout preparations reduced histone deacetylase (HDAC) activity in peripheral blood mononuclear cells, an epigenetic marker linked with tumor suppression. Similarly, in men with recurrent prostate cancer, Cipolla *et al*, (2015) observed a decline in prostate-specific antigen (PSA) levels following oral sulforaphane supplementation. These findings suggest that sulforaphane can act as both a chemopreventive and therapeutic molecule by targeting proliferation, angiogenesis and apoptosis pathways[70].

Neurological disorders

Sulforaphane has neuroprotective properties in neurodegenerative disorders. It activates phase II detoxifying enzymes in the brain and strengthens neural resilience to oxidative assaults. Following sulforaphane treatment, animal models of Huntington's and Parkinson's disease showed better dopaminergic neuron survival and decreased buildup of misfolded proteins. A pilot clinical trial in children with autism spectrum disorder found benefits in social responsiveness and communication after sulforaphane administration, demonstrating its potential beyond typical neurodegeneration.

Cardiovascular and Metabolic Benefits

Sulforaphane's anti-inflammatory and antioxidant properties promote vascular health. In randomized studies, broccoli sprout extracts improved endothelial function and reduced oxidised LDL levels in hypertensive individuals. Furthermore, patients with type 2 diabetes who received sulforaphane-rich preparations had lower fasting blood glucose levels and improved HbA1c compared to controls. These effects are related to regulation of the AMPK pathway, reduction of advanced glycation end products and increased insulin sensitivity.

Anti-microbial Effects

Apart from chronic illnesses, sulforaphane has antibacterial properties. Yanaka *et al*, (2009) found that regular eating of sulforaphane-rich broccoli sprouts dramatically reduced Helicobacter pylori colonization and stomach inflammation in humans. This dual property-direct antibacterial action and inhibition of infection-associated carcinogenesis-distinguishes sulforaphane as a natural antimicrobial chemopreventive drug[71].

Respiratory Health

Respiratory illnesses are another rising topic of attention. Sulforaphane has been proven in clinical tests in patients with COPD and asthma to increase antioxidant gene expression in the airway epithelium. Although the outcomes are mixed, preliminary data suggest that airway oxidative stress and inflammation have improved, perhaps reducing the frequency of exacerbations.

LIMITATION

Despite its vast therapeutic use, sulforaphane has significant limits.

Instability in Food and Formulations

Sulforaphane is extremely unstable and degrades quickly when exposed to heat or lengthy storage. As a result, consuming cooked cruciferous vegetables often results in significantly lower amounts than raw sprouts. Clinical heterogeneity in outcomes frequently derives from this instability[72].

Variable Bioavailability

One key difficulty is the heterogeneity of sulforaphane absorption. Its conversion into glucoraphanin is dependent on myrosinase activity, which can be decreased during cooking or vary according to gut microbiota. For example, one study found that patients who took glucoraphanin supplements without active myrosinase had plasma levels that were nearly ten times lower than those who received sulforaphane-rich extracts[73].

Rapid Elimination

According to pharmacokinetic studies, sulforaphane is swiftly conjugated and removed via the mercapturic acid pathway, with a half-life of less than three hours. To keep therapeutic plasma levels stable, frequent doses or sustained-release formulations are required.

Interindividual Response

Sulforaphane supplementation does not work the same way for everyone. Genetic polymorphisms in detoxification enzymes, such as GSTM1, dramatically change metabolism and excretion, resulting in varying protective effects. This was verified in human trials, where GSTM1-null individuals had higher systemic exposure but increased variability in outcomes[74].

Clinical Evidence Gaps

Although intriguing, existing clinical results are hampered by small sample sizes, brief intervention times and diverse formulations. For example, some autism and cancer trials indicate advantages, while others show little or no clinical change. Without large-scale, standardized research, sulforaphane cannot be recommended as a mainstream medicinal agent.

Potential Adverse Effects

High doses of sulforaphane-rich supplements may produce gastrointestinal distress, bloating, or diarrhea. Furthermore, excessive consumption of cruciferous vegetables might disrupt iodine metabolism, raising concerns among people with thyroid disease[75].

Future Prospects of Sulforaphane

Because of its vast range of biological actions, sulforaphane (SFN) remains one of the most extensively investigated phytochemicals. While preclinical and early-phase clinical studies have shown promise in cancer chemoprevention, metabolic control and neuroprotection, the next phase of research will address formulation, delivery and tailored application problems. Sulforaphane's future prospects include turning laboratory findings into clinically proven medicines and functional meals.

Development of Advanced Delivery Systems

One of the most important future endeavors will be to increase sulforaphane stability and delivery. The molecule is inherently unstable and quickly digested, which limits its bioactive potential. To overcome this, various delivery methods are being studied, such as nanoparticle encapsulation, liposomal formulations and polymer-based carriers. According to research using nanoparticles for administration, sulforaphane has a longer plasma retention duration and better tissue dispersion than standard extract[s76].

Similarly, enteric-coated tablets and microencapsulation technologies are being changed to ensure proper release in the small intestine, leading in increased absorption. These technological developments are expected to make sulforaphane supplementation more consistent and clinically useful.

Role in Personalized Nutrition and Precision Medicine

Future sulforaphane applications are likely to grow within the context of individualized nutrition. Interindividual changes in gut microbiota and genetic variants in glutathione-S-transferase enzymes appear to have a major impact on

sulforaphane metabolism. Personalized techniques based on nutrigenomics and microbiome analysis may allow for the most effective sulforaphane therapies. Individuals with low microbial myrosinase activity, for example, may be given probiotics designed to express this enzyme, resulting in more efficient glucoraphanin-to-sulforaphane conversion. This precision approach has the potential to transform sulforaphane from a general dietary supplement into a tailored nutraceutical intervention.

Integration into Chronic Disease Management

Sulforaphane is increasingly being investigated as an additional therapy for chronic disorders. Its capacity to influence oxidative stress, inflammation, and epigenetic regulation at the same time sets it apart from traditional single-target medications. Sulforaphane is now being studied in clinical studies for type 2 diabetes, cardiovascular disease and autism spectrum disorder. If large-scale, long-term trials show that sulforaphane is helpful, it might be included in dietary guidelines or recommended in addition to conventional therapy. Furthermore, its antibacterial activity against Helicobacter pylori and involvement in respiratory health indicate prospective applications in infection control and pulmonary medicine[77,78].

Agricultural and Food Industry Applications

Another interesting strategy is to biofortify food crops with sulforaphane precursors. Breeding or genetically altering broccoli and other crucifers to contain more glucoraphanin could provide a long-term, dietary source of sulforaphane. Controlled growth of broccoli sprouts is already being sold, and future opportunities may include functional foods enriched with sulforaphane extracts or myrosinase enzymes. This technique could fill the gap between pharmaceutical therapies and preventive nutrition, making sulforaphane more accessible to a larger population.

Combination Therapies and Synergistic Potential

Future studies will also look at sulforaphane in combination with other bioactive chemicals or medications. Preclinical investigations indicate that when sulforaphane is coupled with curcumin, resveratrol, or conventional chemotherapeutic drugs, it enhances apoptosis in cancer cells[79]. Such combination techniques may allow for lower doses of cytotoxic medications while retaining efficacy, reducing adverse effects. This line of research has the potential to greatly enhance sulforaphane's clinical value in oncology and other areas.

Addressing Current Limitations through Research

Although promising, sulforaphane's future clinical success is contingent on overcoming current restrictions. Research must concentrate on addressing heterogeneity in bioavailability, developing optimal dosing regimens and undertaking comprehensive long-term safety assessments. Future trials using bigger cohorts and standardized formulations are required to validate therapeutic benefits across groups. Furthermore, more thorough molecular investigations are required to comprehend sulforaphane's role in epigenetic reprogramming, microbiome modulation and immunological control.

Table No.1: Microbiota-produced glucoraphanin metabolites in *ex vivo* studies, Abbreviations and marks: GRP, glucoraphanin; SFN, sulforaphane

S.No	Experimental conditions	Shown increased production of metabolites	Reference
1	Rat cecal microbiota from rats pretreated with GRP (150µmol/kg bodyweight) cultivated *ex vivo* with 0.5mMGRP	SFN, erucin- nitrile	Lai *et al*, (2010)
2	Rat cecal microbiota from rats fed10% cooked broccoli diet for 0-14 days cultivated ex vivo with 183µM GRP	SFN, erucin	Liu *et al*, (2017)
3	Human fecal bacteria exposed to repeated dose of GRP for seven 12-h cycles	Glucoerucin, SFN, SFN-nitrile	Kellingray *et al*, (2014)
4	Fecal microbiota from healthy individuals fed with standardized meals containing 200g of cooked broccoli cultivated *ex vivo* with 50µM GRP	Total isothiocyanate such as SFN and erucin	Li *et al*, (2011)

Table No.2

S.No	Experimental models	Effect on the gut microbiota	Reference
1	C57BL/6 mice consumed high-fat diet with 150µmol/kg body-weight GRP	Phyla bacteroidetes ↑ and firmicutes↓	Xu *et al*, (2020)
2	C57BL/6 mice consumed high fat diet containing 1% broccoli seed extract with 0.13% GRP	Alpha diversity ↑, phyla firmicutes and verrucomicrobiota ↓, phyla bacteroidetes, Actinobacteriota and Deferribacterota↑	Bankole *et al*, (2024)
3	Hyperuricemic sprague-dawley rats treated with 10mg/kg mixture of GRP and myrosinase by oral gavage	Firmicutes/Bacteroidetes ratio↑, Bacteroides cellulosilyticus and Clostridium boltea↓	Wang *et al*, (2023)
4	43 commensals and pathogens from human fecal or gastrointestinal biopsy samples cultivated with 10µM SFN at 0.1% oxygen	No significant change were found, however, 55% of the isolates showed a tendency to increasd growth. Under 0.01% oxygen, *Escherichia coli* ECE2348/69 showed a significant increase in growth and 20µM SFN. However in aerobic conditions (21% oxygen), SFN at concentration of 5µM-20 inhibited it's growth	Marshall *et al*, (2023)
5	Autism spectrum disorders like rats intrapertioneally injected with SFN 20mg/kg	Bacteroidetes and Actinobacteria↑ , genera Prevotella Peptostreptococcus and Oribacterium were positively correlated with SFN treatment	Yang *et al*, (2023)
6	C57BL/6 mice with ulcerative colitis intragastric administered with 20mg/kg SFN	Phyla Bacteroidetes ↑ and Firmicutes ↓, Firmicutes/ bacteroidetes ratio↑	Zhang *et al*, (2020)

Figure No.1: Broccoli and Cabbage

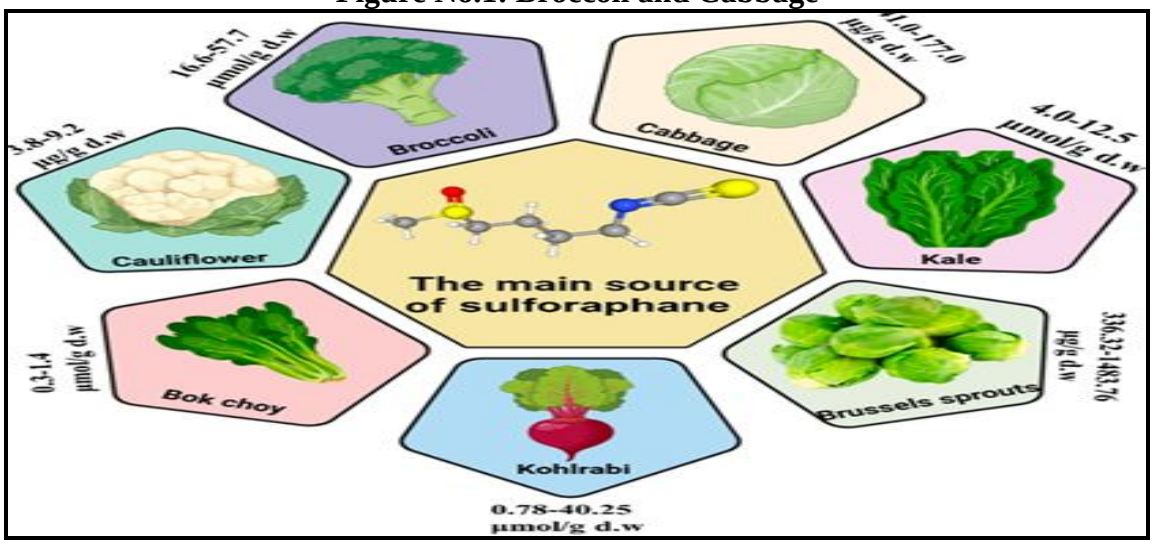

Figure No.2: The main source of Sulforaphane

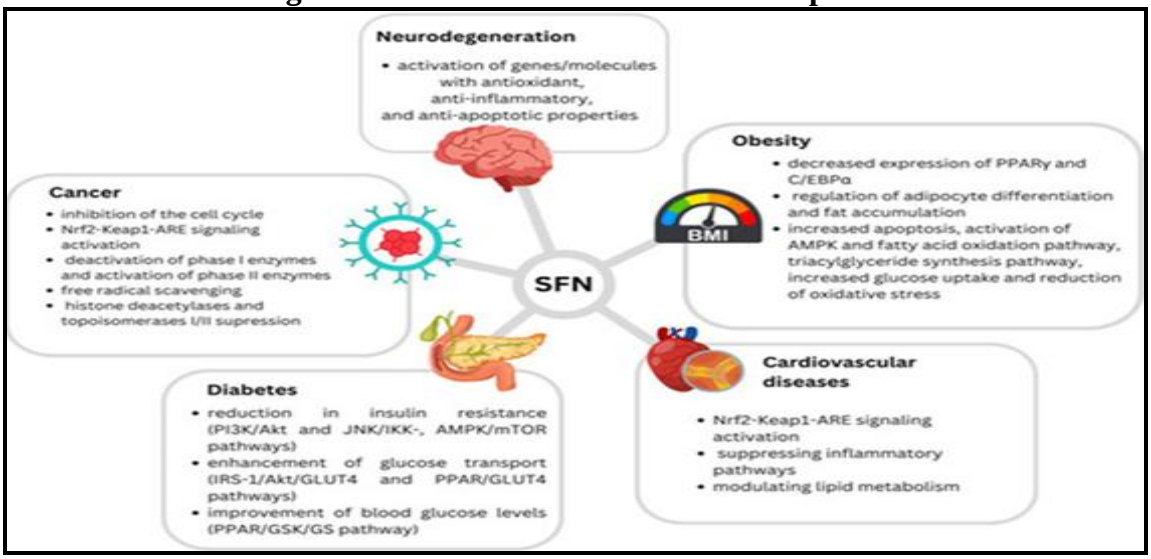

Figure No.3: Proposed mechanisms of SFN's beneficial effects

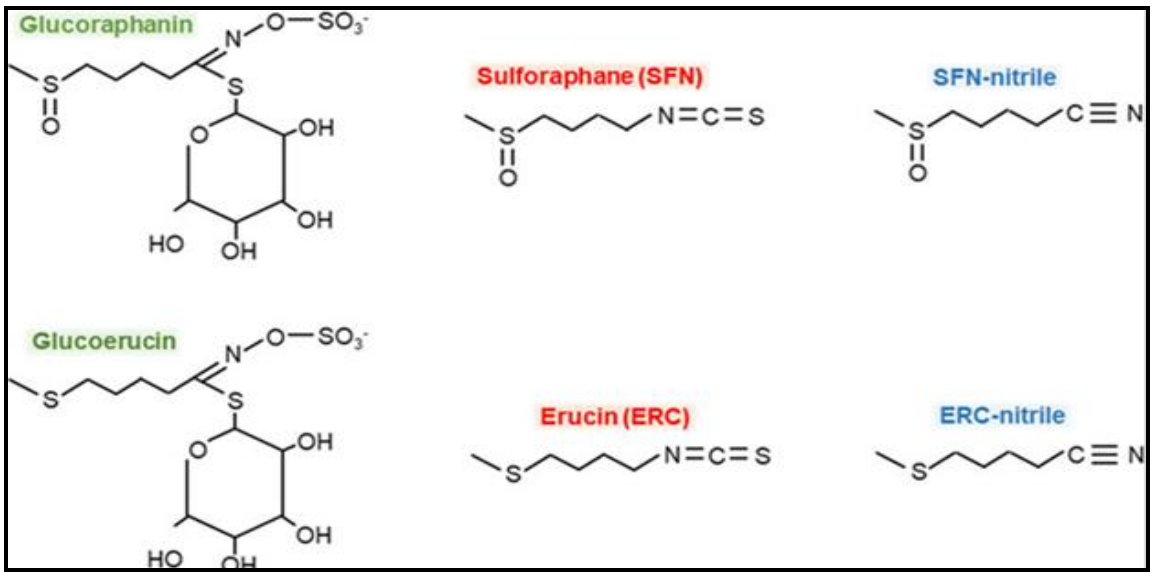

Figure No.4: Chemical formulas of glucoraphanin and its microbiota-produced metabolites, Green color – glucosynolates, red – isothiocyanates, blue – isothiocyanate-nitriles

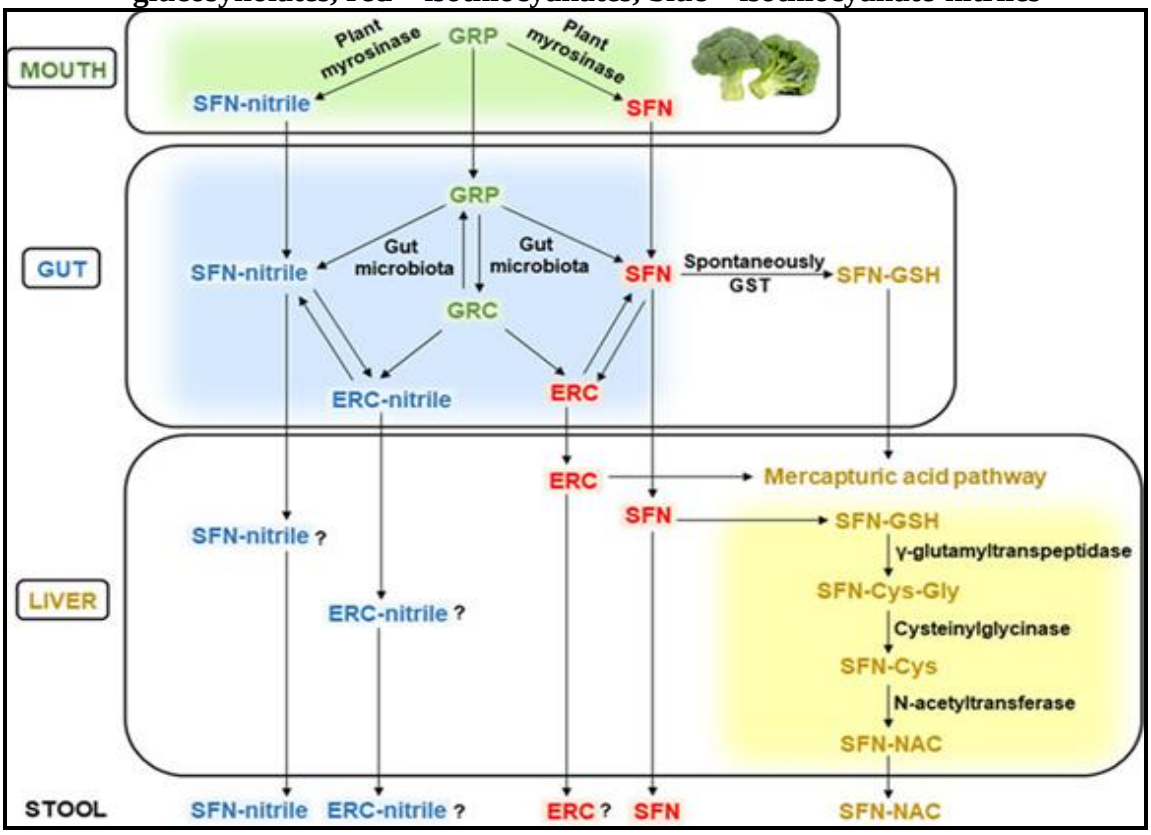

Figure No.5: Metabolism of glucoraphanin in the human body, Abbreviations: GRP, glucoraphanin; SFN, sulforaphane; GRC, glucoerucin; ERC, erucin; GST, glutathione-S-transferase; SFN-GSH, SFN-glutathione conjugate; SFN-Cys-Gly, SFN-cysteinglycine conjugate; SFN-Cys, SFN-cystein conjugate; SFN-NAC, SFN-N-acetylcysteine conjugate. See the text for details

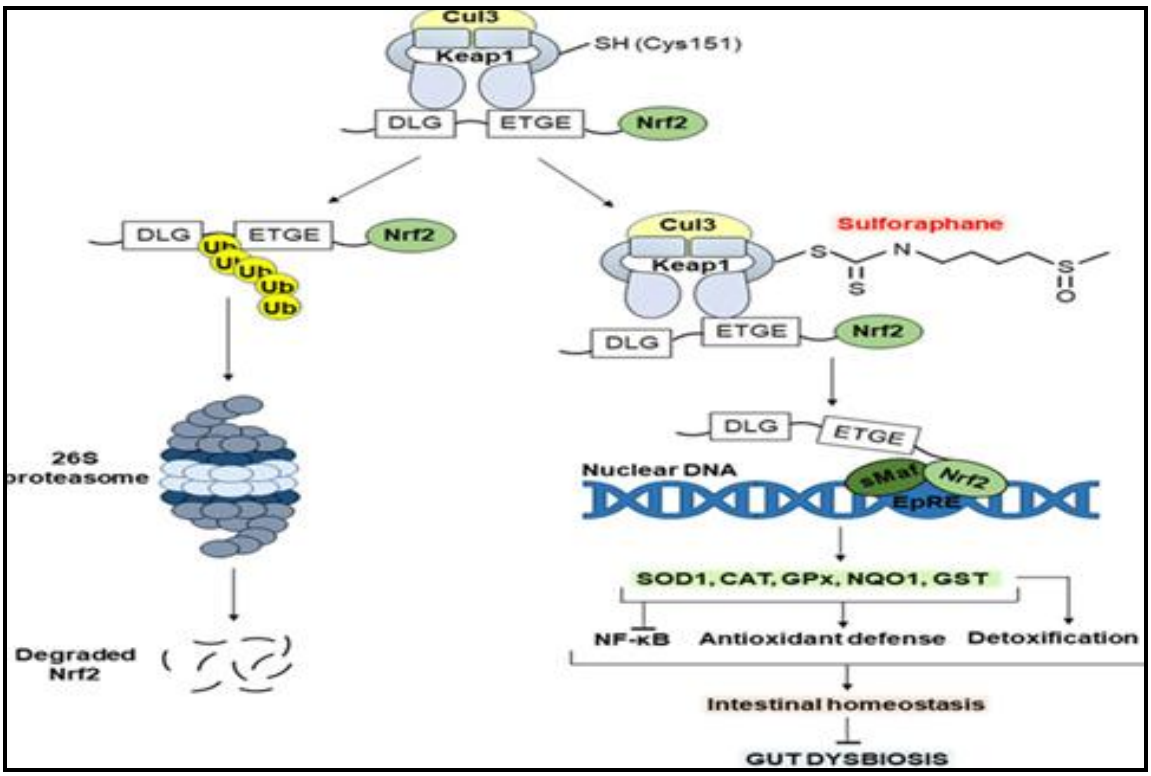

Figure No.6: Molecular mechanism of action of sulforaphane (SFN)

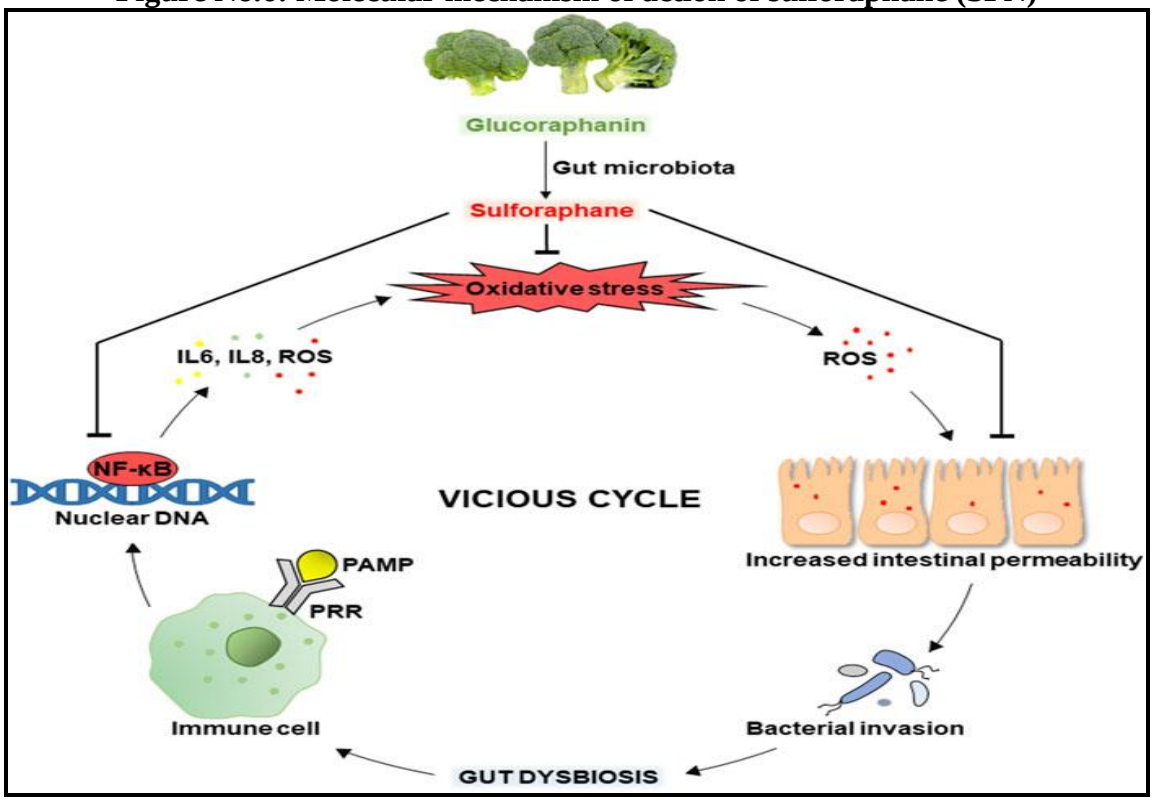

Figure No.7: The vicious cycle of oxidative stress and gut dysbiosis: the role of sulforaphane

CONCLUSION

Sulforaphane has emerged as one of the most intensively researched dietary phytochemicals over the last two decades, owing to its various biological activity and broad therapeutic potential. Sulforaphane, derived from cruciferous vegetables such as broccoli, cabbage and kale, has shown promise in moderating oxidative stress, inflammation and epigenetic regulation, all of which contribute to the pathophysiology of a variety of chronic diseases. A large body of preclinical research has shown its usefulness in cancer chemoprevention, metabolic control, neuroprotection and even antibacterial action. These findings are reinforced by an increasing number of early-phase clinical trials, which demonstrate sulforaphane's potential as both a preventative and therapeutic drug. Despite these positive developments, several difficulties must be overcome before sulforaphane may be effectively integrated into clinical practice. The main concerns include bioavailability, stability and variability in individual responses. The chemical is inherently unstable and undergoes rapid metabolism, resulting in variable absorption among populations. Furthermore, alterations in the composition of the gut microbiota and genetic polymorphisms in detoxification enzymes, such as glutathione-S-transferases, can have a major impact on sulforaphane's bioefficacy. To overcome these obstacles, sophisticated formulation tactics, such as nanoparticle-based delivery systems, encapsulation techniques and food crop biofortification with glucoraphanin precursors, would be required. Another crucial concern as we move forward is the necessity for large-scale, long-term clinical trials. While early human research have yielded useful insights, sample sizes have frequently been small and durations brief. For sulforaphane to progress from a potential phytochemical to a clinically recognized intervention, strong evidence from multi-center randomized controlled studies is required. Such studies will not only determine efficacy, but will also address safety concerns associated with long-term or high-dose use. Furthermore, establishing optimal dosage ranges and explaining interactions with existing drugs will be critical to assuring safe therapeutic applications. Sulforaphane has potential applications beyond clinical treatment, including nutrition, agriculture and public health. Biofortification of cruciferous vegetables, regulated production of broccoli sprouts, and the creation of functional meals supplemented with sulforaphane or myrosinase enzymes can dramatically increase availability to this molecule. Integrating sulforaphane into preventive healthcare initiatives has the potential to lower the burden of chronic diseases at the population level, especially in areas with high incidence of metabolic and inflammatory disorders. Furthermore, sulforaphane's ability to modulate immune responses and enhance detoxification pathways shows its potential as a natural agent for combating environmental toxins and pollutants in urban settings. Looking ahead, the future of sulforaphane research is bright, particularly in the contexts of personalized nutrition and precision medicine. Advances in nutrigenomics and microbiome studies indicate that sulforaphane therapies could someday be personalized to individual genetic and microbial profiles, enhancing therapeutic effects. Furthermore, its synergistic potential when paired with other phytochemicals or chemotherapeutic drugs opens up new possibilities for integrative oncology and chronic illness management. In conclusion, sulforaphane exemplifies how naturally occurring food chemicals can play an important role in modern medicine. It bridges the gap between diet and pharmacology, allowing for both preventative and therapeutic interventions. While issues like as stability, delivery and clinical validation persist, ongoing research and innovation are likely to overcome these obstacles. If present trends in translational research, bioengineering and nutraceutical development continue, sulforaphane could become a key component of functional medicine, with uses ranging from disease prevention to complementary clinical therapy. Finally, the incorporation of sulforaphane into everyday dietary practices,

supported by scientific evidence, may significantly contribute to global policies aiming at increasing human health and lifespan.

ACKNOWLEDGMENT

The authors wish to express their sincere gratitude to Suyash Institute of Pharmacy, Hakkabad, Gorakhpur, Uttar Pradesh, India for providing necessary facilities to carry out this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Ankita Singh *et al*. Sulforaphane: A bioactive phytochemical in disease prevention and health promotion, *International Journal of Research in Pharmaceutical and Nano Sciences,* 14(5), 2025, 236-262.