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Protective Role of Sulforaphane against Multiorgan Toxicity in Rats: An *In-vivo* and *In-vitro* Review Study

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Abstract

Sulforaphane [1-isothiocyanate-(4R) -(methylsulfinyl) butane] is a natural dietary isothiocyanate produced by the enzymatic accomplishment of the myrosinase on glucopharanin, a 4-methylsulfinylbutyl glucosinolate contained in cruciferous vegetables such as broccoli, brussel sprouts, and cabbage. Exploring of this compound against various oxidative degenerative diseases such as hepatic, nephro and cardiac diseases is growing because of its anticarcinogenic and cytoprotective properties. In several invivo and invitro experimental paradigms proved SFN and its compounds are having capacity to protects against various xenobiotics induced oxidative stress mediated diseases such as focal cerebral ischemia, lung inflammation, intracerebral hemorrhage, ischemia and reperfusion induced acute cardiac, hepatic, renal failure, and cancer etc. Sulforaphane is an indirect antioxidant compound is able to induce/activate numerous cytoprotective proteins, including antioxidant enzymes, through the Nrf2/ARE pathway. Because, it poses the powerful electrophiles, attributable to the central carbon atom of the -N= C= S group, which reacts readily with sulfur- nitrogen- and oxygen-based respective antioxidant genes such as heme oxygenase-1, NAD(P)H: quinone oxidoreductase, glutathione-S-transferase, gamma-glutamyl cysteine ligase, and glutathione reductase and induced Nrf2 gene for Phase II enzymes. In conclusion, sulforaphane is a promising antioxidant agent that is effective to attenuate oxidative stress and tissue/cell damage in different in-vivo and in-vitro experimental animals.

Keywords: *Sulforaphane, Oxidative stress, rats, liver, kidney, heart, ROS*

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INTRODUCTION

Nutrition plays an imperative role in our health and well-being. According to the great quotes by *Hippocrates (431 BC)* "*Let food be thy medicine; and medicine be thy food*". Apart from the already known dietary constituent; in the recent years, there has been a growing attention in certain compounds having massive health property which comprises antioxidants and phytochemicals. The term phytochemical refers to a diversity of non-nutritional biologically dynamic compounds occurring in plant foods that give a mixture of health benefits beyond basic nutrition. Phytochemical accurately mean "Plant chemicals". Scientists have recognized thousands of diverse phytochemicals, found in vegetables, fruits, beans, whole grains, nuts and seeds (Table 1). Consumption of plant foods loaded in phytochemical may assist to prevent at least one in every five cases of cancer, as well as other serious ailments such as liver, kidney, heart, lungs, brain and testicular diseases. Since, researchers exploring the way of phytochemicals prevent disease, but not clear. However, they identified the following ancestry. i) It stimulates the immune system, the body's defence against viruses, bacteria and other disease-causing agents. ii) Reduces oxidation that is caused by molecules called "free radicals" can cause abnormalities in cells that may eventually lead to cancer. iii) Triggers death of damaged cells that may be precursors to cancer. iv) Prevents DNA damage and helps with DNA repair mechanisms. v) Helps to regulate hormones, reduces inflammation and slows the growth rate of cancer cells. Table 1 shows the types of phytochemicals derived from different plant sources and its possible benefits. Intake of

Table 1: *Types of Phytochemicals.*

Phytochemicals	Plant sources	Possible benefits
Carotenoids (beta-carotene, lycopene, lutein, zeaxanthin)	Red, orange and green fruits and vegetables including broccoli, carrots, cooked tomatoes, leafy greens, sweet potatoes, winter squash, apricots, cantaloupe, oranges and watermelon.	May inhibit cancer cell growth, work as antioxidants and improve immune response.
Flavonoids (anthocyanins, quercetin)	Apples, citrus fruits, onions, soybeans and soy products (tofu, soy milk, edamame, etc.), coffee and tea.	May inhibit inflammation and tumor growth; may aid immunity and boost production of detoxifying enzymes in the body.
Indoles and Glucosinolates (sulforaphane)	Cruciferous vegetables (broccoli, cabbage, collard greens, kale, cauliflower and Brussels sprouts)	May induce detoxification of carcinogens, limit production of cancer-related hormones, block carcinogens and prevent tumor growth.
Inositol (phytic acid)	Bran from corn, oats, rice rye and wheat, nuts, soybeans and soy products (tofu, soy milk, edamame, etc.)	May retard cell growth and work as antioxidant.
Isoflavones (daidzein, genistein)	Soybeans and soy products (tofu, soy milk, edamame, etc.)	May inhibit tumor growth, limit production of cancer-related hormones and generally work as antioxidant
Isothiocyanates	Cruciferous vegetables (broccoli, cabbage, collard greens, kale, cauliflower and Brussels sprouts)	May induce detoxification of carcinogens, block tumor growth and work as antioxidants
Polyphenols (ellagic acid, resveratrol)	Green tea, grapes, wine, berries, citrus fruits, apples, whole grains and peanuts	May prevent cancer formation, prevent inflammation and work as antioxidants
Terpenes (perillyl alcohol, limonene, carnosol)	Cherries, citrus fruit peel, rosemary	May protect cells from becoming cancerous, slow cancer cell growth, strengthen immune function, limit production of cancer-related hormones, fight viruses, work as antioxidant

Sources: www.villanova.edu/healthpromotion

phytochemicals (polyphenols, tocopherols, tocotrienols, carotenoids, and ascorbic acid) has been associated with the maintenance of good health as well as prevention/treatment of many health conditions including cancer, cardiovascular diseases, diabetes, hypertension, stroke, metabolic syndrome and other degenerative diseases. This review aims to critically analyze the available literature (*in-vivo* and *in-vitro*) regarding the hepato, renal and cardio protective effects of Sulforaphane with special emphasis on its mechanisms of action against different chemical substances induced toxicity in rats.

WHAT IS SULFORAPHANE?

Sulforaphane is a dietary isothiocyanate which is synthesized from precursor found in cruciferous vegetables of the genus Brassica such as cauliflower, broccoli, kale, Cole crops, cabbage, collards and Brussels sprouts and mustards and cress as well as in the other genera Radish (Raphanus sps) [1,2]. Sulforaphane [1-isothiocyanate- (4R) - (Methylsulfinyl) butane] (Figure 1) is natural compound widely studied since the 1980s decade given that it has chemotherapeutic properties including anti-proliferative and anti-angiogenic properties. However, beyond is an anti-cancer property, current research has also strongly focused on the effects of sulforaphane against important pathologies including hyperglycemia and damage to liver, kidney, heart, brain and muscle among others [3].The 4-methylsulfinylbutyl glucosinolate (glucoraphanin) is the sulforaphane precursor, which is generally found in high concentration in broccoli (0.8–21.7 µmol/g of dry weight) [4].

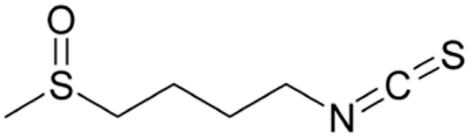

Fig. 1: *Chemical structure of Sulforaphane*

Recent research showed that glucoraphanin (4-Methylsulfinylbutyl glucosinolate) are important constituent in broccoli and it can produce sulforaphane when hydrolyzed by myrosinase. Sulforaphane has attracted researcher's attention as promising cancer chemopreventive agent [5]. Much evidence

suggests that the major mechanisms of chemo protection by isothiocyanates depend on the induction of Phase II detoxication enzymes and the inhibition of Phase 1 enzymes that are involved in the activation of certain carcinogens. Isothiocyanates are powerful electrophiles, a property attributable to the central carbon atom of the =N= C= S group, which reacts readily with sulfur- nitrogen- and oxygen-based nucleophiles. In many studies, sulforaphane can reduce the incidence of a number of forms of tumer [6–9]. Glucosinolates are physically segregated from β-thioglucoside glucohydrolase enzymes (EC 3.2.3.1) also named Myrosinase, which comes into contact with its substrate when the plant is injured in the processes such as pathogen attack, chewing, chopping, and preparing for human consumption and as a result, the enzymatic hydrolyzes formation of sulforaphane as the major reaction product [10,11]. Table 2 shows the protective efficacy of SFN against different xenobiotics with different dose levels in *invitro* and *in-vivo* studies in rats.

SULFORAPHANE EFFECTS ON HEPATOTOXICITY

Liver is responsible for maintaining the body metabolic homeostasis has been considered as the target organ and largest repository soft tissue followed by kidney, hence it can be easily affected by diversified chemical compounds [12]. Beak et al. [13] demonstrated the protective effects of SFN on hepatotoxicity with extract of young radish **(***Raphanus sativus.L*) cultivated with sulfur (sulfur radish-extract) and sulforaphane on carbon tetrachloride induced liver injury in mice. It was observed that increased LPO, ALT, and necrosis in hepatocytes of mice. The hepato-protective effect of SFN was assessed with administration of 0.2 to 5 µmol/L for 24 h, showed induction of phase II antioxidants via Nrf2 pathway and ameliorates the CTC induced hepatic injuries. Similarly, Zhao et al. [14] also, observed the protective efficacy of SFN against intestinal ischemia reperfusion induced hepatic injury, when pretreatment with sulforaphane ameliorates ischemia-reperfusion (increased asparate aminotransferase and alanine aminotransferase in blood serum, decreased SOD and GPx activities and GSH content with increased in myeloperoxidase) in liver. This hepatic protection may be associated with the increased Nrf2 and HO-1 pathway mediated antioxidants production in liver tissue [15].

Jung-Ran-Noh et al. [16] further proved the efficacy of SFN against acetaminophen (APAP) 15 mM incubated with primary hepatocytes for 14 h with 10 µM (SFN) for 6 h. It has been demonstrated that SFN administration significantly arrests the cellular oxidation and reduces the toxic effect of APAP induced lipid peroxidation that led to cellular viability. These results indicate that SFN does not have any toxicity on primary hepatocytes as the tested concentrations. The primary hepatocytes were treated with both SFN and APAP to observe the protective effect of SFN on APAP- induced cell death and lipid peroxidation as a maker of oxidative stress. These results indicated that SFN attenuated the cell toxicity through inhibiting APAP- induced oxidative stress [16]. The mechanism of SFN against various xenobiotics induced hepatotoxicity has been given in Figure 2.

SULFORAPHANE EFFECTS ON NEPHROTOXICITY

The kidney is the potential site of all kind of oxidative toxicity because kidney cells are exposed to relatively high concentration of different xenobiotics substances. Kidney failure is the most sever stage of kidney disease. Yoon et al. [17], have been reported the *in-vivo* efficacy of SFN (500 µg/kg/iv 24 h) against cisplatin induced renal ischemia in rat. It was shown that sulforaphane (a single intravenous injection in rats) able to ameliorate the renal damage by biochemical and histological markers. The protective effect was associated to Nrf2 nuclear translocation, phase II enzymes induction and decrease in oxidative stress in renal tissue (Figure 3). Similarly, Beltron et al. [18] also observed the protective role of SFN against cisplatin administrated with 7.5 mg/kg BW in rats showed elevated kidney intracellular and vascular adhesion molecules in renal tissues due to ROS induced damage. Cisplatin (CIS) markedly increased inflammatory response and renal markers (Urea, uric acid and creatinine) in the kidney; however, SFN

treatment about 500 µg/kg was able to ameliorate the renal hypoxia-re-oxygenation cytotoxicity which was accompanied by induction of phase II enzymes and decrease in Keap 1 protein levels as compared to control. *In-vitro* study in human embryonic kidney 293 cells (HEK293) and human proximal tubule cells (hPTC) revealed the protective efficacy of SFN against cisplatin induced cytotoxicity [19]. This might be possible by SFN via up-regulation of antioxidant gene GCLC and NQO1 in human by inhibiton of proapototic gene by its potent antioxidant and antiapoptotic property.

Table 2: *Protective Effects of Sulforaphane in in-vivo and in-vitro Studies.*

Experimental Model	Sulforaphane and toxic compound dose levels	Biomarkers	References
Mice, Hepatocytes	SFN 0.2 to 5 µmol/L treatment to 24 h. Carbon tetrachloride liver injury	Increase ↑ LPO, ALT, Necrosis. ↑ Expression of the π class of GST through Nrf2 pathway	Beak et al. 2008.
Rat, (*invivo*) Liver injury induced by intestinal ischemia/ reperfusion	Pretreatment of SFN 3 mg/kg/ip, 1 h before Ischemia. Against cisplatin	Regulate the Nrf2/ ARE, Decrease ↓ ALP, AST in blood serum and ↑ SOD, GPx, GST, and ↑ liver expression ion of Nrf2 and HO- 1	Zhao et al.2010.
Rat, Cell (*invivo*) viability, primary hepatocytes	SFN- 5 mg/kg for 6 h, APAP- 300 mg/kg/bw incubate for 14h	AST, ALT ↑, and GSH↓ ↓ Nrf2, and Bcl2	Jung- Ran Noh et al. 2010.
Rat, Renal damage ischemia and reperfusion	SFN-500 µg/kg/iv 24 h before the renal ischemia Against Cisplatin	↓ oxidative stress in renal tissue, ↓ in Keap 1 protein levels.	Yoon et al. 2008.
Rat, (*invivo*) Inflammatory response in kidney	SFN- 500 µg/kg CIS- 7.5 mg/kg	↓ Nrf2 expression ICAM-1, and VCAM-1↑	Beltron et al. 2012.
Rat, Cardiac damage Aortic smooth muscle A10 cells	SFN-0.25 to 5 µM for 48 h Against Cisplatin	Prevent cell death, Ros ↑protection, and oxidative cytotoxicity↑	Zhu et al. 2008.
invitro- cardiac H9c2 cells.	SFN- 2.5 µM DOX- 5 µg/ml	Mitochondrial respiratory complex enzyme, ↑ cardiomyopathy ↑ Protection from DOX toxicity would be Nrf2 dependent.	Singh et al. 2015.
Sprague-Dwelly Rat, Heart damage Ischemia and reperfusion	500 µg/kg/ip daily for 3 days before isolation perused Langendoroff heart	Prevent LPO heart. Prevent the decrease in protein expression (Bax, Bad, Cas3 ↓) of some antioxidants (SOD, CAT ↑)	Piao et al. 2010.

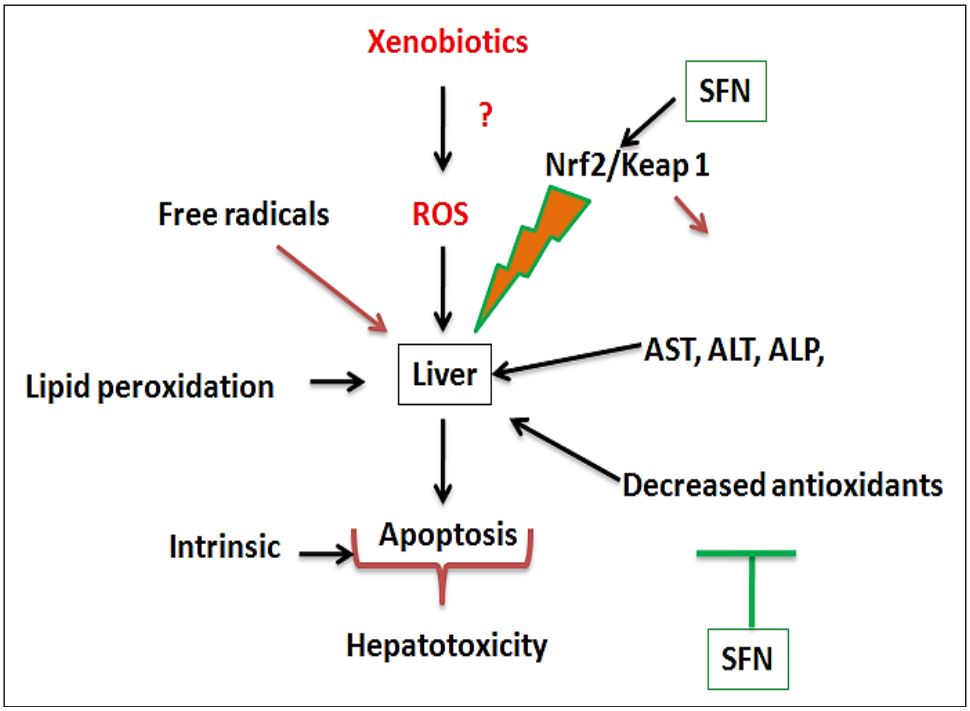

Fig. 2: *Possible Mechanism by which SFN Ameliorates Hepatotoxicity.*

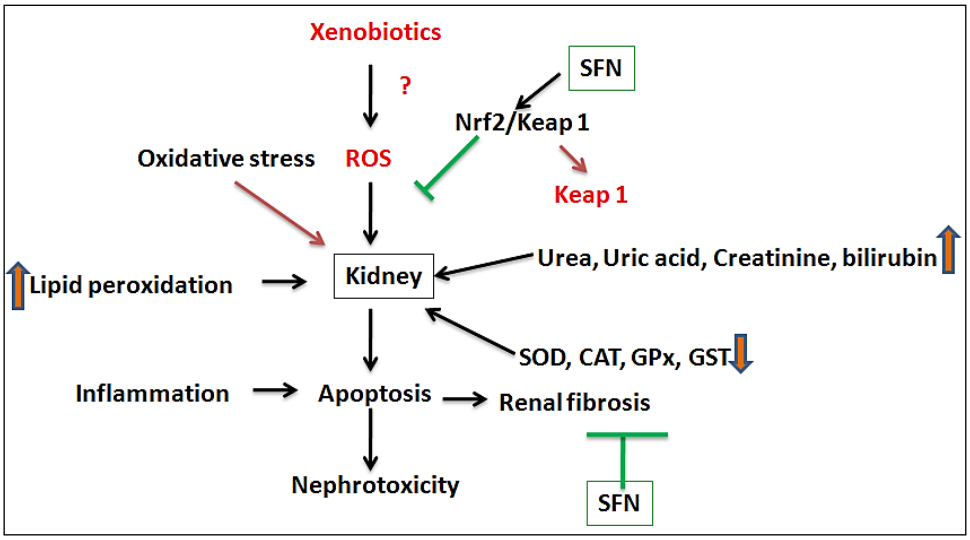

Fig. 3: *Possible Mechanism by which SFN Ameliorates Nephrotoxicity.*

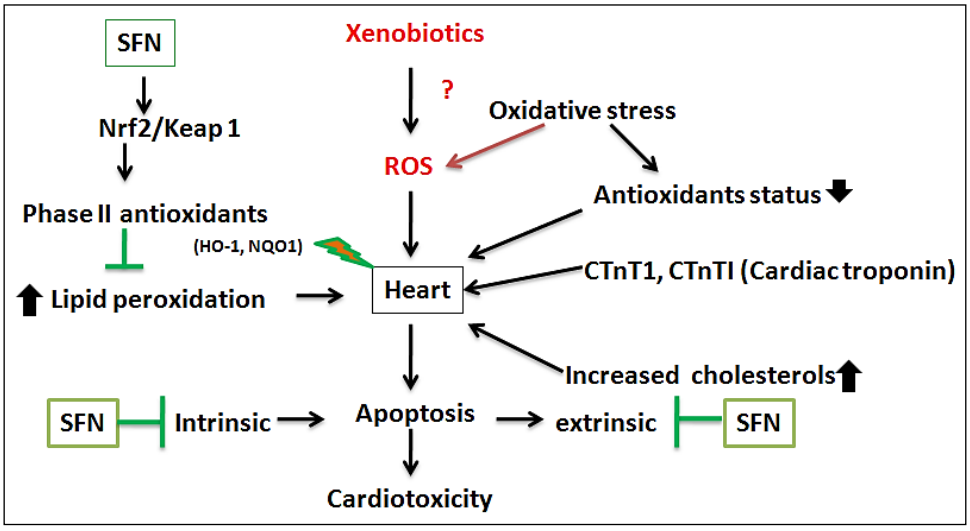

Fig. 4: *Possible Mechanism by which SFN Ameliorates Cardiotoxicity.*

SULFORAPHANE EFFECTS ON CARDIOTOXICITY

Heart is a muscular pumping organ, mainly involved in the purification and circulation of blood in the body. Heart sickness like myocardial infarction is one of the main causes related to sudden death in the world and it continues to cause substantial morbidity and mortality [20]. Heart failure results from sudden reduction in coronary blood flow to a segment of the myocardium which initiates a continuum of progressively more severe cellular changes that, unless interrupted by early reperfusion inevitable culminate in cell death and tissue necrosis [21]. Zhu et al. [22] i*n-vitro* study was revealed the protective effect of SFN incubated with rat cardiac A10 cells (aorta smooth muscle) with different concentration revealed the cytoprotective ability of SFN via activation of phase II enzymes such as catalase, SOD, GP_X, GR, GST, NQO1 and GSH. In the same study, the pretreatment of sulforaphane prevented the cell death, ROS production and oxidative cytotoxicity induced by xanthamine oxidase/xanthine, H_2O_2, 4- hydroxy – 2 nonenal and acrolein [22]. Singh et al. [23] once again proved the SFN protective efficacy through *invitro* study using cadiomyocytes H9C2 against doxorubicin (DOX) toxicity in rats. SFN loaded with 2.5 µM in to 96 well plates against DOX 5 µg/ml significantly decreased the mitochondrial respiratory complex enzymes along with cardiomyopathy and necrosis. This has been proved the SFN efficacies via Nrf2 binding property with ARE

elements and inhibits the Keap 1 protein in cadiomyocytes. On the other hand, *in-vivo* study by Paio et al. [24] proved the cardiac protective nature of antioxidant SFN against Ischemic-heart injury. It has been demonstrated that SFN 500 µg/kg/ip daily for 3 days and global ischemia was performed using isolated perfused Langendoroff hearts in Sprague–Dawley rats. It showed SFN significantly decreased the LPO, LDL-C, VLDL-C with increased SOD, CAT and other inevitable cardiac markers. This may be due to SFN electrophile capable of inducing expression of endogenous antioxidants and phase II enzymes through Nrf2 mediated transcription (Figure 4) [25–28].

CONCLUSION

The study on sulforaphane has been mounting due to hoard data about its positive effects on health. Today, sulforaphane demonstrates miscellaneous beneficial performance building it a strong candidate for individual therapeutic application. The innovation of the fact that sulforaphane encourages cytoprotective proteins via Nrf2/Keap1/HO-1 pathway has provoked the study of this compound in several experimental models associated with oxidative damage and inflammation. It is expected that the potential defending role of this amalgam will be studied in additional experimental paradigms. Nowadays, further studies will be compulsory to discover sulforaphane maximal protective effects, the involving players and the way it acts on diverse human disease models.

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CONFLICT OF INTEREST

The authors declared that there are no conflicts of interest.

ABBREVIATION

- SFN- Sulforaphane
- CTC- Carbon Tetra Chloride
- Nrf2 Pathway- Nuclear factor erythroid- 2 related factor- 2
- ARE- Antioxidant Response Elements
- HO-1- Heme Oxygenase 1
- GSTA 1- Glutothione S- transferase alpha 1
- APAP- Acetaminophen
- CIS- Cisplatin
- Keap 1- Kelch like ECH associated protein 1
- TNF-α- Tumor Necrosis Factor- alpha
- NF- κ B – Nuclear Factor Kappa B
- ICAM- Intracellular Adhesion Molecules
- VCAM- Vascular Cell Adhesion Molecules
- MPO- Myeloperoxidase
- SOD- Superxide Dismutase
- GP_X- Glutothione Peroxidase
- GR- Glutothione Reductase
- GST- Glutothione-S-Transferase
- NQO1- NAD(P)H: quinone oxidoreductase 1
- GSH- Reduced Glutothione
- Mn- SOD- Manganese Superoxide Dismutase
- ROS- Reactive Oxygen Species
- DOX- Doxorubicin

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