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The Most Important Pharmaceutical Benefits of Sulforaphane, a Sulfur-Rich Compound in Cruciferous

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ABSTRACT

Natural products have played a key role in drug discovery and development in modern days. Sulforaphane can be found in a wide variety of cruciferous vegetables, including cabbage, Brussels sprouts, cauliflower, broccoli, Chinese broccoli, broccoli sprouts, broccoli raab, Kohlrabi, collards, kohlrabi, mustard, turnip, kale and radish. The most important health benefits of sulforaphane is its effects again breast cancer, lung cancer cells, human liver cancer cells, gastric cancer cell lines, ovarian cancer, prostate cancer, pancreatic cancer, colon cells cancer, treatment of cancer cell senescence, anti-inflammatory properties, antineoplastic agent, reduction of placental and endothelial oxidative stress, potential in mixed granulocyte asthma, treatment of various neurological disorders, protection again skeletal muscle disease, anti-allergic and its impact against oxidative stress.

Keywords: Natural Compounds, Sulforaphane, Health Benefits, Cancer.

INTRODUCTION

Traditional herbal medicines have been considered as a source of curative remedy (Sun *et al*., 2019a,b; Shahrajabian *et al.,* 2019a,b; Khoshkharam *et al.,* 2020), because chemical components of plants are used to promote health and prevent diseases (Soleymani and Shahrajabian, 2012; Shahrajabian *et al.*, 2019c; Shahrajabian *et al*., 2020a,b,c,d,e,f; Sun *et al.*, 2020a,b,c), and plants are invaluable sources of new drugs (Soleymani and Shahrajabian, 2018; Khoshkharam *et al*., 2019). Sulforaphane which is a compound within the isothiocyanate group of organosulfur compounds, obtained from cruciferous vegetables like cabbages, broccoli, and Brussels sprouts. It is produced when the enzyme myrosinase transforms glucoraphanin, a glucosinolate into sulforaphane upon damage to the plant, which allows the two compounds to mix and react. Young sprouts of broccoli and cauliflower are particularly rich in glucoraphanin. The aim of this mini-review article is survey on the most important pharmacological benefits of sulforaphane.

Sulforaphane

Sulforaphane is a natural occurring cancer chemopreventive, the hydrolysis product of glucoraphanin, and the main glucosinolate in broccoli (Kokotou *et al*., 2017; Akbari and Namazian, 2020). Sulforaphane can be found in a wide variety of cruciferous vegetables, including cabbage, Brussels sprouts, cauliflower, broccoli, Chinese broccoli, broccoli sprouts, broccoli raab, Kohlrabi, collards, kohlrabi, mustard, turnip, kale and radish (Ahn *et al*., 2010; Liang *et al*., 2012). Sulforaphane has anticancer and antimicrobial activity (Cierpial *et al*., 2020), anticarcinogenic compound (Hafezian *et al*., 2019). It can be also considered as antineoplastic candidate (Arcidiacono *et al*., 2018). Sulforaphane inhibits proliferation and induces apoptosis decreasing the stemness of nasopharyngeal cancer cells through a mechanism related to STAT3 signaling in vitro (Li *et al*., 2018). Application of foods rich in sulforaphange can be used in the arena of clinical chemoprevention agent against a variety of cancers such as breast, prostate, colon, skin, lung, stomach, bladder and also cardiovascular disease, neurodegenerative diseases and diabetes (Yang *et al*., 2016). At the molecular level, sulforaphane modulates cellular homeostasis through the activation of transcription factor Nrf2 (Russo *et al*., 2018). Lv *et al*. (2020) recommend both sprouts and seeds as raw materials of functional foods that possess high health-promoting potential. Wang *et al*. (2018) reported the dual roles of sulforaphane which make this natural compound a valuable agent for prevention against cadmium-induced carcinogenesis. Isaacson *et al*. (2020) found that activation of the intrinsic antioxidant defense pathway with sulforaphane can partially prevent the effects of olanzapine and may represent a useful strategy to protect against liver injury. Sulforaphane has a potential value as a therapeutic tool in neurodegenerative disease including prion diseases (Lee *et al*., 2014). The mixture of sulforapahen and chlorogenic are potential nutraceuticals for abdominal pain therapy (Guadarrama-Enriquez *et al*., 2018). It can also prevent hypoxia-induced impairment of mitochondrial membrane structure (Langston-Cox *et al*., 2020). Sulforaphane upregulated the expression of Nrf2 and promoted the nuclear translocation of Nrf2 by decreasing DNA demethylation levels of the Nrf2 promoter which leading to antioxidative and anti-inflammatory effects in a cellular model of Alzheimer ’s disease (Zhao *et al*., 2018). Sulforaphane may inhibit the spread of metastatic tumor cells through the stimulation of cell-mediated immune response, upregulation of IL-2 and IFN-γ, and downregulation of proinflammatory cytokines IL-1β, IL-6, TNF-α, and GM-CSF (Thejass and Kuttan, 2007). Alkharashi *et al*. (2019) reported that intake of sulforaphane-enriched vegetables and fruits are helpful to overcome Cd-induced toxicity in humans. Checker *et al*. (2015) showed the potent anti-inflammatory effects of sulforaphane which mediated via modulation of PI3K/AKT/GSK3β/Nrf-2 and NF-κB pathway in T-cells. It is also effective in preventing estrogen deficiency-induced osteoclastogenic resorption (Lee *et al*., 2014). Sulforaphane treatment is a promising strategy to reduce intestinal injury in chemotherapy (Wei *et al*., 2020). The most important epigenetic regulation of sulforaphane in cancer are histone acetylation, histone phosphorylation, DNA methylation, noncoding RNA, CPG demethylation and histone acetylation at the *Nrf2* promoter (Su *et al*., 2018). The structure of sulforaphane is shown in Figure 1.

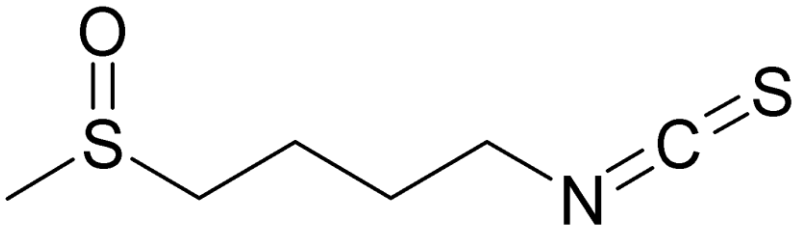

Figure 1- The structure of sulforaphane.

Table 2- The most important pharmacological effects of sulforaphane.

Sulforaphane	Function	Reference
Its effects against breast cancer	a. The treatment of triple negative breast cancer with cytotoxic chemotherapy would be greatly benefited by the addition of sulforaphane to prvent expansion of and eliminate breast cancer stem cell. Sulforaphane shows greater reduction in primary tumor volume and reduce secondary tumor formation. b. Sulforaphane and doxorubicin combination showed a synergistic inhibition on triple negative breast cancer cells growth. Sulforaphane in combination with clofarabine significantly reactivates DNA methylation-silenced CDKN2A tumor suppressor and inhibits cancer cell growth at a non-invasive breast cancer stage. c. Sulforaphane effectively affects histone deacetylases involved in chromatin remodeling, gene expression, and Nrf2 anti-oxidant signaling.	Burnett *et al*. (2017) Lubecka *et al*. (2018) Yang *et al*. (2018) Mielczarek *et al*. (2019) Kaboli *et al*. (2020)
Its effects against lung cancer cells	a. Sulforaphane may diminish the migratory and invasive capacity of lung cancer cells. The inhibitory effect of sulforaphane on lung cancer cell EMT was attenuated by extracellular singnal-regulated kinase 5 silencing.	Chen *et al*. (2019)
Its effects against human liver cancer cells	a. Sulforaphane may affect the activity of oncogenic transcription factors through methylation of its binding sites motifs, which leads to effect of sulforaphane on gene expression and DNA methylation in human hepatocellular carcinoma cells. b. Sulforaphane may protect against lipopolysaccharide (LPS)-induced	Lee *et al*. (2020) Santos *et al*. (2020)

	liver damage. LPS significantly increase mortality, serum levels of liver damage markers and inflammatory cytokines.	
Its effect against gastric cancer cell lines	a. Significant changes in expression of CDX1, CDX2, miR-9 and miR-326 in the gastric cancer lines (AGS and MKN45), were found under different concentrations of sulforaphane. It can influence gastric cancer cell lines at specific doses and change their proliferation rate by altering the expression of CDX1, CDX2, miR-9, and miR-326. b. Sulforaphane could be a potent natural compound targeting gastric cancer stem cells via suppression of Sonic Hh pathway, which might be a promising agent for gastric cancer intervention.	Kiani *et al*. (2018) Ge *et al*. (2019)
Its effects against ovarian cancer	a. Sulforaphave at a concentration of 10 μM effectively inhibits the growth of cancer cells. The effects of sulforaphane on cell growth maybe related to xidation of protein thiols or change in cellular redox status.	Kim *et al*. (2017)
Its effects against prostate cancer cells	a. Sulforaphane may decrease viable DU145 cell number in large part through the generation of reactive oxygen species (ROS) and JNK-mediated signaling to G_2/M arrest and caspase-dependent apoptosis.	Cho *et al*. (2005)
Its effects against pancreatic cancer	a. Sulforaphane potentiates the efficacy of 17-AAG against pancreatic cancer through enhanced abrogation of Hsp90 function.	Li *et al*. (2011) Naumann *et al*. (2011)
Its effects against colon cells cancer	a. Sulforaphane exert a concentration-dependent inhibitory effect on the inflammatory cytokine production by the immune cells. b. Sulforaphane has excellent cytoprotective properties in CRL-1790 cells, as it induce Nrf2-dependent expression of MRP1 and NAD(P)H quinone dehydrogenase 1 (NQO1).	Zeng *et al*. (2011) Rajendran *et al*. (2013) Lubelska *et al*. (2016) Pocasap and Weerapreeyakul (2016) Bessler and Djaldetti (2018) Yasuda *et al*. (2019)
Treatment of cancer cell senescence	a. Sulforaphane + Withaferin A synergistically promote breast cancer cell death through inhibiting cell cycle progression from S to G2 phase in MDA-MB-231 and MCF-7 breast cancer.	Royston *et al*. (2018)
Anti-inflammatory properties	a. Sulforaphane has function as suppressor of the MALP-2-induced inflammatory response, not only by inhibiting the expression of	Lee *et al*. (2016) Haodang *et al*. (2019) Vuong *et al*. (2019) Liu *et al*. (2020)

	cytokines and induction of HO-1 but also by diminishing NF-κB activation in cultured monocytes and the lungs of mice. b. Sulforaphane alleviates pain induced y sciatic endometriosis, which is mediated by inhibiting inflammation.	
Antineoplastic agent	a. The knockdown in the nuclear respiratory factor-1 attenuated sulforaphane-induced effect on prostate cancer cells demonstrating that mitochondrial biogenesis plays an important role in cell death.	Negrette-Guzman *et al*. (2017)
Reduction of placental and endothelial oxidative stress	a. Sulforaphane reduce TNF-α mediated HUVEC secretion of endothelin-1, VCAM1, ICAM1 and E-selectin, and prevented increased endothelial permeability. In placental explants, it can reduce the secretion of soluble Flt-1, soluble endoglin and activin A, induce activation and nuclear translocation of NRF2 in HUVECs, including heme oxygenase 1. It may offer a new adjuvant therapeutic approach for the treatment of preeclampsia.	Cox *et al*. (2019)
Therapeutic potential in mixed granulocyte asthma	a. Activation of Nrf2 by sulforaphane may reduce neutrophilic airway inflammation by upregulation of antioxidants and downregulation of inflammatory cytokines in airways.	Al-Harbi *et al*. (2019)
Treatment of various neurological disorders	a. Sulforaphane protects various neurological disorders by regulating the Nrf2 pathway.	Uddin *et al*. (2020)
Its protection against skeletal muscle disease	a. It is a potential drug to prevent skeletal muscle dysfunction in type 2 diabetic mellitus. It may activate the Nrf2/HO-1 signal pathway, and downregulate the expression of inflammatory and apoptotic associated proteins.	Wang *et al*. (2020)
Anti-allergic	a. Sulforaphane has anti-allergic inflammatory effects by intercepting caspase-1/NF-κB/MAPKs signaling pathways.	Jeon *et al*. (2020)
Its effects against oxidative stress	a. Phloretin up-regulate HO-1 and GCL expression through the ERK2/Nrf2 pathway and protect hepatocytes against oxidative stress.	Yang *et al*. (2011)

CONCLUSION

Sulforaphane can be found in a wide variety of cruciferous vegetables, including cabbage, Brussels sprouts, cauliflower, broccoli, Chinese broccoli, broccoli sprouts, broccoli raab, Kohlrabi, collards, kohlrabi, mustard, turnip, kale and radish. The most important health benefits of sulforaphane is its effects again breast cancer, lung cancer cells, human liver cancer cells, gastric cancer cell lines, ovarian cancer, prostate cancer, pancreatic cancer, colon cells cancer, treatment of cancer cell senescence, anti-inflammatory properties, antineoplastic agent, reduction of placental and endothelial oxidative stress, potential in mixed granulocyte asthma, treatment of various neurological disorders, protection again skeletal muscle disease, anti-allergic and its impact against oxidative stress.

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Authors' Contribution
All authors contributed equally to literature research, writing manuscript, etc.

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Competing interests
The authors declare that they have no potential conflicts of interest.

REFERENCES

Ahn YH, Hwang Y, Liu H, Wang XY, Zhang Y, Stephenson KK, Boroninac TN, Colec RN, Dinkova-Kostova AT, Talalay P, Cole PA. (2010). Electrophilic tuning of the chemiprotective natural product sulforaphane. Proc. Natl. Acad. Sci. U. S. A., 107, 9590-9595.

Akbari E, Namazian M. (2020). Sulforaphane: A natural prouct against reactive oxygen species. Computational and Theoretical Chemistry, 1183, 112850.

Al-Harbi NO, Nadeem A, Ahmad SF, Al Thagfan SS, Alqinyah M, Alqahtani F, Ibrahim KE, Al-Harbi MM. (2019). Sulforaphane treatment reverses corticosteroid resistance in a mized granulocytic mouse model of asthma by upregulation of antioxidants and attenuation of Th17 immune responses in the airways. European Journal of Pharmacology, 855, 276-284.

Alkharashi NAO, Periasamy VS, Athinarayanan J, Alshatwi AA. (2019). Sulforaphane allerviates cadmium-induced toxicity in human mesenchymal stem cells through POR and TNFSF10

genes expression. Biomedicine and Pharmacotherapy, 115, 108896.

Arcidiacono P, Stabile AM, Ragonese F, Pistilli A, Calvieri S, Bottoni U, Crisanti A, Spaccapelo R, Rende M. (2018). Anticarcinogenic activities of sulforaphane are influenced by nerve growth factor in human melanoma A375 cells. Food and Chemical Toxicology, 113, 154-161.

Bessler H, Djaldetti M. (2018). Broccoli and human health: immunomodulatory effect of sulforaphane in a model of colon cancer. International Journal of Food Sciences and Nutrition, 69(8), 946-953.

Burnett JP, Lim G, Li Y, Shah RB, Lim R, Paholak HJ, McDermott SP, Sun L, Tsume Y, Bai S, Wicha MS, Sun D, Zhang T. (2017). Sulforaphane enhances the anticancer activity of taxanes against triple negative breast cancer by killing cancer stem cells. Cancer Letters, 394, 52-64.

Checker R, Gambhir L, Thoh M, Sharma D, Sandur SK. (2015). Sulforaphane, a naturally occurring isothiocyanate, exhibits anti-inflammatory effects by targeting GSK3β/Nrf-2 and NF-κB pathways in T cells. Journal of Functional Foods, 19, 426-438.

Chen Y, Chen J-Q, Ge M-M, Zhang Q, Wang X-Q, Zhu J-Y, Xie C-F, Li X-T, Zhong C-Y, Han H-Y. (2019). Sulforaphane inhibits epithelial-mesenchymal transition by activating extracellular signal regulated kinase 5 in lung cancer cells. The Journal of Nutritional Biochemistry, 72, 108219.

Cho S-D, Li G, Hu H, Jiang C, Kang K-S, Lee Y-S, Kim S-H, Lu J. (2005). Involvement of c-Jun N-terminal kinase in G_2/M arrest and caspase-mediated apoptosis induced by sulforaphane in DU145 prostate cancer cells. Nutrition and Cancer, 52(2), 213-224.

Cierpiatl T, Kielbasinski P, Kwiatkowska M, Lyzwa P, Lubelska K, Kuran D, Dabrowka A, Kruszewska H, Mielczarek L, Chilmonczyk Z, Wiktorska K. (2020). Fluoroaryl analogs of sulforaphane- A group of compounds of anticancer and antimicrobial activity. Bioorganic Chemistry, 94, 103454.

Cox AG, Gurusinghe S, Rahman RA, Leaw B, Chan ST, Mockler JC, Murthi P, Marshall SA, Lim R, Wallace EM. (2019). Sulforaphane improves endothelial function and reduces placental oxidative stress in vitro. Pregnancy Hypertension, 16, 1-10.

Ge M, Zhang L, Cao L, Xie C, Li X, Li Y, Meng Y, Chen Y, Wang X, Chen J, Zhang Q, Shao J, Zhong C. (2019). Sulforaphane inhibits gastric cancer stem cells via suppressing sonic hedgehog pathway. International Journal of Food Sciences and Nutrition, 70(5), 570-578.

Guadarrama-Enriquez O, Gonzalez-Trujano ME, Ventura-Martinez R, Rodrigez R, Angeles-Lopez GE, Reyes-Chilpa R, Baenas N, Moreno DA. (2018). Broccoli sprouts produce abdominal antinociception but not spasmolytic effects like its bioactive metabolite sulforaphane. Biomedicine and Pharmacotherapy, 107, 1770-1778.

Hafezian SM, Azizi SN, Biparva P, Bekhradnia A. (2019). High-efficiency purification of sulforaphane from the broccoli extract by nanostructured SBA-15 silica using solid-phase extraction method. Journal of Chromatography B, 1108, 1-10.

Haodang L, Lianmei Q, Ranhui L, Liesong C, Jun H, Yihua Z, Cuimin Z, Yimou W, Xiaoxing Y. (2019). HO-1 mediates the anti-inflammatory actions of sulforaphane in monocytes stimulated with a mycoplasmal lipopeptide. Chemico-Biological Interactions, 306, 10-18.

Isaacson R, Beier JI, Khoo NKH, Freeman BA, Freyberg Z, Arteel GE. (2020). Olanzapine-induced liver injury in mice: aggrevation by high-fat diet and protection with sulforaphane. The Journal of Nutritional Biochemistry, 81, 108399.

Jeon M, Lee J, Lee HK, Cho S, Lim J-H, Choi Y, Pak S, Jeong H-J. (2020). Sulforaphane mitigates mast cell-mediated allergic inflammatory reactions in in silico simulation and in vitro models. Immunopharmacology and Immunotoxicology, 47(2), 74-83.

Kaboli PJ, Khoshkbejari MA, Mohammadi M, Abiri A, Mokhtarian R, Vazifemand R, Amanollahi S, Sani SY, Li M, Zhao Y, Wu X, Shen J, Cho CH, Xiao Z. (2020). Target and mechanisms of sulforaphane derivatives obtained from cruciferous plants with special focus on breast cancer- contradictory effects and future perspectives. Biomedicine and Pharmacotherapy, 121, 109635.

Khoshkharam M, Shahrajabian M, Sun W, Cheng Q. (2019). Survey the allelopathic effects of tobacco (*Nicotiana tabacum* L.) on corn (*Zea mays* L.) growth and germination. Cercetari Agronomice in Moldova, 4(180), 332-340.

Khoshkharam M, Shahrajabian MH, Sun W, Cheng Q. (2020). Sumac (*Rhus coriaria* L.) a spice and

medicinal plant- a mini review. Amazonian Journal of Plant Research, 4(2), 517-523.

Kiani S, Akhavan-Niaji H, Fattahi S, Kavoosian S, Jelodar NB, Bagheri N, Zarrini HN. (2018). Purified sulforaphane from broccoli (*Brassica oleraceae var. italica*) leads to alterations of CDX1 and CDX2 expression and changes in miR-9 and miR-326 levels in human gastric cancer cells. Gene, 678, 115-123.

Kim SC, Choi B, Kwon Y. (2017). Thiol-reducing agents prevent sulforaphane-induced growth inhibition in ovarian cancer cells. Food and Nutrition Research, 61(1), 1368321.

Kokotou M, Revelou P-K, Pappas C, Constantinou-Kokotou V. (2017). High resolution mass spectrometry studies of sulforaphane and indole-3-carbinol in broccoli, 237, 566-573.

Langston-Cox A, Muccini AM, Marshall SA, Yap Y, Palmer KR, Wallace EM, Ellery SJ. (2020). Sulforaphane improves syncytiotrophoblast mitochondrial function after in vitro hypoxic and superoxide injury. Placenta. DOI: 10.1016/j.placenta 2020.05.005

Lee J-H, Jeong J-K, Park S-Y. (2014). Sulforaphane-induced autophagy flux prevents prion protein-mediated neurotoxicity through AMPK pathway. Neuroscience, 278, 31-39.

Lee E-J, Kim J-L, Kim Y-H, Kang M-K, Gong J-H, Kang Y-H. (2014). Phloretin promotes osteoclast apoptosis in murine macrophages and inhibits estrogen deficiency-induced osteoporosis in mice. Phytomedicine, 21(10), 1208-1215.

Lee J, Ahn H, Hong E-J, An B-S, Jeung E-B, Lee G-S. (2016). Sulforaphane attenuates activation of NLRP3 and NLRC4 inflammasomes but not AIM2 inflammasome. Cellular Immunology, 306-307, 53-60.

Lee C, Yang S, Lee B-S, Jeong SY, Kim K-M, Ku S-K, Bae J-S. (2020). Hepatic protective effects of sulforaphane through the modulation of inflammatory pathways. Journal of Asian Natural Products Research, 22(4), 386-396.

Li Y, Zhang T, Schwartx SJ, Sun D. (2011). Sulforaphane potentiates the efficacy of 17-allylamino 17-demethoxygeldanamycin against pancreatic cancer through enhanced abrogation of Hsp90 chaperone function. Nutrition and Cancer, 63(7), 1151-1159.

Li X, Zhao Z, Li M, Liu M, Bahena A, Zhang Y, Zhang Y, Nambiar C, Liu G. (2018). Sulforaphane promotes apoptosis, an inhibits proliferation and self-renewal of nasopharyngeal cancer cells by targeting STAT signal through miRNA-124-3p. Biomedicine and Pharmacotherapy, 103, 473-481.

Liang H, Yuan Q. (2012). Natural sulforaphane as a functional chemopreventive agent: including a review of isolation, purification and analysis methods. Crit Rev Biotechnol, 32, 218-234.

Liu Y, Zhang Z, Lu X, Meng J, Qin X, Jiang J. (2020). Anti-nociceptive and anti-inflammatory effects of sulforaphane on sciatic endometriosis in a rat model. Neuroscience Letters, 723, 134858.

Lubelska K, Wiktorska K, Mielzcarek L, Milczarek M, Zbroinska-Bregisz I, Chilmonczyk Z. (2016). Sulforaphane regulated NFE2L2/Nrf2-dependent xenobiotic metabolim phase II and phase III enzymes differently in human colorectal cancer and untransformed epithelial colon cells. Nutrition and Cancer, 68(8), 1338-1348.

Lubecka K, Kaufman-Szymczyk A, Fabianowska-Majewska K. (2018). Inhibition of breast cancer cell growth by the combination of clofarabine and sulforaphane involves epigenetically mediates CDKN2A upregulation. Nucleosides, Nucleotides and Nucleic Acids, 37, 280-289.

Lv X, Meng G, Li W, Fan D, Wang X, Espinoza-Pinochet CA, Cespedes-Acuna CL. (2020). Sulforaphane and its antioxidative effects in broccoli seeds and sprouts of different cultivars. Food Chemistry, 316, 126216.

Mielczarek L, Krug P, Mazur M, Milczarek M, Chilmonczyk Z, Wiktorska K. (2019). In the triple-negative breast cancer MDA-MB-231 cell lines, sulforaphane enhances the intracellular accumulation and anticancer action of doxorubicin encapsulated in liposomes. International Journal of Pharmaceutics, 558, 311-318.

Naumann P, Fortunato F, Zentgraf H, Buchler MW, Herr I, Werner J. (2011). Autophagy and cell death signaling following dietary sulforaphane act independently of each other and require oxidative stress in pancreatic cancer. International Journal of Oncology, 39, 101-109.

Negrette-Guzman M. (2019). Combinations of the antioxidants sulforaphane or curcumin and the conventional antineoplastic cisplatin or doxorubicin as prospects for anticancer chemotherapy.

European Journal of Pharmacology, 859, 172513.
Pocasap P, Weerapreeyakul N. (2016). Sulforaphene and sulforaphane in commonly consumed cruciferous plants contributed to antiproliferation in HCt116 colon cancer cells. Asian Pacific Journal of Tropical Biomedicine, 6(2), 119-124.
Rajendran P, Kidane AI, Yu T-W, Dashwood W-M, Bisson WH, Lohr CV, Ho E, Williams DW, Dashwood RH. (2013). HDAC turnover, CtlP acetylation and dysregulated DNA damage signaling in colon cancer cells treated with sulforaphane and related dietary isothiocyanates. Epigenetics, 8(6), 612-623.
Royston KJ, Paul B, Nozell S, Rajbhandari R, Tollefsbol TO. (2018). Withaferin A and sulforabphane regulate breast cancer cell cycle progression through epigenetic mechanisms. Experimental Cell Research, 368(1), 67-74.
Russo M, Spanguolo C, Russo GL, Skalicka-Wozniak K, Daglia M, Sobarzo-Sanchez E, Nabavi SF, Nabavi SM. (2018). Nrf2 targeting by sulforaphane: A potential therapy for cancer treatment. Critical Reviews in Food Science and Nutrition, 58(8), 1391-1405.
Santos PWDSD, Machado ART, Grandis RAD, Ribeiro DL, Tuttis K, Morselli M, Aissa AF, Pellegrini M, Antunes LMG. (2020). Transcriptome and DNA methylation changes modulated by sulforaphane induce cell cycle arrest, apoptosis, DNA damage, and suppression of proliferation in human liver cancer cells. Food and Chemical Toxicology, 136, 111047.
Shahrajabian MH, Sun W, Cheng Q. (2019a). Clinical aspects and health benefits of ginger (*Zingiber officinale*) in both traditional Chinese medicine and modern industry. Acta Agriculturae Scandinavica, Section B-Soil and Plant Science. DOI: 10.1080/09064710.1606930
Shahrajabina MH, Sun W, Cheng Q. (2019b). A review of ginseng species in different regions as a multipurpose herb in traditional Chinese medicine, modern herbology and pharmacological science. Journal of Medicinal Plant Research, 13(10), 213-226.
Shahrajabian MH, Sun W, Cheng Q. (2019c). A review of astragalus species as foodstuffs, dietary supplements, a traditional Chinese medicine and a part of modern pharmaceutical science. Applied Ecology and Environmental Research, 17(6), 13371-13382.
Shahrajabian MH, Sun W, Cheng Q. (2020a). Chinese star anise (*Illicium verum*) and pyrethrum (*Chrysanthemum cinerariifolium*) as natural alternatives for organic farming and health care- A review. Australian Journal of Crop Science, 14(03), 517-523.
Shahrajabian MH, Sun W, Shen H, Cheng Q. (2020b). Chinese herbal medicine for SARS and SARS-CoV-2 treatment and prevention, encouraging using herbal medicine for COVID-19 outbreak. Acta Agriculturae Scandinavica, Section B-Soil and Plant Science. DOI: 10.1080/09064710.2020.1763448
Shahrajabian MH, Sun W, Cheng Q. (2020c). Considering white gold, cotton for its fiber, seed oil, traditional and modern health benefits. Journal of Biological and Environmental Sciences, 14(40), 25-39.
Shahrajabian MH, Sun W, Cheng Q. (2020d). Chinese onion and shallot, originated in Asia, medicinal plants for healthy daily recipes. Notulae Scientia Biologicae, 12(2), 197-207.
Shahrajabian MH, Sun W, Cheng Q. (2020e). A review of plant genomes of some important traditional Chinese fruits and herbs. Cercetari Agronomice in Moldova, 2(182), 217-232.
Shahrajabian MH, Sun W, Cheng Q. (2020f). Product of natural evolution (SARS, MERS, and SARS-CoV-2); deadly diseases, from SARS to SARS-CoV-2. Human Vaccinese & Immunotherapeutics. DOI: 10.1080/21645515.2020.1797369
Soleymani A, Shahrajabian MH. (2012). Response of different cultivars of fennel (*Foeniculum vulgare*) to irrigation and planting dates in Isfahan, Iran. Research on Crops, 13(2), 656-660.
Soleymani A, Shahrajabian MH. (2018). Changes in germination and seedling growth of different cultivars of cumin to drought stress. Cercetari Agronomice in Moldova, 51(1), 91-100.
Su X, Jiang X, Meng L, Dong X, Shen Y, Xin Y. (2018). Anticancer activity of sulforaphane: The epigenetic mechanisms and the Nrf2 signaling pathway. Oxidative Medicine and Cellular Longevity, 2018(6), 1-10.
Sun W, Shahrajabian MH, Cheng Q. (2019a). The insight and survey on medicinal properties and nutritive components of shallot. Journal of Medicinal Plant Research, 13(18), 452-457.

Sun W, Shahrajabian MH, Cheng Q. (2019b). Anise (*Pimpinella anisum* l.), a dominant spice and traditional medicinal herb for both food and medicinal purposes. Cogent Biology, 5(1673688), 1-25.

Sun W, Shahrajabian MH, Khoshkharam M, Cheng Q. (2020a). Adaptation of acupuncture and traditional Chinese herbal medicines models because of climate change. Journal of Stress Physiology and Biochemistry, 16(1), 85-90.

Sun W, Shahrajbian MH, Cheng Q. (2020b). Pyrethrum and organic and natural pesticide. Journal of Biological and Environmental Sciences, 14(40), 41-44.

Sun W, Shahrajabian MH, Khoshkharam M, Shen H, Cheng Q. (2020c). Cultivation of cotton in China and Iran with considering biological activities and its health benefits. Cercetari Agronomice in Moldova, 1(181), 105-120.

Thejass P, Kuttan G. (2007). Modulation of cell-mediated immune response in B16F-10 melanoma-induced metastatic tumor-bearing C57BL/6 mice by sulforaphane. Immuopharmacology and Immunotoxicology, 29(2), 173-186.

Uddin MdS, Al Mamun A, Jakaria Md, Thangapandiyan S, Ahmad J, Rahman MdA, Mathew B, Abdel-Daim M, Aleya L. (2020). Emerging promise of sulforaphane-mediated Nrf2 signaling cascade against neurological disorders. Science of the Total Environment. 7070, 135624.

Vuong LD, Nguyen QN, Truong V-L. (2019). Anti-inflammatory and anti-oxidant effects of combination between sulforaphane and acetaminophen in LPS-stimulated RAW 264.7 macrophage cells. Immunopharmacology and Immunotoxicology. 41(3), 413-419.

Wang Y, Mandal AK, Son Y-O, Pratheeshkumar P, Wise JTF, Wang L, Zhang Z, Shi X, Chen Z. (2018). Roles of ROS, Nrf2, and autophagy in cadmium-carcinogenesis and its prevention by sulforaphane. Toxicology and Applied Pharmacology, 353, 23-30.

Wang M, Pu D, Zhao Y, Chen J, Zhu S, Lu A, Liao Z, Sun Y, Xiao Q. (2020). Sulforaphane protects against skeletal muscle dysfunction in spontaneous type 2 diabetic db/db/ mice. Life Sciences. DOI: 10.1016/j.lfs.2020.117823

Wei L, Wang J, Yan L, Shui S, Wang L, Zheng W, Liu S, Liu C, Zheng L. (2020). Sulforaphane attenuates 5-fluorouracil induced intestinal injury in mice. Journal of Functional Foods, 69, 103965.

Yang Y-C, Lii C-K, Lin A-H, Yeh Y-W, Yao H-T, Li C-C, Liu K-L, Chen H-W. (2011). Induction of glutathione synthesis and heme oxygenase 1 by the flavonoids butein and phloretin is mediated through the ERk/Nrf2 pathway and protects against oxidative stress. Free Radical Biology and Medicine, 51(11), 2073-2081.

Yang L, Palliyaguru DL, Kensler TW. (2016). Frugal chemoprevention: targeting Nrf2 with foods rich in sulforaphane. Seminars in Oncology, 43(1), 146-153.

Yang F, Wang F, Liu Y, Wang S, Li X, Huang Y, Xia Y, Cao C. (2018). Sulforaphane induces autophagy by inhibition of HDAC6-mediated PTEN activation in triple negative breast cancer cells. Life Sciences, 213, 149-157.

Yasuda S, Horinaka M, Sakai T. (2009). Sulforaphane enhances apoptosis induced by *Lactobacillus pentosus* strain S-PT84 via TNFα pathway in human colon cancer cells. Oncology Letters, 18, 4253-4261.

Zeng H, Trujillo ON, Moyer MP, Botnen H. (2011). Prolonged sulforaphane treatment activates survival signaling in nontumorigenic NCM460 colon cells but apoptotic signaling in tumorigenic HCT116 colon cells. Nutrition and Cancer, 63(2), 248-255.

Zhao F, Zhang J, Chang N. (2018). Epigenetic modification of Nrf2 by sulforaphane increases the antioxidative and anti-inflammatory capacity in a cellular model of Alzheimer 's disease. European Journal of Pharmacology, 824, 1-10.