Review Article

Chemopreventive effects of dietary sulforaphane in oral cancer-A review

Pankaj Gupta[1]

From [1]*Private Dental Practitioner, Swami Vivekanda Medical Mission, Ambphalla, Jammu, India.*

Correspondence to: Dr. Pankaj Gupta, House no-74, ward no-15, Shakti nagar, Udhampur, Jammu and Kasmir, India- 182101
Email ID: pankajtherock3@gmail.com

Received – 06 August 2020 *Initial Review – 16 August 2020* *Accepted – 31 August 2020*

ABSTRACT

Oral cancer is a potentially fatal disease which constitutes an important part of tumors occurring in the head and neck region. It not only affects the overall health but also affects the mental health, appearance, employment, social life and family living. It can also cause serious changes in the functioning of the upper aero digestive tract that affects the quality of life in patients. The use of conventional treatment modalities depend on tumor respectability and location as well as feasibility of organ preservation approach. However, their role in oral cancer treatment is non-selective and can cause damage to normal tissue. In particular, chemo radiotherapy is associated with systemic toxicities that often reduce patient compliance and prevent timely completion of therapy. Scientists around the world are now developing a new treatment known as 'green chemoprevention' in which broccoli and other vegetables are used to prevent the onset of carcinoma. In this review article, the author presents a detailed review about the chemotherapeutic effect of sulforaphane, a dietary component from broccoli sprouts in the prevention of oral cancer.que is a shear-based moment, a force obtained from a twisted spring wire in its effort to un-twist itself which causes rotation. In dentition, it pertains to facio-lingual root movement and control. Also, it refers to the amount of twist applied to an arch wire in bracket engagement or activation. Despite the advent of numerous treatment philosophies, appliance systems and torque prescriptions and considerable research done in the past, torque is still an enigma. The key is to understand not only how we reach where we are but also to learn how to manage the torque properly, focusing on the technical and biomechanical purposes that led to the change of the torque values over time. The present review focuses on application of torque in orthodontics.

Key words: *Broccoli, chemoprevention, cytotoxic, oral squamous cell carcinoma, sulforaphane*

Oral squamous cell carcinoma (OSCC) or oral cancer is the sixth most common type of cancer worldwide with a 5-year mortality rate of approximately 50% [1] which has not changed significantly over the last 50 years [2]. Oral cancer is considered to account for an estimated 650,000 new cancer cases and 350,000 cancer deaths worldwide per year [3]. High-risk regions for the disease include, South-central Asia for cancers of the oral cavity and South America and Western Asia for laryngeal cancers [3]. It is well established that the major risk factors for oral cancer are tobacco and alcohol consumption, constituting approximately 75% of cases. Among consumers of both products, risks of oral cancer tended to combine more in a multiplicative than additive fashion and were increased more than 35-fold among those who consumed two or more packs of cigarettes and more than four alcoholic drinks per day [3]. Recent evidence suggests the role of human papilloma virus (HPV) in the oral cancer. HPV-16 is considered to be associated with approximately 20% oral cancer cases and 60–80% oropharyngeal carcinoma [1].

Although there are numerous treatment modalities for oral cancer such a surgery, radiation, and/or chemotherapy, however, are associated with many side effects. Scientists are now emphasizing on studies to halt the progress of oral

cancer at an early stage. Recent studies have suggested that the regular consumption of cruciferous vegetables, such as broccoli, brussels sprouts, cabbage, cauliflower, kale, swede and turnip, is associated with a reduced incidence of cancer [4]. The anticancer activity of these vegetables has been linked to the high content of sulfur-containing glucosinolates. The hydrolysis of the inactive glucosinolate by the plant enzyme myrosinase or by gut bacteria leads to the formation of biologically active isothiocyanates or indoles [5]. This article presents a detailed review of dietary sulphoraphone (SFN), and its chemopreventive actions in oral cancer.

CHEMOPREVENTIVE ACTIONS OF PHYTOCHEMICALS

Carcinogenesis is a process wherein the normal cells are transformed into cancer cells. It is characterized by changes at the cellular, genetic, and epigenetic levels and abnormal cell division through three separate but closely linked stages such as initiation, promotion, and progression. Single use of subcarcinogenic dose of a carcinogen initiates the process. Promotion, the second step, results via repeated usage of an irritating agent. Cellular explosion and selective clonal growth which occur in this stage are although reversible during the early stages, however become irreversible with time. Cells in humans and other organisms are frequently interpretative to a variety of oxidizing agents which are necessary for life. These factors may be present in air, food and water or may be created during metabolic activity within cells. Equilibrium must be maintained between oxidants and antioxidants to prolong the optimal physiological conditions.

During infections, an imbalance is created by producing high amounts of oxidants, which leads to oxidative stress. This affects large biomolecules like lipids, proteins and DNA, resulting in an increased risk for cancer. The process of transformation from normal to malignant cells is slow and requires years for the transformation. Therefore, delaying or preventing the process is a viable and possible objective for the future. The results of many laboratory animal studies evidently denote that different cancers can be prohibited using certain chemicals. In order to avoid and/or slow the oxidative stress created by free radicals, adequate amounts of antioxidants are necessary to be used. Cancer chemoprevention is the main cancer preventive approach that exploits naturally dietary phytochemicals or remedial drugs with fairly low toxicity [6]. Anti-cancer properties of phytochemical compounds are presented in Table 1.

Table 1: Chemopreventive actions of various phytochemicals [6]

Phytochemicals	Chemopreventive effects
Phenolic compounds	Reduced incidence of neoplasia induced by chemical carcinogens. Preventing nitrosation of amines and amides. Inhibition of promotion process. Inhibitors of kinases by reducing hyperproliferation of epithelial cells
Organosulfur compounds	Induction of carcinogen detoxification. Inhibition of cancer cell proliferation.
Alkaloids	Modification of cancer metabolism. Inhibition of tumor cell growth.
Carotenoids	Inducers of differentiation.
Nitrogen compounds	Inhibit the metabolic activation and carcinogenicity

Table 2: Health benefits of SF and proposed underlying mechanisms [7]

Disease condition	Underlying mechanism
Cancer	Modulation of drug metabolizing enzymes, Induction of apoptosis, Cell cycle arrest
Respiratory disorders	Up regulation of Glutathione and Quinine reductase in the airway epithelial cells
Neurodegenerative diseases- Alzheimer's disease cerebral ischemia	Inhibition of acetyl cholinesterase, up regulation of antioxidant gene expression
Kidney diseases, renal fibrosis and ROS-mediated kidney damage	Nuclear factor eryhthroid-derived 2 (Nrf-2) mediated induction of phase 2 enzymes
Retinal disorders, age related macular degeneration	Upregulation of retinal Thiredoxin, Thiredoxin receptor, and Nrf-2, Up-regulation of retinal GSH and QR
Diabetes, micro- and macro-vascular disorders	Reduction of oxidative stress and restoration of endothelial function
Cardiovascular disorders	Nrf-2 mediated reduction in the pro-inflammatory state
Gastrointestinal disorders	Nrf-2 dependent eradication of H. pylori

CYTOTOXIC AND CHEMOPREVENTIVE EFFECTS OF SULFORAPHANE

Epigenetic dysregulation, such as increased activity of histone deacetyltransferases (HDACs) and DNA methyltransferases (DNMTs) and changes in noncoding RNA expression, may lead to alterations in the transcription and expression of genes involved in the regulation of cell proliferation and differentiation, cell cycle and apoptosis. Sulforaphane has shown pleiotropic anticarcinogenic effect on a variety of experimental cancer models including repression of cancer cell proliferation, stimulation of cancer cell apoptosis, and inhibition of tumor progression and metastasis [11].

1. Inhibition of histone deacetylase (HDACs)

Many malignant neoplasms are characterized by an increased expression and activity of HDACs. HDAC overexpression and overactivity are closely associated with transcriptional repression of the tumor-suppressor genes that are responsible for dysregulation of cell cycle, proliferation, differentiation, and apoptosis in malignances [12, 13]. Additionally, HDACs can also affect DNA damage and repair by altering the acetylation status of c-terminal-binding protein interacting protein (CtIP), a critical DNA repair protein [14]. The food-based compound SFN is a HDAC inhibitor, has been shown to exert cancer preventive effects [12, 13]. Treatment of various cancers, such as prostate, colon and lung cancer with SFN has shown to attenuate the cell growth through inhibition of HDACs, accompanied by an increase in global or local histone acetylation [14]. It also reduces histone H1 phosphorylation by enhancing protein phosphatase 1β and 2A (PP1β and PP2A). Additionally, SFN-mediated inhibition of HDACs also contributes to the reactivation of the tumor suppressor gene p21 [15]. The above findings suggests that SFN may exert its anticancer effects through inhibition of HDACs, enhancement of phosphatases and preventing H1 phosphorylation.

2. Modulation of DNA Methylation

DNA methylation is an important step in tumorogenesis, resulting in gene modifications mainly occurring within cysteine and Guanine (CPG) islands in gene promoter regions. Main Enzymes promoting DNA methylation are DNA methyltransferases (DNMTs) including DNMT1, which maintains methylation, and DNMT3a and DNMT3b, which catalyze de novo methylation, thus making them targets of cancer chemoprevention [16]. Growing evidence indicates that SFN is a potential modulator of DNA methylation in cancer development and progression [14]. Furthermore, the inhibitory effects of SFN on DNMTs can restore the expression and activation of silenced or repressed genes in cancer cells via promoter demethylation. A study involving the breast cancer cells assessed the effects of SFN on human telomerase reverse transcriptase (hTERT), the catalytic regulatory subunit of telomerase. The results showed that SFN, at a dosage of 10 μM, induced inhibition of DNMT1 and DNMT3a causing site-specific CpG demethylation in the first exon of the hTERT gene, thereby facilitating binding of the CTCF transcription repressor and hTERT repression [17]. The above results show that SFN functions as a cancer chemopreventive agent by modulating the expression of tumor-related genes through DNA methylation modification.

3. Regulation of Noncoding RNAs

A noncoding RNA (ncRNA) is an RNA molecule that functions without being translated into a protein. Abundant and functionally important ncRNAs include transfer RNAs and ribosomal RNAs, as well as small RNAs, such as microRNAs (miRNAs) and long ncRNAs (lncRNAs). Several miRNAs, such as miR200c, miR-616-5p, and microRNA-21 (miR-21), have been shown to be targets of SFN in some human cancers. Cancer stem cells (CSCs) are considered to be the driving force of carcinogenesis in oral squamous cell carcinoma (OSCC). In a study, treatment with 20 μM of SFN has shown to impair the cancer stemness by inducing the tumor-suppressive miRNA miR200c, which subsequently inhibited the migration, invasion, and clonogenicity of OSCC-CSCs in mouse models [18]. Another study showed that SFN down regulated miR-616-5p levels in NSCLC, which was accompanied by inactivation of the GSK3β/β-catenin pathway and inhibition of EMT to prevent NSCLC recurrence and metastasis [19].

SULFORAPHANE IN OSCC

A study was conducted by Bauman et al to evaluate the bioavailability and pharmacodynamic activity of three different Broccoli Sprout extract (BSE) regimens, based upon urinary sulforaphane metabolites and NQO1 carcinogen 4-nitroquinoline-1-oxide (4NQO) transcripts in

buccal scrapings, respectively. Results of the study demonstrated greatest and consistent bioavailability increased mucosal bioactivity, increased upregulation of NQO1 mRNA with ingestion of sulforaphane-rich BSE [20]. In another study conducted by Jee HG et al, the growth inhibition of oral carcinoma cell lines by sulforaphane was determined using aqueous soluble tetrazolium salts. It was observed that the growth of various oral cancer cell lines was attenuated, there was decreased migration and invasion activities of the cells. At the molecular level, the secreted forms of MMP-1 and MMP-2 were down-regulated. The expressions of MMP-1 and MMP-2 did not change when a conventional tumoricidal agent paclitaxel was used. This study findings indicate that sulforaphane may have therapeutic potential as an inhibitor of metastasis in oral carcinoma patients [21].

CONCLUSION

Towards the development of 'Green Chemoprevention', numerous agents have been proposed which play a beneficial role as inhibitors in oral cancers. Cruciferous vegetables such as broccoli, cabbage, and garden cress have a high concentration of the naturally occurring molecular compound sulforaphane, which previously has been shown to protect people against environmental carcinogens. The identification of a cost-effective, green chemopreventive agent would have a major global impact on mortality and quality of life in patients at risk. There are very limited studies which clearly demonstrate the cytotoxic and chemopreventive effects of SFN on oxidative stress-associated oral carcinogenesis. Further studies are required in the future to establish the clinical effects and epigenetic modifications of oral cancers by sulforaphane.

REFERENCES

1. Myers JN, Elkins T, Roberts D, et al. Squamous cell carcinoma of the tongue in young adults: Increasing incidence and factors that predict treatment outcomes. Otolaryngol Head Neck Surg. 2000;122:44-51.
2. Sparano A, Weinstein G, Chalian A, et al. Multivariate predictors of occult neck metastasis in early oral tongue cancer. Otolaryngol Head Neck Surg. 2004;131:472-6.
3. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J. 2005; 55:74-108.
4. Hayes JD, Kelleher MO, Eggleston IM. The cancer chemopreventive actions of phytochemicals derived from glucosinolates. Eur J Nutr. 2008;47(2):73–88.
5. Lampe JW. Sulforaphane: from chemoprevention to pancreatic cancer treatment? Gut 2009;58(7):900–2.
6. Meybodi NM , Mortazavian AM, Monfared AB, et al. Phytochemicals in cancer prevention: A review of the evidence. Int J Cancer Manag. 2017;10(1):e7219
7. Xuling Su, Xin Jiang, Meng L. Anticancer Activity of Sulforaphane: The Epigenetic Mechanisms and the Nrf2 Signaling Pathway. Oxid Med Cell Longev. 2018;2018:5438179.
8. Elbarbry F, Nehad Elrody N. Potential health benefits of sulforaphane: A review of the experimental, clinical and epidemiological evidences and underlying mechanisms. J Med Pla Res. 2011;5(4):473-84.
9. Li Y, Zhang T, Korkaya H, et al. Sulforaphane, a dietary component of broccoli/broccoli sprouts, inhibits breast cancer stem cells. Clin Cancer Res. 2010;16:2580-90.
10. Kensler TW, Chen JG, Egner PA, et al. Effects of glucosinolate-rich broccoli sprouts on urinary levels of aflatoxin DNA adducts and phenanthrene tetraols in a randomized clinical trial in He Zuo Township, Qidong, People's Republic of China. Cancer Epidemiol Biomarkers Prev. 2005;14:2605-13.
11. Lozanovski, VJ, Polychronidis G, Gross W, et al. Broccoli sprout supplementation in patients with advanced pancreatic cancer is difficult despite positive effects—results from the POUDER pilot study. Inv New Drugs. 2020;38(3):776-84.
12. Tortorella SM et al. Dietary sulforaphane in cancer chemoprevention the role of epigenetic regulation and HDAC inhibition. Antioxid Redox Sign. 2015;22(16):1382–1424.
13. Kaufman-Szymczyk A, Majewski G. Lubecka-Pietruszewska K, et al. The role of sulforaphane in epigenetic mechanisms, including interdependence between histone modification and DNA methylation. Int J Mol Sci. 2016;16(12):29732–43.
14. Jiang LL, Zhou SJ, Zhang XM, et al. Sulforaphane suppresses in vitro and in vivo lung tumorigenesis through downregulation of HDAC activity. Biomed Pharmacother. 2016;78:74–80.
15. Abbaoui B, Telu KH, Lucas CR, et al. The impact of cruciferous vegetable isothiocyanates on histone acetylation and histone phosphorylation in bladder cancer. J Proteom. 2017;156:94–103.
16. Denis H, Ndlovu MN, Fuks F, Regulation of mammalian DNA methyltransferases: a route to new mechanisms. EMBO Reports. 2011;12(7):647–56.

17. Meeran SM, Patel SN, Tollefsbol TO. Sulforaphane causes epigenetic repression of hTERT expression in human breast cancer cell lines. PLoS One. 2010; 5(7), e11457.
18. Liu CM, Peng CY, Liao YW et al. Sulforaphane targets cancer stemness and tumor initiating properties in oral squamous cell carcinomas via miR-200c induction. J Formos Med Assoc. 2017;116(1):41–48.
19. Wang DX, Zou YZ, Zhuang XB, et al, Sulforaphane suppresses EMT and metastasis in human lung cancer through miR-616-5p-mediated GSK3β/β-catenin signaling pathways. Acta Pharmacologica Sinica. 2017;38(2):241–51.
20. Jee HG, Lee KE, Kim JB. Sulforaphane inhibits oral carcinoma cell migration and invasion in vitro. Phytother Res. 2011;25(11):1623-8.
21. Bauman JE, Zang Y, Sen M, et al. Prevention of carcinogen-induced oral cancer by sulforaphane. Cancer Prev Res (Phila). 2016;9(7):547–57.

How to cite this article: Gupta P. Chemopreventive effects of dietary sulforaphane in oral cancer-A review. J Orofac Res. 2020;9(3):39-43.

Funding: None; Conflict of Interest: None Stated.