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A PERSPECTIVE REVIEW ON ROLE OF NUTRACEUTICALS PRESENT IN CRUCIFEROUS VEGETABLES IN THE PREVENTION OF CANCER

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ABSTRACT

Cruciferous vegetables include a multitude of commercially significant species, primarily edible oil plants, vegetable species, spice plants, and feed plants. Cruciferous vegetables have a high nutritional content and a high dietary fiber content. Moreover, cruciferous vegetables have a variety of bioactive substances called glucosinolates and S-methyl cysteine sulfoxide, including substances that prevent cancer and include sulfur. Many studies have shown that eating sulphurous vegetables on a regular basis lowers the incidence of cancer and helps prevent its creation through a variety of mechanisms, particularly in colorectal cancer. According to experimental research, these substances may prevent cancer through the following mechanisms: they may shield cells from DNA damage, neutralize substances that cause cancer, exhibit antiviral and antibacterial properties, cause apoptosis in cells that have structural defects, prevent tumor cells from migrating and spreading, and prevent the growth of angiogenesis, the process by which tumors feed into vessels. The research mainly links the favorable anticancer benefits of cruciferous vegetables to their composition of glucosinolates and some secondary metabolites, in addition to other phenolic compounds, seed oils, and dietary fiber. Examining the functions of cruciferous vegetables and their significant bioactive metabolites in the prophylaxis and management of colorectal cancer is the goal of this review.

KEYWORDS: Nutraceuticals, Cancer, Cruciferous vegetables, Phytochemicals, Sulforaphane.

INTRODUCTION

Plant-derived compounds possess phytochemicals agents that have been exert its good health effects either direct, by altering particular atomic targets, or indirect, by impacting metabolic processes through stable conjugates. Plants have evolved a broad spectrum of phytochemicals properties to protect it-selves from highly ROS (Reactive oxygen species) and as a defensive mechanism.[1] These products, which include phytochemical-rich extracts to achieve favourable physiological benefits, cannot be termed "food."

As a result, a new word called Nutraceuticals was established to describe the combination of nutrients and medications. In 1989, Stephen DeFelice invented term i.e., nutraceuticals, defining it as "food, food constituents, or dietary nutrients that exhibit unique healthiness or therapeutic advantages beyond basic nutritional functions, including the treatment and prevention of diseases". Until 1990, nutraceuticals were thought likely naturally originated foods that provided energy as a suggested daily need in human body for optimum health.[2]

With increased usage of nutraceuticals as self prescription, the relevance of nutraceuticals as useful in many nutritional problems was acknowledged. Nutraceuticals as effective medicinal supplements have grown in popularity in the new century, together with notion of nutraceutical medicine as a new era of "complementary and alternative medicine" being widely acknowledged (CAM).[3] Hippocrates, the popular founder of medicine, proposed "Let food be thy medicine and medicine be thy food" over 2000 years ago, highlighting the links between nutrition and human health, particularly the therapeutic effects of proper meals for health. Depending on the separation process, plant originally generated products have been classified as food, super food, health supplements, functional food, and nutraceuticals. Nutraceuticals are virginally derived phytomolecules, while functional foods are semi purified plant products that are not consumed as food. Food supplements are items that may be consumed as food on a daily basis to maintain good health. Different vitamins and minerals, PUFA (polyunsaturated fatty acids), and secondary metabolites such as indoles, glucosinolates, flavonoids, phytochemicals categories like polyphenols, phytosterols, phytoestrogens, nonsoluble fibre (lignans), terpenes, and antinutritional factors like phytates are all found in plant based foods.[4]

Nutraceuticals have been recognised as a feasible neutraceutical remedial treatment in the prevailing sector of health education and well-being for past nine years by national and federal agencies.[5] The healthcare sector has shown how a rising population is shifting away from medical cancer therapy and toward self medication using non-prescription nutraceuticals for cancer management and prevention. Growing public knowledge of nutraceuticals diet advantages and a swerve in healthier economical in view of nutraceuticals have propelled neutraceutical drugs to forefront of administartion health practices on the efficient usage of nutraceuticals in the reduction and supermacy of a variety of persistent illnesses.

Nutraceuticals are bioactive chemical substances that are found in nature. Nutraceuticals have health supporting, ailment-prevention, or partial-therapeutic characteristics. Nutraceuticals are original compounds derived via the food processing, natural/herbal and dietary supplement industries, the pharma industry, and recently developed genetically engineer microbes, agroproducts, or active biomolecules.[6] It can include isolate food nutrients, herb items, nutritional supplemental, and dietary items, as well as genetically modified "custom" foods and processed foods including cereals, soups, and drinks.

Nutraceuticals compounds can be categorised chemically into different section:[7]

- Isoprenoid derivatives (terpenoids, carotenoids, saponins, tocotrienols, tocopherols, terpenes),
- Phenolic compounds (couramines, tannins, lignins,anthrocynins, isoflavones, flavonones, flavanoids),
- Carbohydrate derivatives (ascorbic acid, oligosaccharides, non-starch polysaccharides),
- Fatty acid and structural lipids (n-3 PUFA, CLA, MUFA, sphingolipids, lecithins),
- Amino acid derivatives (amino acids, allyl-S compounds, capsaicnoids, isothiocyanates, indols, folate, choline),
- Microbes (probiotics, prebiotics) and minerals (Ca, Zn, Cu, K, Se).

NUTRACEUTICALS AS PHYTOCHEMICALS IN GLUCOSINOLATE CONTAINING CRUCIFEROUS VEGETABLES

At different cellular levels, phytochemicals have diverse mechanisms of action. Most of them have showed as a flexible cause of antioxidants that alter the redox-mediated transcription factor signalling pathway. They also have direct outcome on endocrine functions, the immune functions, and inflammation related enzymes. Some of them have been found to have a direct impact on DNA repair and cleavage.[8] Nutraceuticals may also assist to reduce the adverse effects of cancer related therapies like chemo and radiation, as well as better and healthy life by lowering cancer cachexia.

The use of phytochemicals found in widely consumed glucosinolate-containing Cruciferous vegetables to prevent and/or protect against chemical carcinogens is of significant interest, since they offer a safe and cost-effective way to treat cancer.[9] Various sources epidemiologic inspection have frequently found a negatively connection within the intake of cruciferous vegetables and the risk of cancer in a variety of locations

Brassicacaceae genus of cruciferous family vegetables derive from plants, which botanists call Cruciferae or Brassicacae. The Cruciferous family includes plants with blooms that have four equal-sized petals in the form of a crucifer cross. Cabbage is known in Latin name as "brassica" Broccoli, Brussels sprouts, cauliflower, collard greens, cabbage, kale, mustard, rutabaga, turnips, and Chinese cabbage are among most regularly eaten cruciferous vegetables.[10] Arugula, horseradish, radish, wasabi, and watercress are all cruciferous vegetables, although not belonging to the Brassica genus. Brassica or Cruciferous vegetables, include a variety of minerals and phytonutrients that have cancer preventive qualities, such as folate, fibre, carotenoids, and chlorophyll like other vegetables. Cruciferous vegetables, on the other hand, are distinctive most of them high in glucosinolates, sulfurcontaining chemicals that give them their pungent odours and spicy (some say bitter) flavour. Cruciferous vegetables are high in nutrients including Betacarotene, lutein, and zeaxanthin, as well as Vitamins C, E, and K, folate, and micro minerals.[11] They possess excellent source of fibre.

The plant enzyme myrosinase hydrolyzes glucosinolates, forming physiologically active chemicals such as indoles and isothiocyanates in the process. Plants have been shown to have over 100 glucosinolates with distinct hydrolysis products.[12] Broccoli, for example, is high in glucoraphanin, a glucosinolate precursor of sulforaphane (SFN), and glucobrassicin, an indole-3-carbinol precursor (I3C). Watercress, furthermore, is high in gluconasturtiin, a precursor to phenethyl isothiocyanate (PEITC). Some of the isothiocyanates and indoles, as well as their glucosinolate precursors, that are currently being studied for chemopreventive characteristics as shown in Table no. 1. The chemopreventive action of these vegetables is thought to be mediated by isothiocyanates (hydrolytic product of glucosinolatess). Glucoraphanin in broccoli, glucoerucin in rocket salad, glucoraphasatin in radish, and gluconasturtiin in watercress are all examples of glucosinolates. In addition, myrosinase, an intestine microbial enzyme, can aid in the production of isothiocyanates from their glucosinolate precursors.[13]

NUTRACEUTICALS AS CHEMO-PREVENTIVE AGENT MECHANISMS OF ACTION

Chemopreventive agent is defined as the make use of natural or manufactured substances to cease, slow, or stop the progression of cancer. Intraepithelial neoplasia or carcinoma in situ, which correlate to the promotion and progression stages, are the most common early signs of solid malignancy.[14] As a result, medicines that inhibit 'promotion' and 'progression' may be of special therapeutic importance. Such drugs, in the end, hinder the development and survival of cells that have already committed themselves to malignancy. Even at extremely low concentrations, bioactive chemicals in food compounds may have a significantly bigger influence on gene expression regulation than previously thought. Continued study into the impact of nutraceuticals on gene expression should shed light on the processes of dietary alterations in the prevention of illnesses including over weight/obese, NIDDM(diabetes), heart related problems, high blood pressure, and cancer problems. Some recent experimental studies on the effects of certain nutraceuticals on the activity of transcription factors such as activator protein (AP-1), nuclear factor kB (NFkB), sterol response element binding proteins (SREBPs), peroxisome proliferator-activated receptor-gamma (PPARgamma)[15], and modulation of the expression of antioxidant genes such as Bcl-2 as final targets in the signal transduction spurt and gene regulation have break ground for more research into these mole.

Cruciferous vegetables contains glucosinolates that have been broken down during cooking, chewing, and digestion to developed physiologically active chemicals such indoles, nitriles, thiocyanates, and isothiocyanates.[16] The anticancer properties of indole-3-carbinol (an indole) and sulforaphane (an isothiocyanate) have been studied the most. Sulphorphanes are made up of two different phytochemicals: By interacting with kelch like ECH-associated protein 1(KEAP1), 1-isothiocyanol-(4R)- (methylsulfinyl) butane, present in brassica family like broccoli, suppresses the stimulation of Nuclear factor *kappa B* (NF-kB) and regulates the activation of mitogen- activated protein kinase (MAPKs) and nuclear factor erythroid 2- related factor 2(Nrf-2).[17] Isothiocyanates' chemoprevention functioning affect different phases of oncogenesis; however, one of the utmost important is the disablement of the formation of DNA adducts with chemical mutagen agents by restraining the generation of their reactive intermediates via modulation of carcinogen-metabolizing enzyme systems; decreased bioavailability of genotoxic intermediates can be achieved by inhibiting cytochrome P450 bioactivation and/or induction of phase I.[18]

In rats and mice, indoles and isothiocyanates have been proven to suppress cancer formation in various human organs, including the breast, colon, liver, lung, bladder, and stomach.[19] Several possible methods in which these chemicals may help prevent cancer have been found through animal studies and laboratory experiments:

- They aid in the prevention of DNA damage in cells.
- They aid in the inactivation of carcinogens.
- Antiviral and antibacterial properties.
- They help to reduce inflammation.
- They are capable of causing cell death (apoptosis).
- They stop tumour blood vessels from forming and tumour cells from migrating (angiogenesis) (needed for metastasis).[20]

EVIDENCE OF CRUCIFEROUS VEGETABLES IN REDUCTION OF CANCER RISK

Epidemiological studies show that a broccoli rich diet lowers cancereous hazard and growth. Isothiocyanates, such as sulforaphane, have been linked to a lot of this. Sulforaphane is a plant extract is well-known for its antioxidative properties, an anti-inflammatory agents, and chemo-preventive properties in the treatment of cancers such as prostatic, breast, liver, and colon.[21] Scientists or Researchers have been looked into possible association between cruciferous vegetable consumption and the cancer endanger.

Various experimenters have been discussed the evince. The following are some of the most important research on four types of cancer.

Table 1: Some food sources of selected isothiocyanates and their glucosinolate precursors that are under investigation for their cancer chemopreventive properties.[22-24]

Glucosinolate (precursor)	Indole or Isothiocyanate
Glucobrassicin	Indole-3-Carbinol
Glucoraphanin	Sulforaphane
Gluconasturtiin	Phenethyl-Isothiocyanate
Glucotropaeolin	Benzyl-Isothiocyanate
Sinigrin	Allyl-Isothiocyanate

Prostate Cancer

Sulforaphane demonstrated that have a role in number of critical metabolic activities processes implicated in prostate cancer growth, including angiogenesis, apoptosis, and cell proliferation, induction.[25-28] Sulforaphane therapy lowered expression of important glycolytic genes such as hexokinase II and pyruvate kinase M2 in prostate cancer cell lines LNCaP, 22RV1, and PC-3, as well as TRAMP and Hi-Myc in transgenic mice models. In the prostate cancer cell lines DU145 and PC-3, sulforaphane triggered S-phase and G2/M-phase cell cycle arrest, increased histone acetylation, and up-regulated cell cycle proteins, suggesting that sulforaphane therapy reduces cell proliferation activity. Numerous human research have looked at the effects of sulforaphane on prostatic cancer. In a case–control study, consumption of brassica family vegetables and broccoli, a good source of sulforaphane, were found to be linked with lower the prostate cancer risk at every level above the lowest consumers.[29-35]

Zhang and co-workers evaluated the impact of day to day ingestion of 200 mol broccoli sprout extract or placebo in males scheduled for prostate biopsy and found alterations in gene expression, including down regulation of genes linked to prostate cancer development.[45]

Breast Cancer

Sulforaphane have been associated to a reduced the risk formation of breast cancer progression in both cell-based and human studies, including the induction of cell cycle arrest and death. By altering cysteine residues in the promyelocytic leukaemia protein, known to enhance proliferation of the Michigan Cancer foundation-7(MCF-7) breast cancer cell line, sulforaphane therapy inhibited cell proliferation and induced cytotoxic activity in MCF-7 and MDAMB-231 is a epithelial human breast cancer cell lines. Sulforaphane has also been determined to affect cell migration and the expression of epithelialmesenchymal transition markers, which are important in the spread of breast cancer.[36-40] Zhang & colleagues investigated the association between cruciferous vegetable consumption and biomarkers in women undergoing breast biopsies and discovered a negative relationship between total cruciferous vegetable intake and cell proliferation in DCIS breast tissue, implying that sulforaphane might play role in breast cancer chemoprevention.[51]

Liver Cancer

In the liver cancer cell line HepG2, sulforaphane treatment decreased migration and adhesion while inhibiting production of critical angiogenesis markers such as VEGF, STAT3, and HIF-1. In HepG2 and Huh7 cell lines, along with in a xenograft mouse model, sulforaphane treatment reduced cell growth by down regulating critical cell cycle-related genes.[41-44] In HepG2 cells, sulforaphane reduced release of the pro-inflammatory cytokine interleukin-6 and was not associated with cellular damage, indicating that sulforaphane may have anti-inflammatory effects and modify liver carcinogenesis. While there is a lot of cell based evidence supporting sulforaphane's function in liver cancer, there are few animal studies and none in humans.[45,46] Researchers studied the effects of diethylnitrosamine on mice before they were put on a Western diet or a Western diet supplemented with 10% w/w freeze-dried broccoli powder. The broccoli diet reduced liver damage and fatty liver progression, but it did not prevent the development of liver cancer. Mice were fed a control or Western diet with or without the addition of 10% w/w freeze-dried broccoli before being administered diethylnitrosamine in another investigation. In mice given freeze-dried broccoli, the onset and development of liver cancer was decreased. To fully understand the effect of sulforaphane on liver cancer, more animal based and human-being research are needed.[47,48]

Colon Cancer

Dietary habits are strongly linked to colon cancer incidence; diets heavy in red meat are linked to a higher risk, whereas diets high in fruits and vegetables are linked to lower risk. Sulforaphane inhibited cell proliferation in human colon cancer cell lines HCT116 a human colon cancer cell and SW480 in a dose dependent manner and boosted apoptosis triggered by Lactobacillus via the TNF pathway. In HCT116 and SW480 spheroids, sulforaphane therapy suppressed important colorectal cancer stem cell markers including

CD44 and CD133, which was assisted via the TAp63/ Lgr5/-catenin pathway, suggesting that sulforaphane exposure might lead to reduced cell proliferation activity. In p53-wild-type HCT116 cells, sulforaphane treatment (10 M) enhanced cell proliferation and decreased expression of critical apoptotic proteins Bcl- 2 and Bax, whereas dosages larger than 10 M induced cell death. Sulforaphane's effect on colon cancer has been studied in just a few animal and human research.[49] Suzuki and colleagues discovered that sulforaphane consumption decreased the formation of microscopic aberrant crypt foci and macroscopic tumours in mice and people with colon cancer, implying that broccoli consumption might slow the course of colon cancer. Brassica genus cruciferous vegetables have active phytochemicals compounds that have been shown in some research beneficial impression on carcinogen agents related biomarker progression. In a study, indole-3-carbinol was found to be more efficient than placebo at reducing the proliferation of aberrant cells on the cervix's surface.[50]

SUMMARY AND FUTURE PERSPECTIVE IN RECOMMENDATION OF NUTRACEUTICAL

Nutraceuticals are natural and bioactive items with dietary value that help the body maintain energy balance and may have significant therapeutic potential in a variety of disorders. Major nutraceuticals are increasingly included in nonprescription nutrition supplements, and their self-prescription is increasing on

a huge scale. The existing research supports the usage of nutraceuticals compounds in cancer risk preclusion and management in the vast majority of cases. The molecular mechanism of nutraceuticals is little understood, and the majority of research focuses on their effectiveness in experimental animals. The number of people diagnosed with cancer is increasing all the time.

Phytomedicines, on the other hand, are becoming increasingly essential as they become more widely utilised. Many research paper have been shown on pharmacological activities and the clinical evaluation of some of them association with cancer progression in lower stage. Despite the fact that certain research have shown the beneficial response, the procedure of action are yet unknown. Among them some have the same mechanisms and they can be classified as a group based on that pathway.[51] Cruciferous veggies are distinctive in that they are high in glucosinolates, sulfur-containing chemicals. When you chop or chew cruciferous vegetables, bioactive glucosinolate hydrolysis products such isothiocyanates and indole-3- carbinol are formed. Isothiocyanates are derived from the hydrolysis of glucosinolates for specific constituents of Brassica family vegetables, and compounds like sulforaphane might assist in prevent cancer by improving the removal of potential carcinogens from the body and increasing the transcription of tumour suppressor proteins, including those silenced by epigenetic mechanisms.

Isothiocyanates from cruciferous vegetable diet can reduce cancer risk, according to epidemiological research, although the preventive benefits may be impacted by individual genetic diversity in isothiocyanate metabolism and clearance from the body in human exposure. Although cruciferous vegetables contain significant levels of glucosinolates, heating, particularly boiling and high-power microwaving, can reduce the bioavailability of isothiocyanates. By deactivating CYP 450 and bioactivating Phase II detoxifying enzymes, glucosinolates and related isothiocyanates can modify the activity of carcinogenmetabolising enzyme systems, which is expected to have an influence on the chemopreventive activity connected to cruciferous vegetable consumption.[27]

In certain epidemiological studies, a high consumption of cruciferous vegetables has been linked to a decreased risk of lung and colorectal cancer, however there is evince that genetic polymorphisms may alter the effectiveness of cruciferous vegetables on human cancer risk. Furthermore, cruciferous vegetables include a range of additional nutrients (vitamin C, vitamin K, selenium, chromium, carotenoids, and flavonoids) that are recognised to have substantial health benefits. As a result, it's difficult to distinguish the effects of glucosinolates from those of these other substances when analysing the outcomes of cruciferous vegetable therapies based on diet. There are many proofs that sulforaphane inhibits cancereous formation in human cell line, further study into the underlying molecular pathways is required to completely comprehend the function of sulforaphane in cancer progression metabolic reprogramming. This shows that sulforaphane might be utilised in connection with current anti-cancer therapies as well as as a prospective therapeutic candidate.[29,52]

CONCLUSION

In addition to their nutritious qualities, cruciferous vegetables constitute a large source of bioactive metabolites. These characteristics indicate a strong relationship with colorectal cancer, one of the most important clinical and public health concerns of our day. The active elements of cruciferous veggies, which were the subject of the greatest discussion in the literature on colorectal cancer, were looked at in this review. In light of this, it can be said that a variety of metabolic, genetic, and prospective processes pertaining to these veggies and their bioactives have the ability to prevent colorectal cancer in addition to lowering its occurrence rates, which would have a therapeutic impact.

Despite the fact that these vegetables and their bioactive metabolites have been the subject of numerous studies that have been published in the literature, it is evident that further research is required to fully understand their therapeutic effects (in terms of the right dosage to consume, the method of extraction, potential side effects, etc.). Since the bulk of these research appear to be focused more on preventative functions—both in primary prevention and secondary prevention/slowing progression—than on therapeutic roles, when the cumulative literature is reviewed. Additionally, a large number of in vitro research have been conducted expressly to examine their therapeutic benefits; still, additional human clinical investigations are required to corroborate these findings. This should cover a wide range of questions about the antagonistic or synergistic interactions between their bioactive components.

By extracting bioactive metabolites, these vegetables have the potential to be utilized as a natural medicine in addition to being used for natural nourishment. These characteristics highlight their importance for sufficient, balanced, and clinical nutrition from both a dietetic and pharmaceutical perspective, and they should be a larger part of our diets.

CONFLICT OF INTEREST

The authors declare that the review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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