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Biopharmaceutical aspects of *Brassica* vegetables

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Abstract
Brassica is a genre of plants belonging to family *Brassicaceae* commonly used as vegetables and oilseed. The members of *Brassicaceae* are devoured by natives throughout the world. They comprise important food crops in Europe, Japan, China and India and thus symbolize a vital portion of human regimen worldwide. *Brassica* vegetables frequently exploited for food include broccoli, cauliflower, Brussels sprouts, cabbage and certain seeds. They are important source of bioactive compounds and nutrients like Vitamin E and C, soluble fiber, enzymes owing antioxidant activity for example peroxidase, superoxide dismutase (SOD) and catalase and carotenoids which have persuasive antiviral, antibacterial and anticancer activity. *Brassica* vegetables have positive impacts on human vigour which are somewhat accredited to their composite blend of phytochemicals possessing antioxidant activity that fights against free radicals by acting on complementary and transformed levels. They basically lead to the stimulation of detoxification enzymes, induce immune system, preclude oxidative stress, diminution of threat of cancers, obstruction of carcinogenic mutations and malignant transformation besides lessening explosion of cancerous cells. These vegetables are also a major source of valuable metabolites, which embrace anthocyanins, terpenes, S-methyl cysteine sulfoxide, sulforaphane, selenium, coumarins and glucosinolates. Glucosinolates breakdown into diverse metabolic products which act as modulators to protect against DNA damage. They may abolish or nullify innumerable mutagenic and carcinogenic factors through consequently inhibiting DNA methylation which mainly occurs via the initiation of enzymatic systems I and II phase of xenobiotics metabolism. Genetic makeup, environmental impact, cultivation strategy, biochemistry of plants and type of processing and storage, fundamentally outline the concentration and bioavailability of these constituents. Therefore, we can say that the consumption of vegetables including *Brassica* species is strongly connected with the prevention against threat of numerous types of chronic diseases like Alzheimer's disease, cardiovascular disease, diabetes, cancer, age-related efficient waning and cataracts etc. and thus plays a crucial function in maintaining healthy human life.

Keywords: Anticancer, *Brassica* vegetables, glucosinolates, isothiocyanates, neurodegenerative diseases, phytochemicals, sulforaphanes.

1. Introduction
Plant-centred diets comprise substantial quantities of bioactive compounds, which deliver necessary health profits yonder simple nourishment [1]. The consumption of a diet rich in *Brassica* vegetables has progressive insinuations for human health which have been implied by various epidemiological evidences (Fig.1) [1, 2]. Greater devotion has been waged towards edible plants in the last decades, exclusively those that are rich in phytochemicals (secondary metabolites) and nowadays, a special interest is developing in the antioxidant activity of such phytochemicals [1]. Cruciferous vegetables rich diet has been related with inferior rates of coronary heart disease and cancer [3-8]. Plant-based terpenes, flavonoids, phenols, glucosinolates, isoflavones together with many other compounds that are existing in the daily diet are described to have anticarcinogenic and antioxidant properties plus a catholic gamut of anti-tumor actions [4, 7, 9, 10].These protective effects of *Brassica* vegetables are mainly accredited to the presence of vast quantities of glucosinolates, that distinguishes them from other vegetables. Vegetables of the *Brassica* genus, including broccoli, kale, cabbage, Brussels sprouts, cauliflower, black and brown mustard, kohlrabi, root crops like turnips and rape subsidize utmost to glucosinolates intake [11].

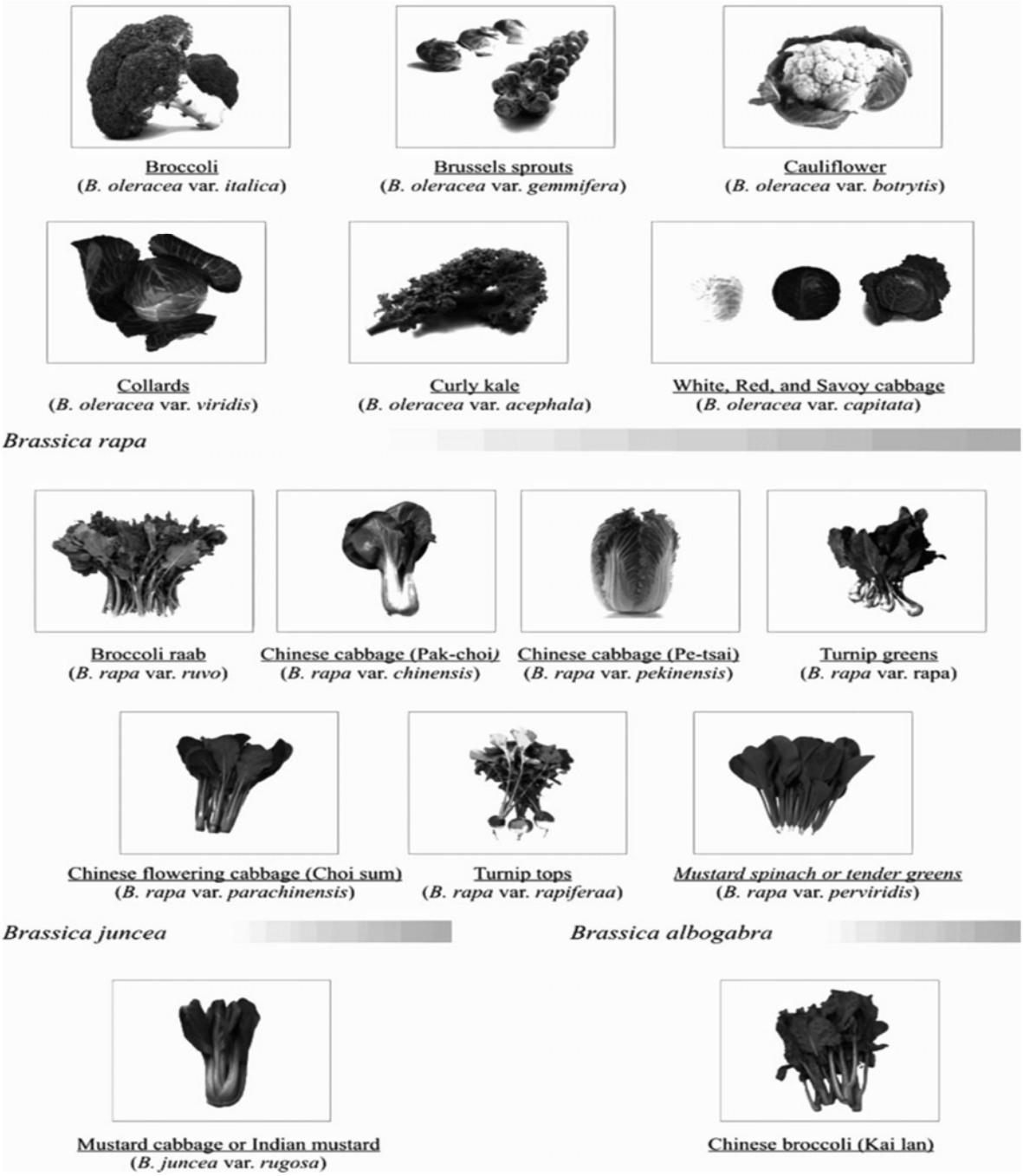

Fig 1: Scientific and dialect names of marketed *Brassicaceae* [2].

Glucosinolates are hydrolysed into two principal components i.e., isothiocyanates and indoles owing anti-carcinogenic properties. Glucosinolates together with their consequent products have been reported to reduce the menace of certain types of cancers in humans like lung, breast, colon, rectum, and prostate cancers and thereby provide vital health benefits [10]. An enzyme called myrosinase is present in the membranes of plant cells which is responsible for the hydrolysis of glucosinolates. This enzyme comes in contact with glucosinolates only when plant gets damaged (e.g. by cutting or chewing) and as a result hydrolysis takes place. All glucosinolates present in *Brassica* family primarily show a familiar basic frame, with having difference in only their side chain (R) where R may be an alkenyl, aryl, alkyl, alkylthioalkyl, indolylmethyl or 3-hydroxyalkyl (Fig. 2) [12].

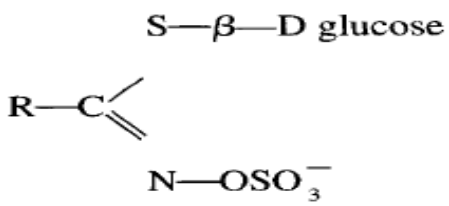

Fig 2: Basic structure of glucosinolates.

The hydrolysis products of glucosinolates entail equimolar amounts of sulfate, glucose and aglucon. The aglucones are unsteady and experience additional reactions that may lead to the production of various useful components, like nitriles, thiocyanates, isothiocyanates, or indoles (Fig. 3) [12, 13]. The

behaviour of these hydrolysis products may vary depending principally upon the presence of cofactors, the hydrolysis conditions and the side chain of glucosinolate [12].

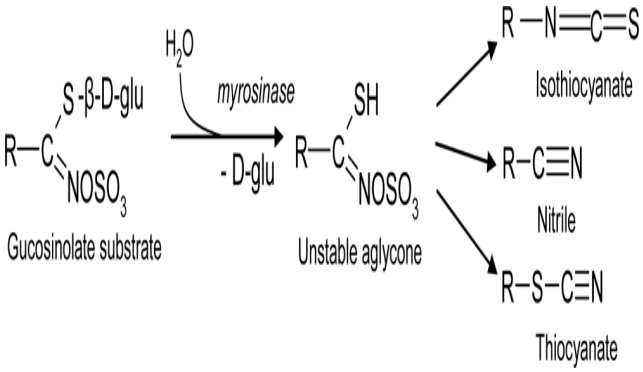

Fig 3: Conversion of Glucosinolates into Isothiocyanates by Plant Myrosinase [13]

Several experimental studies have demonstrated that the intake of isothiocyanates and indoles in animals (after a carcinogen) is associated with the reduction of tumour incidence and multiplicity [14-17]. The plausible inhibitory activity of isothiocyanates and indoles in opposition to tumorigenesis is mainly because of their capability of influencing enzyme activities of phase 1 and 2 biotransformation and as a result several processes correlated with chemical carcinogenesis get manipulated, such as DNA binding potential of carcinogens and their metabolism [18-20].

Owing to the wide range of bioactive compounds in *Brassica* genus, the attention of food scientists has shifted towards the hidden function of isolated phytochemicals. For instance, an essential nutrient of *Brassica* members i.e., Vitamin C, deficiencies an integrative approach to recognize its functions on health across with the habituation of food matrix on its bioavailability and rest of bioactive components in their usual food concentrations [21-26].

2. Phenolic Compounds

The health potential of *Brassica* vegetables are partially attributed to their intricate fusion of phytochemicals owing antioxidant activity. Recently, considerable research has been aimed at the detection of plant derived natural antioxidants which can be utilized for human consumption for prevention of non-transmissible chronic diseases and promotion of health. Phenolic compounds are one of the most vital groups among phytochemicals that possess antioxidant capacity [27]. The term "Phenolic compounds" refers to a large number of compounds, nearly 8000, extensively distributed all over the plant kingdom exemplified by having at least one aromatic ring with involvement of one or more hydroxyl groups. They are one of the most important secondary metabolites in plants and are produced via shikimic acid pathway [1]. The aromatic amino acid phenylalanine act as a precursor for their biosynthesis and the enzyme involved is known as phenylalanine ammonialyase (PAL).

Phenolics range from single aromatic-ringed, modest and low molecular weight compounds to multifarious and heavily stemmed polyphenols and tannins (Fig. 4) [28-30]. They have been classified depending on the arrangement and number of their carbon atoms in flavonoids (flavanones, flavones, anthocyanidins, flavan-3-ols, isoflavones, flavonols and many others) and non-flavonoids (stilbenes, hydroxycinnamates, phenolic acids and others) [29]. Phenolics are usually discovered conjugated to organic acids and sugars [1]. The most pervasive and diverse group of polyphenols in *Brassica* species are hydroxycinnamic acids and the flavonoids (mainly anthocyanins and flavonols). But the composition of phenolic compounds can be pretty diverse among crops from the same species or even in the single species itself.

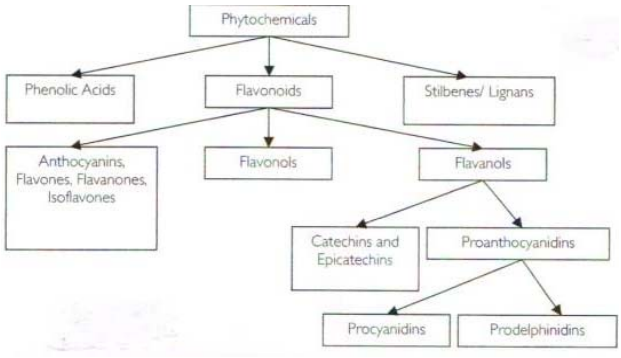

Fig 4: Classification of Phytochemicals [30].

The qualitative and quantitative profiles of different *Brassica* species have been elucidated showing their diverse polyphenol composition as well as antioxidant activity [1]. For example, Phenolic profiles of several *Brassica* species has been comprehensively reviewed by Podsedek [31]. The highest antioxidant activity was exhibited by red cabbage followed by green cabbage, while Chinese cabbage, Mustard cabbage and Chinese white cabbage have been shown to possess lower antioxidant potential as compared to these two [31]. According to a study done by Podsedek *et al*. [32] as compared to *B. oleracea*, red cabbage and Brussels sprouts have 5 to 2.2-fold higher antioxidant activity than savoy and white cabbages which may be attributed to different range of bioactive compounds in the respective species.

3. Health Benefits of *Brassica* Vegetables

The potential health benefits of polyphenols mainly depend on their bioavailability and disbursed amount [1].The concern in the biological possessions and the bioavailability of flavonoids and phenolics in food plants is being rising over the past few decades. Attracting insects for pollination and seed dispersion is one of the important supplementary roles of phenolic compounds. Moreover, they also provide resistance against fungi, insects, bacteria and viruses by acting as vital hormone controllers of plants. Likewise, because of their potential health-promoting effects, phenolic compounds have been intensively investigated in recent years [26, 33-36].

Phytochemicals from *Brassica* vegetables may act on distinctive and complementary levels [36] and they possess many advantages for the health benefits for human beings including enzyme inhibition, anti-inflammatory, antimicrobial, cytotoxic and vascular antitumor activity, antiallergic etc., but the antioxidant potential of phenolics is their most crucial attribute [31, 32, 35, 37-40]. Moreover, phenolic compounds owe other vital aspects such as the inhibition of nitrosation reactions, chelating metal ions and production of hydrogen peroxide in the incidence of some metals etc. They also have the aptitude of scavenging electrophiles and consequently, they act by blocking the onset of wide range of human diseases [31, 41-43].

The phenolic compounds impart positive effects on human health by virtue of antioxidant activity associated with their

chemical structure which bestows redox properties. These compounds can play a vital role in decomposition of peroxides, adsorbing and neutralizing reactive oxygen species (ROS) and quenching of singlet and triplet oxygen. Reactive oxygen species (ROS) can instigate DNA damage, protein and lipid oxidation, modulation of gene expression and base modification in the body [36].Moreover, they also play a central role in etiopathology of diseases, like atherosclerosis, vasospasm, cancers, stroke, heart attack and liver injury. ROS, originate in the body from various processes of oxidation, are significant ingredients of the resistant mechanisms against infection. However, if generated in excess, these free oxygen radicals may lead to the damage of the tissue [1]. Disparity between ROS and antioxidants may lead to oxidative stress due to accumulation of lipid peroxides. The various reasons of oxidative stress includes antioxidant scarcity in the diet or increased production of free radicals by stress, smoking, environmental contaminations, which immigrate into water and food (heavy metals, pesticides, nitrates, nitrites, nitrosamines etc.) [44]. Other risks are mutagenic and carcinogenic substances present in food products due to inappropriate storage conditions (eg. mycotoxins) or heat treatment (e.g. heterocyclic aromatic amines, acrylamide, genotoxic lipid peroxidation products) [36]. The existence of antioxidants, and chiefly their release during heat treatment, suggest that cabbage can effectively protect other food ingredients against thermo-oxidative changes [45].

Consumption of vegetables including *Brassica* species has been strongly connected with the reduced risk of chronic diseases, like cancer, cardiovascular disease, Alzheimer's disease, diabetes, age-related functional decline and cataracts etc. [46-48]. Vitamin C which is a vital component of *Brassica* vegetables plays a major role in the maintenance of body functions. It demonstrates a broad array of therapeutic properties that include anticarcinogenic, antioxidant, iron absorption promoter and also acts as a cofactor in the synthesis of collagen. The health-promoting properties of vitamin C have been validated by several reports [49].Vitamin C and phenolic compounds account for 80 % natural antioxidant activity in *Brassica* vegetables [31]. In cabbage and broccoli, vitamin C is accountable of 10–12% of the total antioxidant capacity [31]. Vitamin C is involved in a broad array of essential reactions in the body responsible for human fitness despite of that the phenomenon is not fully understood yet. Many health promoting properties of Vitamin C have been suggested such as the protection against free radicals, its antioxidant properties, cytoprotective functions like prevention of DNA mutation, repairing amino acid residues to save the integrity of protein and protection against lipid peroxidative damage etc. [50-52].

4. Role of Isothiocyanates (ITC)

The existence of glucosinolates in cruciferous vegetables is their most prominent and distinctive chemical property. Both the glucosinolates and their hydrolysis products i.e., isothiocyanates are eminent armaments to counter carcinogenesis which signifies that if these vegetables are consumed in large amount, they may dampen the hazard of several forms of cancer. Around 130 chemically diverse glucosinolates have been recognized [53]. In animal models, isothiocyanates (both natural and synthetic) have captivated mounting and significant research as efficient and imperative protectors against chemical carcinogenesis, since the early 1960s [54]. However, due to unavailability of satisfactory quantities of these compounds, only a few glucosinolates have been examined which seem to be very effective in impeding carcinogenesis [54].

Specific attention has been focused on the isothiocyanates, befalling in *Brassica* vegetables, for their potential anti-cancer abilities [36]. However, the structure of ITCs have a major impact on transactivation of NF- κB and also possess anti-inflammatory action, but only a few studies have been carried out [55, 56]. ITCs, specific to diverse range of cruciferous vegetables, can prevent human from a number of diseases like cancer, chronic–degenerative diseases, diabetes, cardiovascular diseases and neurodegeneration etc. [57]. Constant inflammation plays a critical role in sundry human illnesses and ITCs reduce inflammation by permanently inactivating the migration of inhibitory factor of macrophages and restraining of cyclooxygenase 2 [57].

Sulforaphane (SFN), one of the most important ITCs of *Brassica* vegetables has been established to possess a range of defensive effects in models of cancer and tissue injury. There are two types of xenobiotic metabolizing enzymes i.e., Phase I and II which are expressed in epithelial cells (including those of colon) and in liver whose equilibrium can be amended by sulforaphane [58]. Glutathione transferase family (GST) represents an important type of Phase II enzymes that can metabolize the products of Phase I activity and thus, may lead to the formation of water-soluble and sedentary conjugates which are promptly defecated in urine [58].

5. Acute Neurodegeneration

a.) Ischemic brain injury: Basically involves specific biochemical mechanisms, like the origination of ROS, glutamate-mediated excite-toxicity and apoptosis together with inflammation [59]. In case of neonatal hypoxia model, [60, 61] scrutinized that the expressions of Nrf2 and HO-1 were pointedly increased by SF which was escorted by reduced infarct volume.

b.) Traumatic Brain Injury (TBI): Initiated by external mechanical force and characterized by the mutilation of brain [62]. Recently it has been shown that administration of SF after TBI reduces the cerebral edema and BBB impairment in rats [63, 64]. Also Zhao *et al.* [64] reported that after the interval of 24 h and 3 days following TBI, the attenuation of SF resulted in the loss of aquaporin-4 (AQP4) channel in the core of injury together with the increment of AQP4 protein levels in the penumbra region. AQP4 channels functions as to clear the excess water and thus maintain the water homeostasis of brain which was proved by monitoring the diminution in cerebral edema only at 3 days of TBI [65].

6. Chronic Neurodegeneration

a.) Alzheimer's Disease: It is the most ordinary neurodegenerative disease suffered by older people that results in dementia. The consequences of Alzheimer's Disease involves impairment of at least one cognitive function and progressive decline in memory [66]. In this context, the neuroprotective effects of SF against oxidative stress has been revealed by Kwak *et al.* [67], in terms of cytotoxicity elicited by hydrogen peroxide and formation of protein carbonyl which occurs as a result of induction of proteasome expression in Neuro2A cells (murine neuroblastoma) by SF. Park *et al.* [68] also demonstrated the capacity of SF to protect the neuronal cells from Aβ1–42-mediated cytotoxicity and increase in activities of proteasome, in other similar cellular models.

b.) Parkinson's Disease: Parkinson's disease, a type of neurodegenerative disease related with age, is characterized by congregation of neuronal inclusions identified as Lewy bodies and with gradual loss of dopaminergic (DA) neurons in the substantia nigra pars compacta [69]. However, the exact etiology of PD has not been fully elucidated, it mainly has an environmental [70, 71] or a genetic [72] origin, or a combination of both as recommended by many reliable theories. The crucial protein which is involved in the pathogenesis [73-75] of this disorder is a prime component of Lewy body inclusions namely α-synuclein protein [76] as demonstrated by diverse genetic studies. Although it has been detected that a superfluous of α-synuclein protein can cause loss of DA neuron, but the mechanism by which mutations in this gene lead to neuron loss and precise biological function of α-synuclein are still not clear [77].

SF is also capable of significantly diminishing the levels of DA quinone in dopaminergic cell lines, for example SK-N-BE(2)C, CATH.a in addition to mesencephalic dopaminergic neurons (aroused by BH4 and 6- hydroxydopamine (6-OHDA) [78] as indicated by in vitro studies. According to Han *et al.* [79], SF can safeguard dopaminergic cells from the cytotoxicity of 6-OHDA and BH4 as the activity of NQO1 enzyme and mRNA level are amplified and the amount of quinone-modified proteins is diminished by SF treatment.

7. Cancer Prevention

The development of cancer is a multifaceted and prolonged process involving initiation, elevation and progression [80]. The consumption of Cruciferous vegetables seems to lower the threat of certain types of cancers, like prostate, colorectal and renal cancers due to the presence of glucosinolates [81]. However, the evidence for breast, oral and lung cancers is not as strong [81]. The extracts of fresh *Brassica* vegetables including Brussels sprouts, cauliflower and broccoli has been shown to possess the highest antioxidant and anti-proliferative activities on carcinoma HT-29 cells and moreover, the tested samples were free from any genotoxic activity [80].

The anti-myeloma activity of the phenethyl isothiocyanate and sulforaphane on human primary myeloma tumor cells along with panel of myeloma cell lines showed that isothiocyanates may hold powerful anti-myeloma activities together with the enhancement of action of additional anti-multiple myeloma agents [82].

The chief descriptive of the flavonol subclass in *Brassica* vegetables, i.e., quercetin (found at high concentration in broccoli) has gained significant attention in recent years because of its high potential for preventing the oxidation of LDL by chelating transition metal ions and scavenging free radicals [1]. These properties are deliberated due to a 4-oxo function at the C-ring, unsaturation at the C-ring and dihydroxylated B-ring [1]. Hence, quercetin can prevent humans from various kinds of fatal diseases, for example, chronic inflammation, atherosclerosis and most importantly cancer by induction of enzymes which can detoxify 30 types of carcinogens that may cause cancer and through retardation of oxidative degradation [83-85]. The reduction of the risk of prostate cancer through the intake of diet rich in broccoli have been suggested through different epidemiological studies. It has been shown that if one or more portions of broccoli is consumed per week, it can significantly lessen the incidence and the development of prostate cancer from confined to belligerent forms [86, 87].

The inhibition of the expansion of colorectal cancer in animal models has been indicated through some experimental evidences, when given either before, or after, treatment with a carcinogen [88]. It has been shown that a diet enriched in sinigrin, which is a glucosinolate precursor of allyl isothiocyanate, can suppress the induction of enhanced level of apoptosis and mitosis in the colorectal crypts of rats, 48 h after treatment with the colon carcinogen dimethyl hydrazine (DMH) in an *in vivo* study [89]. However, it resulted in the substantial destruction of aberrant crypt foci (kind of precancerous lesions) [88]. But, importantly, there was no momentous effect on kinetics of crypt cell and their apoptosis, in the colon of control rats (not treated with a carcinogen) due to sinigrin [90]. The effects similar to those of AITC on HT29 cells have been shown to be exerted by the juice of uncooked Brussels sprout tissue (prepared by mechanical disruption) in vitro [91]. Moreover, in a rodent model, there was a marked increment in the apoptosis of crypt cell after treatment with DMH by the same juice given by gavage [91]. All these results collectively suggest that a discriminatory effect in contradiction of the evolution of colorectal epithelial cells carrying DNA damage may be exerted by the isothiocyanates together with their dietary components *in vivo.* Nevertheless, it has not yet been recognized that the intake of diet rich in breakdown products of glucosinolates leads to the induction of suppression and apoptosis of the cell cycle in the colorectal mucosa of human, hence warrants further research.

8. Conclusions

Brassica vegetables have long been regarded as excellent source of nutraceuticals attributed to the structural diversity of the bioactive components and their wide array of beneficial effects on human health. These possess a large gamut of therapeutic effects, like antibacterial, antifungal, antitumor, anti-mutagenic, anti-inflammatory, neuroprotective and anti-oxidative activities that have been demonstrated and validated through many in vivo and in vitro pharmacological studies. Increased consumption of these vegetables is highly desirable in recent times. The numerous types of supplements containing purified compounds which are derived from *Brassica* species, should be viewed with prudence. The protective effects from *Brassica* vegetables may be increased through content-enhanced functional foods, however, these should be tested for safety. Diverse kinds of cooking methods like boiling, frying and microwave cooking etc. should also be optimized in order to maintain the original and natural content of bioactive compounds in processed foods. Therefore, we can conclude that *Brassica* vegetables play a vital role in prevention of non-transmissible chronic diseases and maintenance of healthy wellbeing.

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