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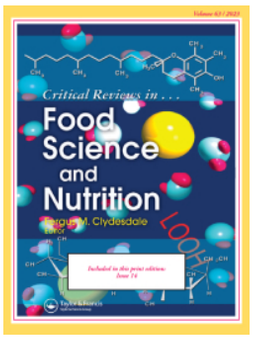

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REVIEW

Anticancer activity of broccoli, its organosulfur and polyphenolic compounds

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ABSTRACT

The use of natural bioactive constituents from various food sources for anticancer purposes has become increasingly popular worldwide. Broccoli (*Brassica oleracea* var. *italica*) is on the top of the consumed vegetables by the masses. Its raw matrix contains a plethora of phytochemicals, such as glucosinolates and phenolic compounds, along with rich amounts of vitamins, and minerals. Consumption of broccoli-derived phytochemicals provides strong antioxidant effects, particularly due to its sulforaphane content, while modulating numerous molecules involved in cell cycle regulation, control of apoptosis, and tuning enzyme activity. Thus, the inclusion of broccoli in the daily diet lowers the susceptibility to developing cancers. Numerous studies have underlined the undisputable role of broccoli in the diet as a chemopreventive raw food, owing to the content in sulforaphane, an isothiocyanate produced as a result of hydrolysis of precursor glucosinolates called glucoraphanin. This review will provide evidence supporting the specific role of fresh florets and sprouts of broccoli and its key bioactive constituents in the prevention and treatment of different cancers; a number of studies carried out in the *in vitro* and *in vivo* conditions as well as clinical trials were analyzed.

KEYWORDS

Antitumor effect; *Brassica oleracea* var. *italica*; Chemoprevention; Flavonoids; Glucosinolates; Sulforaphane

Introduction

According to the WHO, cancer is the second leading cause of death globally, exceeded only by cardiovascular diseases (Nguyen et al. 2021; Kubczak, Szustka, and Rogalinska 2021). As the world population gradually ages, cancer incidence is increasing rapidly (Gu, Mao, and Du 2022). Malignant neoplasm is a leading cause of morbidity and mortality around the world which poses a noticeable burden for modern society (Kaiser et al. 2021). In the United States, breast cancer (30%) was the prevailing type of case of females' neoplasms in 2022, while prostate cancer (26%) dominated in mails (Siegel et al. 2022). Thus, novel strategies and drugs are needed for cancer therapy, especially with regard to the most common types of malignant neoplasms in the population.

Cancer is a life-threatening disease that involves extensive growth of abnormal cells capable of metastasizing in various parts of the body, ultimately leading to death. The complexities of cancer as a neoplastic disease are several biological features acquired during its multistep development including evading growth suppressors, sustaining proliferative signaling, resisting cell death, enabling replicative immortality, and activating invasion and metastasis (Hanahan and Weinberg 2011). Despite the progress in developments in diagnostic methods and therapies, resistance to administrated drugs and metastasis are the main obstacles to its successful treatment (Kubczak, Szustka, and Rogalinska 2021). In this regard, the search for effective drugs against cancer is complicated by the multifaceted nature of the process of tumorigenesis.

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Given the fact that chemotherapeutics induces a lot of side effects, dietary phytocompounds are regarded as alternatives for the prevention and suppression of cancer due to their effectiveness along with low toxicity and fewer adverse effects (Nguyen et al. 2021; Gu, Mao, and Du 2022). People who suffer from chronic diseases, including cancer, are increasingly using the huge panoply of plant extracts available as a source of drugs (Dar et al. 2017; Anand, Sugumaran, and Narayanasamy 2019). Indeed, natural products and their derivatives are rich sources of bioactive molecules for drug discovery. More than one-third of all Food and Drug Administration (FDA) approved drugs being from natural origin (Patridge et al. 2015).

Recently, an increasing interest has been stated in investigating the anti-cancer potential of raw vegetables rich in isothiocyanates, polyphenols, vitamins and some trace elements (Miękus et al. 2020; Kim et al. 2020; Ansari et al. 2021; Gasmi, Mujawdiya, Noor, et al. 2022). For example, *Brassicaceae*, a Cruciferous plant family, is very rich in raw substances eliciting a great interest in anticancer research (Liu et al. 2020; Georgikou et al. 2020; Mandrich and Caputo 2020). Vegetables that belong to the *Brassicaceae* family, such as broccoli, are gaining increasing popularity, since many epidemiological studies have proved that vegetables rich in some phytochemicals are associated with a lesser incidence of many types of cancer, cardiovascular diseases, type 2 diabetes mellitus, etc. (Shimoda et al. 2018; Nguyen et al. 2020; Chaika et al. 2020).

Broccoli (*Brassica oleacea* var. *italica*) is a well-known green vegetable very common in the Mediterranean diet habits due to its recognized health benefits (Eve et al. 2020; Connolly et al. 2020). One of the major bioactive effects acknowledged for broccoli is its potential anticancer effect. A multitude of studies has shown that ingestion of broccoli as well as other Cruciferous vegetables (plants belonging to the *Brassiciceae* or *Cruciferae* family) may lower overall cancer risk, especially for breast, prostate, colorectal, lung and bladder cancer (Kaiser et al. 2021).

Broccoli-derived bioactive phytochemicals appear particularly effective in breast cancer management (Palliyaguru et al. 2020; Ferguson and Schlothauer 2012). In females, breast cancer is a well-known type of malignant tumor (Ezzati et al. 2020; Siegel et al. 2022), and coupled with this, the currently available chemotherapeutic agents have been linked to several adverse effects; for this reason, the use of natural products with immunomodulatory activities is gaining increased popularity (Jeyashree et al. 2019; Shinkovenko et al. 2018). The antioxidant role of broccoli has also been well-documented (Ansar et al. 2020).

Among all bioactive constituents of broccoli, glucosinolates are extremely important phytochemicals, owing to their anticancer potential (Yu et al. 2020). It should be mentioned that to date about 200 glucosinolate have been identified (Zhang et al. 2022). Broccoli is rich in organosulfur compound sulforaphane (1-isothiocyanato-4-methylsulfinylbutane) which belongs to the isothiocyanate family of phytoconstituents where -N = C=S considered as the most important active group (Zhang et al. 2022).

Many researchers suggest using broccoli sprouts and seed extracts for making functional foods or pharmaceutical products (Yanaka et al. 2009; Favela-González, Hernández-Almanza, and De la Fuente-Salcido 2020). Tříska et al. (2021) found that broccoli sprouts contain up to 100 times higher amount of bioactive compound sulforaphane than mature plants. Broccoli sprouts and seed extracts have been applied as chemopreventive agents in preclinical studies (Klomparens and Ding 2019; Ferreira et al. 2018). Arora, Sharma, et al. (2022) investigated the positive remote effect of broccoli sprouts' influence on transcriptome and methylome in the prevention of mammary cancer in offspring. In *in vitro* and *in vivo* studies, it has been reported that the induction of apoptosis is crucial for the anticancer properties of sulfur-containing compounds of garlic, onion, and *Brassica* vegetables which are able to modulate apoptosis by a wide range of mechanisms (De Gianni and Fimognari 2015).

Sulforaphane has been a widely studied phytochemical for its chemopreventive characteristics (Samanta et al. 2022). For instance, it inhibits the histone deacetylases (HDAC) activity, which is responsible for tumor expression. HDAC inhibition has been well documented in the literature in circulating peripheral blood mononuclear cells of individuals who consumed broccoli (Mitsiogianni et al. 2021; Hossain, Liu, and Wood 2020).

Numerous preclinical studies have been pointed toward the anticancer effect for sulforaphane, along with indole-3-carbinol, and diindolylmethane which are also abundantly present in broccoli (Capuano et al. 2017; Mangla et al. 2021). It was also reported by numerous case-control clinical studies that broccoli exerts a strong role in cancer protection, being even stated a strong interplay between broccoli intake and cancer inhibition (see Table 1). Recently, scientists have named broccoli as "Green chemoprevention" because its consuming is more cost-effective and affordable than most traditional chemopreventive drugs (Nandini et al. 2020).

In this sense, the present review aims to provide an overview of broccoli composition and the action of its key constituents on cancer prevention and treatment, with special emphasis on brest and prostate cancers as the most common types of malignant neoplasms in humans. A general perspective on how the consumption of Cruciferous vegetables leads to a reduced frequency of cancer is also given.

Bioactive compounds in broccoli

Broccoli (*Brassica oleacea* var. *italica*) belongs to the *Brassicaceae* family and is an edible green plant comprised of a huge flowering head and an edible stalk. Its flowering head, chiefly dark green, shows a tree-like arrangement with a light green stalk (Baenas et al. 2017; Kellingray et al. 2021; Li et al. 2011; Charron et al. 2018). 100 g of broccoli serving make up to 34 calories. Raw broccoli contains 89% water, 3% proteins, 7% carbohydrates, and fats in traces.

Broccoli is rich in glucosinolates and some flavonoids (Sarvan et al. 2017). Glucosinolates give Cruciferous vegetables a specific pungent smell and piquant taste (Finley 2005). The main function of glucosinolates in plants is accelerating the resistance against herbivores. It should be

Table 1. Some examples of recent clinical trials planned to investigate the anticancer potential of broccoli and its bioactive components (from ClinicalTrials.gov).

Clinicaltrialgov.code	State	Title	Protocol	Subjects and institution
NCT03665922	In progress	Biomarkers of Sulforaphane/Broccoli Sprout Extract in Prostate Cancer	RCT vs placebo	40 Bruce Jacobs, University of Pittsburgh (NCT03665922 2023)
NCT01228084	Recruitment Completed	Sulforaphane in Treating Patients with Recurrent Prostate Cancer	RCT (interventional)	20 OHSU Knight Cancer Institute Portland, Oregon, United States (NCT01228084 2023)
NCT00982319	Recruitment Completed Results posted	Study to Evaluate the Effect of Sulforaphane in Broccoli Sprout Extract on Breast Tissue	Double blind RCT	34 Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (NCT00982319 2023)
NCT02404428	Terminated	Utilizing MRI to Study the Effect of Sulforaphane on Prostate Cancer (ESCAPE-ING)	Double blind RCT	20 planned (only 5) Quadram Institute Bioscience (NCT02404428 2023)
NCT01108003	Terminated Results posted	Broccoli Sprout Extract in Treating Patients With Transitional Cell Bladder Cancer Undergoing Surgery	Pilot study RCT	12 planned (only 7) Roswell Park Cancer Institute (NCT01108003 2023)
NCT03182959	Active	Broccoli Sprout Extract in Preventing Recurrence in Patients With Tobacco-Related Head and Neck Squamous Cell Cancer	Pilot study Crossover RCT	40 University of Arizona (NCT03182959 2023)
NCT01753908	Recruitment Completed	Broccoli Sprout Extract in Treating Patients With Breast Cancer	Randomized pilot trial	30 Roswell Park Cancer Institute (NCT01753908 2023)
NCT03232138	Active, not recruiting	Clinical Trial of Lung Cancer Chemoprevention with Sulforaphane in Former Smokers	Double blind RCT	67 University of Pittsburgh (NCT03232138 2023)

noted that glucosinolates are available in broccoli in two main forms, namely indole glucosinolate and aliphatic glucosinolate, according to the structure of the amino acid precursors (Zhang et al. 2022). Benzyl isothiocyanate and phenyl isothiocyanate, other hydrolysis products of glucosinolates from various *Brassicaceae* species, have an aromatic nature (Yu et al. 2020).

The R-group of the aliphatic glucosinolates derives from methionine, leucine, alanine, or valine, and those of heterocyclic glucosinolates derive from tyrosine, phenylalanine, or tryptophan (Finley 2005). Broccoli is a rich source of healthy compounds as it contains flavonoids that usually occur in the form of two main flavonoles, namely quercetin and kaempferol, in its florets (Ashoush et al. 2017).

In the raw state, broccoli contains high amounts of ascorbic acid, vitamins B, carotenoids and some mineral micronutrients (Renna et al. 2020; Zhang, Zhao, and Yang 2018; Bjorklund, Shanaida, et al. 2022). For instance, broccoli possesses the ability to accumulate selenium many-fold higher than other plants from the selenium-enriched soil which enhances its potential in preventing many types of cancers (Finley 2003). It should be noted that Finley (2005) proposed to recognize the significant chemoprotective role of plant foods enriched in glucosinolates, polyphenols, carotenoids, and selenium-containing compounds. Abdalla, Sulieman, and Muhling (2020) described the data that selenium-biofortified broccoli can exhibit significant chemopreventive potential.

Some people perceive broccoli taste as bitter, being attributed to the presence of the gene TAS2R38 which encodes for a Taste receptor 2 member 38 protein, a bitter taste receptor, and other components like isothiocyanate and polyphenols (Mohd Nor et al. 2021; Duffy et al. 2010; Miao et al. 2017). Another factor responsible for the anticancer activity of broccoli is the presence of HDAC inhibitors, which work by reactivating the epigenetically-silenced genes promoting apoptosis of cancer cells (Li et al. 2018; Hać et al. 2020; Juengel et al. 2018; Beaver et al. 2018). Many reports have suggested that HDAC inhibitors, like isothiocyanate, are the chief constituents of broccoli (Choudhary, Gupta, and Bhatt 2020; Gupta, Bhatt, and Momin 2019; Mitsiogianni et al. 2021). It is well known that broccoli is rich in sulforaphane and that the production of isothiocyanates resulting from the mercapturic acid pathway leads to inhibition of HDAC achieving in breast, prostate, and colon cells (Schäfer et al. 2017; Singh et al. 2020; Zhang et al. 2021). Co-treatment by the isothiocyanates with 4-hydroxytamoxifen can reduce the breast cancer cell viability and clonogenic potential more effectively than the treatment with any single agent (Pawlik et al. 2013).

Kaempferitrin is a flavonoid, of which broccoli is enriched, and is an active component known to induce phagocytic activity and increase the production of NK cells (Alonso-Castro et al. 2013). Other polyphenols from natural sources, like genistein, curcumin, and quercetin prevent DNA damage and deregulate the cell's uptake of toxic substances. In mature parts of vegetables, glucobrassicin is present in a greater amount (Paśko et al. 2018). The combinations of such natural phytochemicals as sulforaphane and isoflavon genistein were reported to have synergistic impact on cancer inhibition (Sharma and Tollefsbol 2022).

The formation of isothiocyanates from glucosinolates depends mainly on several plant-intrinsic factors, including the concentration of glucosinolates and myrosinase activity, and several extrinsic factors, such as the peculiarities of processing, preparation, and digestion. Sulforaphane releases from glucoraphanin upon damage to the fresh plant

(chopping during the preparation of food or chewing) which allows the glucosinolates to mix and react with the enzyme β-sulphoglucosidase myrosinase. Hovewer, the enzyme myrosinase, which is responsible for the hydrolysis of glucosinolates, becomes inactivated by boiling (Mangla et al. 2021). Boiling this vegetable lessens the amount of glucosinolates, while when steamed, and microwaved, there is no significant change in their levels; thus, cooking and harvesting are fundamental standpoints to save glucosinolates in edible broccoli. Mangla et al. (2021) summarized that boiling of broccoli should be avoided due to inactivating myrosinase enzyme. Among different processing techniques, steaming and microwaving seem to enhance glucosinolates' extractability because they only slightly reduce the glucosinolates content (Nugrahedi et al. 2015; Nugrahedi et al. 2017).

Anticancer components in broccoli and other Cruciferous vegetables

Aliphatic glucosinolates

Aliphatic glucosinolates (β-thioglycoside-N-hydroxysulfates) are compounds present in relatively high amounts in many Cruciferous vegetables (Nguyen et al. 2020). For example, in *Arabidopsis thaliana*, both the profile and the level of glucosinolates are regulated by gene transcription factors such as MYB28 and MYB29 (Ishida et al. 2014). The content of glucosinolates in broccoli is greatly dependent on pre- and post-harvesting factors, so that the different ability of broccoli to prevent cancer may be due to plant harvesting and storage, as they can modify the content of glucosinolates in these Cruciferous species (Ilahy et al. 2020; Wang et al. 2019; Brown et al. 2002). Aliphatic glucosinolates include progoitrin, glucoerucin, glucoraphanin, glucoiberin, sinigrin, and gluconapin, particularly important in the reported anti-cancer effects of edible plants from the *Brassica* genus (Miękus et al. 2020; Mastuo et al. 2020).

In the *Brassicaceae* family, compounds such as glucoiberin, progoitrin, epi-progoitrin, sinigrin, glucoraphanin, glucoerucin, and gluconapin, along with gluconasturtiin and further indolyl glucosinolates, such as glucobrassicin, 4-hydroxyglucobrassicin, 4-methoxyglucobrassicin, and neoglucobrassicin, have been found (Bhandari et al. 2020). These thiocyanate-related compounds are reported to be active, at least *in vitro*, in several cancer models (Wu, Zhou, and Xu 2009; Mitsiogianni et al. 2019; Liu, Behray, et al. 2018). Glucosinolate-derived isothiocyanates (ITCs) showed inhibitory effects on colorectal cancer cell line K562, particularly with ITCs from epi-progoitrin, glucocheirolin, sinigrin, progoitrin, and glucotropaeolin (Leoni et al. 1997). The isothiocyanate family encompasses at least four major members from Cruciferous vegetables, i.e., allyl-isothiocyanate, which inhibits cell growth in RT4 urinary bladder cancer cells and T24 urinary bladder transitional cell line (Savio, da Silva, and Salvadori 2015) as well as impairs the reparation of DNA in human breast cancer cells (Liao et al. 2021), sulforaphane, benzyl-isothiocyanate, and phenethyl-isothiocyanate (Mastuo et al. 2020). Fundamentally, isothiocyanates are biochemical desulfurated byproducts of gluconosilates, principally coming via the activity of a myrosinase (Figure 1) (Ishida et al. 2014).

The metabolic degradation of glucosinates occurs in the gut via the gut microbiome (Narbad and Rossiter 2018; Tian et al. 2018; Liou et al. 2020). Among major aliphatic gluconosilates, gluconapin, and glucobrassicanapin are found in abundance, concentrated mostly in floret and leaves compared to stems (Cámara-Martos et al. 2021). Sinigrin and gluconapin are present in larger quantities in Brussels sprouts. Sinigrin has been shown to exert potent antiproliferative effects in Sprague Dawley rats with hepatotoxicity induced by a carcinogen (Mazumder, Dwivedi, and Du Plessis 2016; Jie et al. 2014). Progoitrin occurs in moderate quantities in many Cruciferous vegetables, whereas glucobrassicin is mainly present in cauliflower, sprouts, and cabbage (Hayes, Kelleher, and Eggleston 2008). Both progoitrin and sinigrin are fundamental gluconosilates in *Brassicaceae* able to assess the typical bitterness and taste hallmark of these vegetables (Doorn et al. 1998).

The ability of Cruciferous vegetables to prevent cancer depends on the different cultivars and genetic diversity, but also on the ability of their bioactive glucosinolates to be extracted by the edible parts, a circumstance largely conditioned by storage, cooking, and other processes downside the raw plant harvesting (Ríos et al. 2020; Jones, Faragher, and Winkler 2006; Rangkadilok et al. 2004). According to some recent data, the total amount of aliphatic or even glucosinolates may range from 3.91 to 5.21 (Sun et al. 2019) to values ≥13.00 µmol/g/dry weight in *Brassica* genus florets (Bhandari et al. 2020). The concentration of aliphatic glucosinolates is based on the expression of MAM3 genes, which play a major role in the synthesis of long-chain glucosinolates (Possenti et al. 2017).

One of the most frequent glucosinolates is glucoraphanin (4-methylsulphinylbutyl glucosinolate), the major precursors of sulforaphane, which has notorious anticancer properties (Yagishita et al. 2019; Kuran, Pogorzelska, and Wiktorska 2020; Zhang et al. 2022). Sprouts of broccoli can contain glucoraphanin in higher glucosinolate levels, which can be converted into sulforaphane, and glucoraphanin is particularly abundant in broccoli florets (Possenti et al. 2017). However, the genotype of broccoli may significantly impact the glucoraphanin concentrations (Park et al. 2013).

Progoitrin is another major biochemical component, which belongs to the glucosinolate family and is extracted from broccoli; it is also present in a dormant state but becomes active as soon as it is ingested (Narbad and Rossiter 2018; Choi, Zhang, and Kwon 2014). Upon ingestion, it is converted into goitrin which is associated with goiter development in the young age group (Zhu et al. 2018). Glucobrassicin and progoitrin undergo hydrolysis resulting in a byproduct, known as indole-3-carbinol and crambene (Farnham, Stephenson, and Fahey 2005).

As indicated above, literature also suggests that glucosinolates, like progoitrin, and sinigrin are responsible for the bitter taste in broccoli (Doorn et al. 1998; Mohd Nor et al. 2021). Due to the presence of these compounds, a negative preference for intake has been found in vegetable

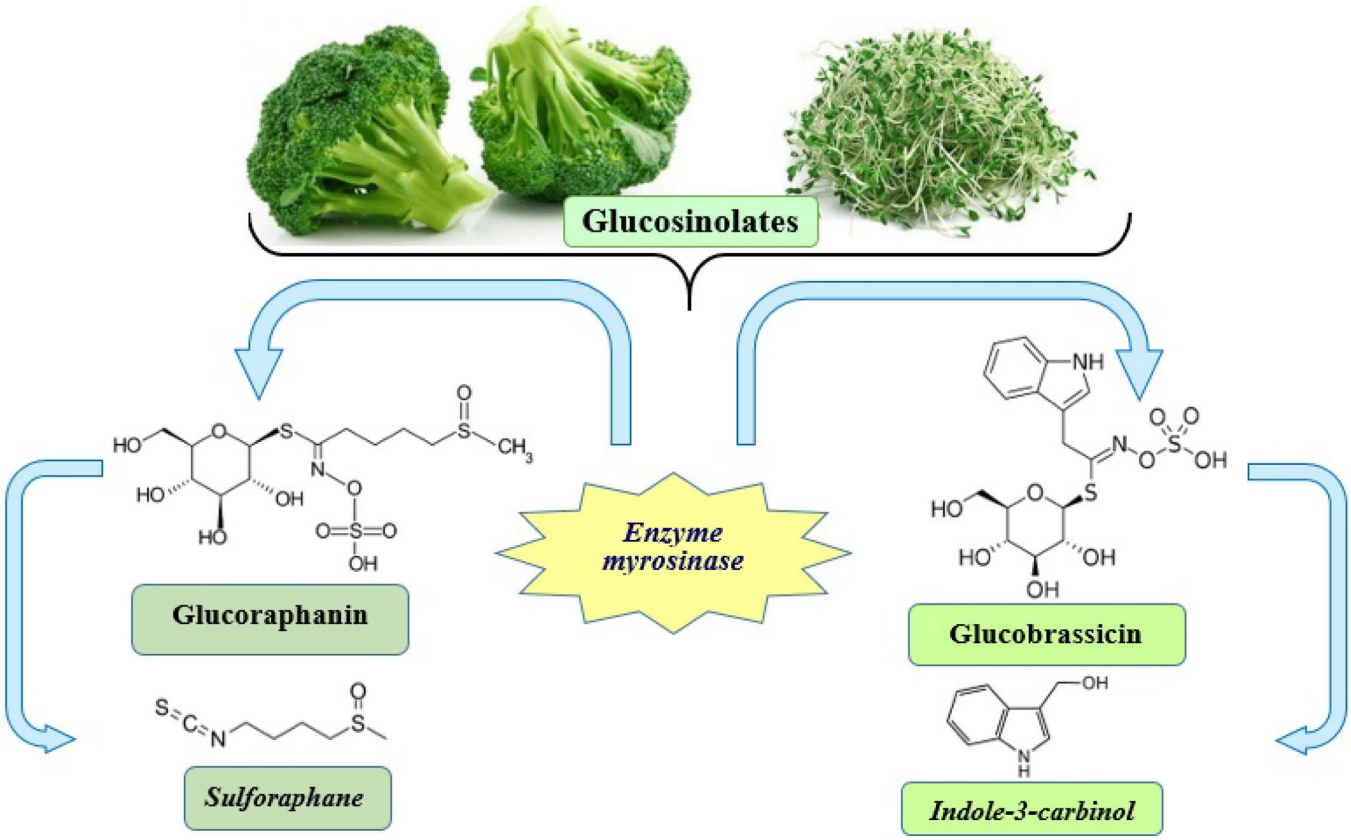

Figure 1. The main organosulfur compounds of Broccoli.

consumers (Vecchio et al. 2019), a circumstance that might affect consumers' choice and the possibility to prevent cancer with diet (Feng et al. 2018), although bitterness may even "adjust" to perform a much more pleasant taste (Bakke et al. 2018). A relationship was also found between the presence of sinigrin and progoitrin and the poor flavor of broccoli sprouts; hence, the flavor can be improved by limiting the content in both molecules (Wieczorek et al. 2018). Sinigrin and progoitrin, along with indole-glucosinolates, are frequently found in *Brassicaceae* and are formed from methionine in a process involving the side-chain extension. Aliphatic glucosinolates, like glucoerucin, and glucoraphanin can mediate carcinogen-metabolism enzymes (Ashari et al. 2018).

Glucoraphanin, myrosinase, and sulforaphane

In broccoli (*Brassica oleacea* var. *italica*), glucosinolates hydrolyze and yield sulforaphane and sulforaphane-nitrile (Ngo and Williams 2021). Sulforaphane is a phytochemical forming molecules of isothiocyanate, with a high abundance in broccoli and other *Brassica* species.

Several animal and human models have shown that sulforaphane exerts beneficial effects from an anti-cancer perspective (Axelsson et al. 2017; Bose et al. 2020; Licznerska, Szaefer, and Krajka-Kuźniak 2021; Chen et al. 2020; Rong et al. 2020). Glucoraphanin is a chief glucosinolate presents in broccoli, which on hydrolysis by myrosinase, yields sulforaphane (Matusheski and Jeffery 2001). Sulforaphane is then metabolized through the mercapturic acid pathway, conjugated with the glutathione system (Vanduchova, Anzenbacher, and Anzenbacherova 2019).

The activity of sulforaphane in the organism is mainly associated with the regulation of the oxidative stress response, like many other bioactive phytochemicals (Bose et al. 2020; Ogunlade, Adelakun, and Iteire 2020; Santos et al. 2020). It is widely known that oxidative stress underlies several pathological conditions, including cancer, aging, metabolic syndrome, obesity, type 2 diabetes, and cardiovascular as well as neurodegenerative disorders (Chirumbolo et al. 2018; Bjørklund et al. 2018; Gasmi et al. 2021; Koshovyi et al. 2021). Sulforaphane can activate a lysosome-dependent transcriptional program as a potent inducer of antioxidant responses (Zhou et al. 2020; Li, Guo, et al. 2020).

Sulforaphane is capable of activating multiple mechanisms, including suppressing cytochrome P450 enzymes, and inhibiting the cell cycle progression, and angiogenesis (Juge, Mithen, and Traka 2007; Li, Zhou, et al. 2020; Huang et al. 2020; Shankar, Ganapathy, and Srivastava 2020). The molecular pathways involved in sulforaphane's role in cancer treatment have been recently reviewed (Chen et al. 2020; Liu et al. 2021; Bhattacharjee and Dashwood 2020; Wu et al. 2020; Jabbarzadeh Kaboli et al. 2020).

A number of preclinical and clinical studies have been performed to evaluate the potential of sulforaphane in the last decades (Mangla et al. 2021). Several laboratory (*in vitro*), animal and human models have shown that

sulforaphane exerts beneficial effects from an anti-cancer perspective (Axelsson et al. 2017; Bose et al. 2020; Licznerska, Szaefer, and Krajka-Kuźniak 2021; Chen et al. 2020; Rong et al. 2020; Mangla et al. 2021).

According to Mangla et al. (2021), sulforaphane is mainly administered using oral and peritoneal (during animal studies) routes. Yagishita et al. (2019) concluded that its median effective dose is 175 µmol/kg when given orally and 113 µmol/kg using peritoneal route. After oral administration, sulphoraphane is absorbed from the intestine (Mangla et al. 2021).

Sulforaphane suffers from some biopharmaceutical issues, i.e. poor aqueous solubility, low bioavailability and extensive first pass metabolism (Mangla et al. 2021). Tříska et al. (2021) emphasized that the epithiospecifier protein (co-factor of a myrosinase) which is involved in the formation of sulforaphane through hydrolysis of glucosinolates, is temperature-specific. Such technological factors as the level of temperature and heating time were recognized as very important for the final sulforaphane content in the homogenate of broccoli sprouts. The generally recommended temperature of 60–70 °C was regarded as the most effective for obtaining sulforaphane, and even local overheating above 100 °C significantly reduced the activity of myrosinase and the yield of sulforaphane as the final product of glucoraphanin hydrolysis (Tříska et al. 2021). These researchers used different solvents (hexane, ethanol, and β-cyclodextrin) with the aim of increasing the amount of extracted sulforaphane. The extraction efficiency was the highest for ethanol (184 µg/g dry weight), less for hexane (101 µg/g d.w.), and only 15 µg/g d.w. for β-cyclodextrin. It was found also that the addition of *Raphanus sativus* sprouts with greater myrosinase activity also led to an increase in the content of sulforaphane in the final preparation of broccoli sprouts.

Sulforaphane is metabolized through the mercapturic acid pathway, and conjugated with the glutathione system (Vanduchova, Anzenbacher, and Anzenbacherova 2019). It rapidly accumulates in the cells due to conjugating with glutathione and forming bioactive compound glutathione-S-transferase (Kaiser et al. 2021; Mangla et al. 2021).

From a biochemical point of view, sulforaphane is a sulfur-rich compound activated from glucoraphanin due to myrosinase activity (Fahey et al. 2015). Generally, glucoraphanin remains in an inactive state before being metabolized by myrosinases, exerting a defensive role in plants against their damage (Textor and Gershenzon 2009). Myrosinase has the potential to break down glucosinolates, producing sulfate and glucose and detoxifying chemical carcinogens through phase I/II enzymes which inhibit carcinogenic activity (Conzatti et al. 2014). It has been shown that sulforaphane takes part in the induction of Hsp90 degradation and blocks the Hsp90 interaction in pancreatic cancer cells (Chen et al. 2020). During cell proliferation, ITCs halts the differentiation of carcinogenic cells in the human body, promotes modification of epigenetic events, and responds to stress by providing an anti-inflammatory effect (Zhang, Tang, and Gonzalez 2003). Antioxidant characteristics of this compound are probably responsible for its protective qualities, many of which promote expression and activation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2). Sulforaphane, as a Nrf2 inducer, has the ability to prevent the metastasis of implanted breast cancer cells in mice and the growth of breast cancer cells in humans (Kanematsu et al. 2011). The effect of this natural organosulfur compound has also been reported to be linked to its ability to protect neural stem cells via the Wnt-β catenin-DKK1 pathway (Dar et al. 2017). The ability of sulforaphane to act on cancer cells has been widely assessed in *in vitro* cellular models, such as breast cancer (Licznerska, Szaefer, and Krajka-Kuźniak 2021; Ngo and Williams 2021; Palliyaguru et al. 2020; Simões et al. 2020), colorectal cancer (Hossain, Liu, and Wood 2020), and other forms of tumors, usually linked to chemopreventive therapy (Mangla et al. 2020).

In the preclinical experiments, sulforaphane has shown anticancer properties through exerting antioxidant effects, promoting the detoxification process in cancer cells, cardiac regulation, exhibiting antibiotic effects, in addition, acting on blood sugar levels (Bose et al. 2020; Warpsinski et al. 2020; Faridvand et al. 2020; Lv et al. 2020; Li, Guo, et al. 2020).

Studies have shown that a complete breakdown of glucoraphanin into sulforaphane occurs when exogenous myrosinase hydrolyzes glucosinolates in broccoli (Barba et al. 2016; Román et al. 2018). A study suggested that the greatest sulforaphane levels are present in raw broccoli, which is almost 10-fold more than that of cooked broccoli (Vermeulen et al., 2008). To optimize sulforaphane content, steaming broccoli, or cooking with a microwave is recommended (Lu et al., 2020). According to some reports, cooking below 140 °C is recommended for the vegetable, as higher temperatures can promote a significant loss of glucosinolates like glucoraphanin (Yuan et al. 2009; Hwang and Kim 2013).

It was found that benzyl isothiocyanate, an another hydrolysis product from broccoli glucosinolates, interferes with mitosis by targeting the serine/threonine-protein kinase 6 (also known as Aurora A kinase), shows promising developments as an anticancer compound (Yu et al. 2020). Even via an apoptotic pathway, its antiproliferative activity has also been reported in human pancreatic BxPC-3 cancer cells (Srivastava and Singh 2004). Preclinical evidence supports the role of broccoli glucosinolates and sulforaphane in cancer therapy and prevention, particularly for breast cancer (Ngo and Williams 2021; Maina et al. 2020). The compound 3,3′-diindolylmethane, coming from glucobrassicin, directly inhibits the double mouse minute 2 homolog (MDM2), a major, pluri-functional oncogenic molecule, usually well recognized for its negative regulation on the tumor suppressor protein p53 (Gao et al. 2020). This action is particularly enhanced if associated with imidazoline MDM2 inhibitors (Nutlin-3a and Idasanutlin/RG-7388) (Gao et al. 2020). Sulforaphane acts most probably in two fundamental ways, of which one is to modulate epigenetics (Kumari et al. 2022), and the other to tune many fundamental signaling pathways in oxidative stress and xenobiotics turnover, for example, by modulating various p450 cytochromes (CYPs 19, 1A1, 1A2, and 1B1) in MCF7 breast cancer cell lines endowed with estrogen receptors and MDA-MB-231 breast cancer cell lines, lacking estrogen receptors (Licznerska, Szaefer, and

Krajka-Kuźniak 2021). Sulforaphane can reduce the stemness in colorectal cancer stem cells by the participation of Tap63α targeting the Lgr5/β-catenin pathway (Chen et al. 2020), whereas, in U2OS and Saos2 osteosarcoma cells, the broccoli's isothiocyanate compound promotes apoptosis via the modulation of the FSTL1/NF-κB pathway (Zhang, Jin, et al. 2020). The Nrf2 signaling is probably the major pathway used by these glucosinolates and isothiocyanate to exert a beneficial action besides epigenetics. A role for the thiol reductase system, i.e., the thioredoxin/thiol reductase system, has been recently addressed: auranofin, an inhibitor of thioredoxin reductase, enhances the anticancer effect of sulforaphane in hepatocellular carcinoma Hep3B (Hwangbo et al. 2020). The same extract from broccoli increases the chemopreventive drug-cytotoxicity on the staminality of head and neck squamous cell carcinoma (Elkashty and Tran 2020). The major issue to be addressed is how much the simplest raw vegetable ingestion can counteract cancer onset regarding purified isothiocyanates and other biochemical active principles. This remains a scientific challenge for the next future.

As for the safety of the phytocomponents of broccoli, Kaiser et al. (Kaiser et al. 2021) reported that mild side effects such as gastrointestinal distress and heartburn were found in clinical trials. Milder forms of side effects have also been reported with sulforaphane and precursors, like glucoraphanin (including diarrhea, constipation, and gas) (Prieto, López, and Simal-Gandara 2019). However, it should be noted that the significant antineoplastic and chemopreventive properties of sulforaphane greatly outweigh these minimal adverse effects (Kaiser et al. 2021; Mangla et al. 2021).

The bioavailability of sulforaphane and its dose-dependent pharmacokinetic behavior have been widely studied in the latest years, particularly if associated with the fundamental role of the host's gut microbiome (Abukhabta et al. 2021; Langston-Cox et al. 2020; Budnowski et al. 2015). It has been demonstrated a rapid absorption and good absolute bioavailability of sulforaphane (Abukhabta et al. 2021; Langston-Cox et al. 2020; Hwang, Bornhorst, et al. 2019), despite its decreases significantly with an increase dose; the same happens with its biological half-life, the volume of distribution, and the absorption rate. As a consequence, many novel approaches in sulphoraphane delivery have been reported (Soni et al. 2020; Soni, Rizwanullah, and Kohli 2018; Hanlon et al. 2009).

Despite the increasing bulk of evidence regarding the anticancer role of sulforaphane, its assumption with diet and plasma bioavailability represents important items to be addressed in oncology. Laboratory animal models often reach promising results, despite the need to translate evidence from bench to bed in clinics. Oral administration of sulforaphane or its precursor glucoraphanin was revealed to be capable of inhibiting breast carcinogenesis in rats when given orally by altering gene expression. It was observed a 3-fold increase of cytoprotective NAD(P)H: quinone oxidoreductase enzymatic activity, as well as 4-fold elevated immunostaining of and heme oxygenase-1 in rat mammary epithelium (Cornblatt et al. 2007).

Zhang et al. (2022) found that sulforaphane significantly inhibited the TGF-β1-induced migration as well as invasion in breast cancer cells through affecting formation of their cytoskeleton.

Sulforaphane quickly interacts with glutathione in case of going into cells that leads to its intracellular accumulation, i.e. accumulation in cancer cells due to their high glutathione content, and such interactions promote the anti-cancer effect of sulforaphane (Gu, Mao, and Du 2022). Recently was found that sulforaphane demonstrates its anti-cancer through inducing epigenetic modifications, promoting autophagy as well as suppressing glycolysis in cancer cells (Gu, Mao, and Du 2022). Furthermore, sulforaphane can inhibit cancer stem cells (Gu, Mao, and Du 2022; Liu et al. 2017). Generally, sulforaphane can act against cancer through pleiotropic effects at different levels, from its development to progression (Russo et al. 2018).

The clinical application of sulforaphane has several limitations because of its hydrophobicity and poor bioavailability. Several studies describe the instability and poor oral bioavailability of sulphoraphane (Kaiser et al. 2021; Saavedra et al. 2022). It should be noted that such a problem also applies to many other phytosubstances (Bilia et al. 2017). Mangla et al. (Mangla et al. 2021) emphasized the necessity of the developing of an appropriate drug delivery system for sulforaphane that could increase its bioavailability and thereby its concentration at the site of action.

Mangla et al. (2021) concluded that increased bioavailability, solubility and efficacy of sulforaphane-containing supplementations can be achieved using nano-engineered delivery systems. The encapsulation of sulforaphane inside monomethoxypoly (ethylene glycol)-poly (ε-caprolactone) micelles has been proposed as an effective strategy for breast cancer treatment in the future (Danafar et al. 2018). Nowadays scientists believe that nanoformulations make it possible to successfully solve the above mentioned problems (Mangla et al. 2021; Bilia et al. 2017). The administration of sulphoraphane nanoparticles combined with chemotherapy drugs led to superior outcomes of antitumor therapy in breast cancer (Saavedra et al. 2022).

Recently was found that a combined therapy using three phytochemicals, such as sulforaphane, piperine, and thymoquinone may improve the chemopreventive potential of sulforaphane against breast cancer even better than single treatments, like surgery, radiotherapy or chemotherapy (Aumeeruddy and Mahomoodally 2019). In addition, sulforaphane has also the ability to potentiate the potential of several anticancer agents, including gemcitabine, paclitaxel, and docetaxel through exerting synergistic effects (Burnett et al. 2017; Kamal et al. 2020). Combining sulforaphane with withaferin A resulted in a positive effect on breast cancer cell cycle progression through epigenetic mechanisms (Royston et al. 2018).

Sharma and Tollefsbol (Sharma and Tollefsbol 2022) found that the combinations of such natural phytochemicals as sulforaphane and isoflavone genistein were reported to have a synergistic impact on cancer inhibition. The combined consumption of broccoli sprouts and green tea polyphenols demonstrated great potential in reducing the risk of breast cancer through the regulation of epigenetic mechanisms (Arora, Li, et al. 2022). Sinha et al. (Sinha et al.

2021) revealed that combination of anti-cancer drug cisplatin with sulforaphane inhibited the stemness potential and metastasis of triple-negative breast cancer cells by down-regulating epithelial-to-mesenchymal transition cascade. Co-treatment by the isothiocyanates with 4-hydroxytamoxifen can reduce the breast cancer cell viability and clonogenic potential more effectively than the treatment with any single agent (Pawlik et al. 2013). More efforts are required to elucidate the integration of experimental and clinical studies, particularly concerning the selection of dose and route of administration of sulforaphane in clinics (Yagishita et al. 2019).

Indole glucosinolates

Indole glucosinolates are naturally-occurring B-thioglucoside N-hydroxysulfates, which carry an indole ring as a side chain. Glucobrassicin, neoglucobrassicin, 4-hydroxyglucobrassicin, and 4-methoxyglucobrassicin are their major derivatives (Kumar et al. 2022). Indole glucosinolates carry a chain that originates from tryptophan, and have received increasing attention in recent years owing to their bioactive effects, biosynthetic pathways, and metabolites produced (Agerbirk et al. 2009). They have been found in abundance in broccoli leaves. The breakdown of indol-3-ylmethylglucosinolate leads to tissue disruption by glucosinolates-degrading enzymes, myrosinases, into glucosinolates, resulting in the production of nitrile or isothiocyanates (Rybarczyk-Plonska et al. 2016).

Glucobrassicin is synthesized from tryptophan through the shikimic acid pathway. Conversion of tryptophan takes place into indole-3-acetaldoxime using cytochrome p450 enzymes. Glucobrassicin is a type of indole methylglucosinolates hydrolyzed in an unstable form of isothiocyanates (Liu, Zhang, et al. 2018). These amino acid-derived aglycones are pungent and present in broccoli, cabbages, and mustards. Neoglucobrassicin is a similar product to glucobrassicin. Indole-3-carbinol and thiocyanate ion are the products obtained by hydrolysis of glucobrassicin (Haack et al. 2010).

The product obtained due to neoglucobrassicin hydrolysis contains a weaker reduction property of quinone reductase (Borowski et al. 2008) It has also been reported that glucobrassicin has more efficient chemopreventive properties than indole-3-carbinol (Renner and Fritz 2020). Numerous derivatives of glucobrassicin have been isolated and identified, including 1-methoxyglucobrassicin (neoglucobrassicin), 4-methoxyglucobrassicin, 4-hydroxyglucobrassicin, 1,4-dimethoxyglucobrassicin, 6-iso-feruloyl glucobrassicin, and 1-sulfoglucobrassicin (Borowski et al. 2008).

4-Hydroxyglucobrassicin is a major indole-carrying glucosinolate present in Cruciferous vegetables. In contrast to glucobrassicin, little is documented about conversion products that result from 4-hydrocyglucobrassicin, but it is well known that 4-hydrocyglucobrassicin is responsible for forming oligomeric compounds when in an acidic environment, being such compounds dangerous to health (Vo et al. 2014).

The biological properties of indole-glucosinolates were investigated for many years (McDanell et al. 1988). Usually, their activity targets the Nrf2/ARE oxidative stress scavenging system with a cytoprotective role (Hajra et al. 2017). Indole-glucosinolate properties depend on the number and amount of these compounds in raw food (Bhandari et al. 2020; Renner and Fritz 2020; Sun et al. 2020; Hwang, Park, et al. 2019; Revelou, Kokotou, and Constantinou-Kokotou 2020).

Recently the chromatographic methods have been employed for the analysis of glucoraphanin present in broccoli seeds and sprouts. It has been found that the, levels of 4-hydroxyglucobrassicin depend on cultivars, with most of them being sources of potentially unwanted glucosinolates, like 4-hydroxyglucobrassicin and glucoerucin (Zuluaga et al. 2019).

Indole-3-carbinol and diindolylmethane

Indole-3-carbinol is a hydrolytic product of progoitrin and glucobrassicin with anticancer properties (Pani et al. 2021; Rupa et al. 2020). It is readily available in vegetables like broccoli, cauliflower, kale, mustard greens, subpages, Brussels sprouts, cabbage, and collards (Wang et al. 2012). In fresh florets of broccoli the sulforaphane content varied in the range 72-304 mg/100 g whereas indole-3-carbinol was between 77-117mg/100g (Revelou, Kokotou, and Constantinou-Kokotou 2020). The differences in cultivar origin, season, and environmental factors should be considered during the quantification of sulforaphane and indole-3-carbinol contents in broccoli.

Indole-3-carbinol is produced following cutting these raw vegetable foods or cooking at moderate temperate or even chewing in the oral cavity (Upadhyaya et al. 2018; Fujioka et al. 2014; Adwas et al. 2016). In addition, it can be derived in the laboratory. Indole-3-carbinol and 3,3′-diindolylmethane demonstrate several mechanisms of anticancer activity (Maruthanila, Poornima, and Mirunalini 2014; Banerjee et al. 2011). Among other effects, it is able to up-regulate phase II enzymes, employing an antioxidant response element mediated mechanism (Hayes, Kelleher, and Eggleston 2008; Sturm and Wagner 2017), acts on the Nrf2/Keap1 signaling by sequestering protein Keap1, allowing Nrf2 to translocate to the nucleus, where it starts interacting with ARE, enhancing the targeted transcription genes for oxidative stress response and survival genes (Yarmohammadi, Rezaee, and Karimi 2021; Munakarmi et al. 2020).

When exposed to an acidic environment, indole-3-carbinol undergoes condensation, producing a group of compounds, known as acid condensates (Megna et al. 2016). Indole-3-carbinol has a beneficial role in treating diseases aside from cancer, such as systemic lupus erythematosus, respiratory tract disease, and others (Eghbalpour et al. 2020; Guzmán-Navarro et al. 2021). However, very little is known about its role so far. Many types of research have been conducted on indole-3-carbinol and its role in chemoprevention, particularly exploring its effects in breast cancer (Katz, Nisani, and Chamovitz 2018). For this reason, a diet with a greater concentration of this compound has been linked to a decreased chance of developing cancer. Indole-3-carbinol presence in vegetable might also protect against carcinogenic activity in cells (Quirit et al. 2017; Chu et al. 2016).

However, there is slight evidence about its effectiveness in cervical dysplasia, ovarian cancer, systemic lupus erythematosus, papillomatosis, breast cancer, and other cancer types. In ovarian cancer patients, indole-3-carbinol used in combination with chemotherapy allows women who had undergone surgery to have increased life expectancy and overall prognosis (Taylor-Harding et al. 2012). Possible side effects, like diarrhea and skin rash, can occur following the use of indole-3-carbinol (Busbee et al. 2020).

Diindolylmethane or 3,3′-diindolylmethane is another phytochemical (Wang et al. 2012) Cruciferous found in vegetables. It is the metabolite of indole-3-carbinol. Diindolylmethane can arrest the cell cycle and promote apoptosis in cancer cells, making diindolylmethane an attractive therapeutic compound (Nikulin et al. 2020). It has a strong impact on estrogen metabolism by maintaining a balance between either increase or decrease of estrogen activity (Greco et al. 2020; Isabella, Mirunalini, and Pandiyan 2018). Diindolylmethane functions by acting on estrogen present in the body, but it can even block estrogen effects, besides influencing the process of DNA methylation in cancer cells (Palomera-Sanchez et al. 2017; Xie et al. 2017). Many studies have suggested a possible connection between chromatin modification and histone methylation as well as regulation of transcription processes associated with diindolylmethane (Elackattu, Feng, and Wang 2009).

Findings of Penta et al. (2022) suggest that diindolylmethane-based nutraceuticals can be used in cancer therapy along with centchroman in the treatment of dysregulated triple-negative breast cancer. Diindolylmethane caused metabolic catastrophe in triple-negative breast cancer cells by interrupting aerobic glycolysis and inhibiting the proliferation of highly proliferative triple-negative breast cancer cells. Besides this, combination of the diindolylmethane with centchroman significantly inhibited the tumor growth.

As it is known, low bioavailability is a challenging factor with most dietary phytocompounds, and diindolylmethane is no exception to this rule (Penta et al. 2022). For instance Penta et al. (2022) mixed diindolylmethane in corn oil to improve its bioavailability.

Flavonoids in broccoli

A study (Koh et al. 2009) examining 80 samples of broccoli regarding flavonoids content, showed that a quercetin and kaempferol (Figure 2) levels ranged between 0.03 and 10.85 mg/100 g of fresh weight. When daily reference intake was assessed, it was seen that quercetin consumption was estimated to be 0.23 mg, and kaempferol was 0.32 mg from

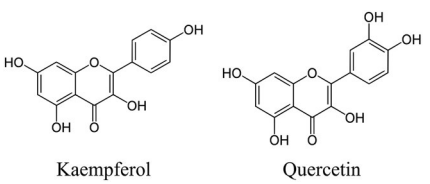

Figure 2. The main flavonoids of Broccoli.

the intake of broccoli. One of the potential benefits of quercetin include reducing the aging process (Abharzanjani et al. 2017; Gasmi, Mujawdiya, Lysiuk, et al. 2022). Flavonoids were considered promising pro-apoptotic and anti-metastatic phytoconstituents that act in a pleiotropic and poorly specific manner, but they can inhibit the reactive oxygen species (Chirumbolo et al. 2018).

Kaempferol is a common flavonoid present in broccoli and some other plants. It gives the specific yellow color to fruits and vegetables. Kaempferol and other flavonoids, like genistein, quercetin, exhibit anti-inflammatory and antioxidant effects (Kim and Park 2020; Gasmi, Mujawdiya, Noor, et al. 2022). It has been reported that a significant and positive association exists between kaempferol intake and lowering the chances of developing many chronic conditions, like cancer and cardiovascular diseases (Calderon-Montano et al. 2011).

Alonso-Castro et al. developed a study supporting the anticarcinogenic and immunomodulatory influence of bioactive kaempferitrin, a naturally-occurring kaempferol glycoside, through the initiation of cell death in carcinogenic cells (Alonso-Castro et al. 2012). That study also explained the kaempferitrin's immune-boosting ability to counter tumor expression by promoting a phagocytic and macrophage response in elevating numbers of NO and H_2O_2 secretion along with induction of NK activity. This mechanism attributes anti-inflammatory properties to kaempferol (Mohamed, Jantan, and Haque 2017). Recent studies have shown that kaempferol along with other flavonoids modulates a variety of therapeutic activities, like antioxidant, antimicrobial, anxiolytic, antidiabetic, anti-osteoporotic, and analgesicsssw (Ashrafizadeh et al. 2020). Antioxidant properties of kaempferol are due to its structure and a double bond at C2-C3, a characteristic feature that favors its antioxidant effects (Hofer et al. 2020). The somatic mutation theory suggests that kaempferol in fewer concentrations confer protection against DNA damages. However, the majority of chemical carcinogens require enzymes like P450 to get activated, and some studies have demonstrated that kaempferol has the potential to inhibit P450 (Calderon-Montano et al. 2011). According to Qattan et al. (2022) kaempferol can modulate the cell signaling pathways in the treatment of cancer.

Quercetin is another flavonol widely present in fruits and leaves of many vegetables, including broccoli (Bischoff and Care 2008). The antioxidant, anti-inflammatory, and anti-toxic effects of quercetin are well known (Gasmi, Mujawdiya, Noor, et al. 2022; Bjorklund, Rahaman, et al. 2022). Hence, quercetin in diet plays a key role in helping the body to combat damage caused by free radicals, while helping to reduce inflammation, blood pressure, and allergic reactions (Bule et al. 2019). Experimental studies have shown that quercetin is a powerful antioxidant compared to traditional vitamins (Miean and Mohamed 2001). Quercetin has been reported to exert anticancer effects owing to its prominent anti-inflammatory and antioxidant activity (Dabeek and Marra 2019; Ghazi et al. 2020; Suraweera et al. 2020). It can inhibit enzymes like lipoxygenase and cyclooxygenase which participate in

Table 2. Some examples of clinical studies on the anti-tumoral effects of broccoli sprouts and their bioactive components.

Study protocol	Subjects		Effects	References
RCT on breast cancer	30		Ability to improve some indicators of the immunity involved in fighting cancer	(Wang et al. 2022)
RCT on breast cancer	69	↓	Marker of oxidative stress 8-hydroxy-2′-deoxyguanosine	(Wirth et al. 2017)
RCT on breast cancer	54		Broccoli seed extract modulates the HDAC activity which results in decreased cell proliferation	(Atwell et al. 2015)
RCT on pancreatic cancer	40	inc	POUDER trial Pancreatic ductal adenocarcinoma trial	(Lozanovski et al. 2014)
RCT db plac prostate cancer	199	↓	Reduction levels of prostate-specific antigen	(Thomas et al. 2014)
RCT	n.r.	↓	Reduction risk of cancer and CVD	(Armah et al. 2013)
Prospective clinical survey	4035 case cohort analysis	↓	Reduced association with squamous cell carcinoma, esophageal adenocarcinoma, risk	(Steevens et al. 2011)
Cross over clinical trial	50		Bioavailability in plasma and urine excretion	(Egner et al. 2011)

tumorigenesis, and forms part of detoxifying enzymes, like glutathione S-transferase.

Quercetin exerts an antiproliferative effect causing an alteration in matrix metalloproteinase that leads to the activation of the mitochondrial pathway while triggerring changes in caspases 3 and 7 (Shi et al. 2019). This flavonoid also reduces inflammatory markers like TNF-alpha (Peluso, Raguzzini, and Serafini 2013). Quercetin has a role in arresting the cell cycle involved in breast cancer cells in line with MDAA-MB-231 through the mechanism that down-regulates cycling A and cycling B during its S and G2/M phase. It is also responsible for expressing genes like p21, p27, and p53, chiefly participating in the G1 phase of the cyclin-dependent kinases kinases pathway (Samini 2020).

Levels of quercetin in broccoli depend on various factors like environmental conditions and cultivars, as well as agriculture methods. Other factors like transportation and storage after harvesting also influence its levels.

In summary, kaempferol and quercetin are outstanding antioxidants that significantly reduce different human cancers. Their high inhibiting effect against cancer cells is accompanied by no side effects to normal cells (Imran et al. 2019). Their action mechanisms include cell cycle arrest at the G2/M phase, downregulation of epithelial-mesenchymal transition-related markers, apoptosis, and phosphoinositide 3-kinase/protein kinase B signaling pathways (Imran et al. 2019). Besides it, treatment by quercetin combined with another polyphenol, curcumin, leads to a synergistic effect in anticancer activity against triple-negative breast cancer cells by modulating tumor suppressor genes. Kaempferol is a representative of phytoestrogens with similar molecular structures and functions to endogenous steroid hormones in the human body and is used as hormone replacement therapy to prevent breast cancer and osteoporosis (Kim, Hwang, and Choi 2016).

Sprouts of broccoli after germination (3 days) from seeds were recommended as functional foods with high health-promoting potential because of maximum sulforaphane contents as well as total phenolics, and flavonoids (Lv et al. 2020).

Clinical evidence regarding anticancer effects of broccoli: Some keynotes

To date, few papers dealt with the anticancer effects of broccoli in humans. Thus, recently Kaiser et al. (2021) revealed that the majority (i.e., 192) of the current scientific literature focused on preclinical studies of anticancer properties of sulforaphane, whereas only 19 studies investigated the effects of sulforaphane-containing products in clinical trials. The majority of reports regarding the effect of broccoli sprouts on cancer focused on the activity held by sulforaphane from Cruciferous plants (Fujioka et al. 2016).

Among 26 studies found in a database of clinical trials conducted around the world (ClinicalTrials.gov 2023) searching keywords 'Sulforaphane' and 'Cancer', the most have been related to such types of malignant neoplasms as breast cancer and prostate cancer. Tables 1 and 2 shows the most recent clinical trials and clinical projects using broccoli in diet to address its anticancer potential. For instance, in the clinical trial of prostate cancer NCT01228084 (see Table 1), sulforaphane was given 200 µmol daily by the oral route in four 50 µmol capsules during 20 weeks. The investigators of NCT02404428 clinical trial proposed to undertake a pilot study of men with prostate cancer to determine whether a broccoli-rich diet induces the changes in tumor size. The patients obtained 300 g/week of broccoli soup consumed for a period of 6 months due to delivering of glucoraphanin (sulforaphane precursor). Yuan (2021) described the clinical trial of sulforaphane in lung cancer chemoprevention in former smokers (NCT03232138). This dietary supplement is studying over a period of twelve months consuming by former smokers.

In a recent randomized controlled trial (RCT), 98 men scheduled for prostate biopsy were treated with 200 µmL/day of broccoli sprout extracts. A large change in gene expression was observed in prostate cancer (Zhang, Garzotto, et al. 2020). This evidence was also assessed by the group of Traka and coworkers, who recruited in their study 49 men treated with a 300 ml broccoli soup (control) and a glucoraphanin enriched soup (treated) (Traka et al. 2019). It has been shown that broccoli consumption would alter the composition and functional capacity of the human gastrointestinal microbiota compared to control (Kaczmarek et al. 2019). In an RCT, it was reported a study where 69 post-menopausal women, who were affected by breast cancer, received Cruciferous vegetables such as broccoli sprouts (≥14 cups/day) for three weeks and followed four 24-hrs recalls. Women with breast cancer showed a significant decrease in post-intervention 8-hydroxy-2′-deoxyguanosine values in urine and in the intervention arm versus the control arm (i.e. 1.1 ng/mL vs. 3.2 ng/mL, $p = 0.01$), following

an adjustment for baseline levels of 8-hydroxy-2′-deoxyguanosine (Wirth et al. 2017).

However, the Phase II study with 20 patients allowed the group of Alumkal et al. to show that 200 µmoles day of sulforaphane-rich extracts did not lead to ≥50% prostate-specific antigen declines in the majority of patients and probably other biomarkers should be evaluated to ascertain the effect of broccoli in the diet against cancer (Alumkal et al. 2015).

The clinical study conducted by Livingstone et al. (2022) demonstrated that sulforaphane occurred in noticeably higher levels in the prostate tissue of men consuming the glucoraphanin-containing supplement compared to those not consuming it. As a consequence, the accumulation of sulforaphane in prostate cells results in healing effect which explains the reduced risk of cancer progression following consumption of Cruciferous vegetables. Wang et al. (2022) involved 30 postmenopausal breast cancer women in clinical research of isothiocyanates-rich extract from broccoli sprouts (200 µmol isothiocyanates per day for two weeks). This study showed high compliance (100%) and low toxicity of the administrated extract as well as its ability to improve some indicators of the level of immunity, which are involved in fighting cancer. Atwell et al. (2015) conducted a double-blind trial of 54 women with abnormal mammograms that daily consuming of 250 mg of broccoli seed extract containing 30 mg of glucoraphanin for 2–8 weeks. They revealed that it can modulate HDAC activity which results in decreased cell proliferation.

Conclusion

Natural products have been increasingly recognized for their chemo-protectant and therapeutic effects, while triggering minimal or no side effects. The above-stated literature has provided a detailed description of the role of broccoli and other Cruciferous plants as well as their bioactive compounds against cancer cells, while also making emphasis on their impact at the level of the immune system's activation mechanisms. The consumption of broccoli florets and sprouts as part of the daily diet may contribute as a valuable source of phytoconstituents capable of preventing different cancers, mainly glucosinolates, flavonoids and some micronutrients. There is still a need for further evidence-based research to identify and explore the molecular mechanism and transcriptional pathways through which broccoli-derived phytochemicals act at molecular level, ultimately preventing life-threatening conditions, like is the case of breast and prostate cancers.

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