

evra®



# BROC- COX®

Granular dry extract of broccoli  
0,3-0,5 % sulforaphane (HPLC)

- **Cancer prevention**
- **Control of redox stress and silent inflammation**
- **Cardiovascular prevention**
- ***H. pylori* infection**

# BROCCOX® PRODUCT DATA SHEET:

**Product code:** SGLBRSIC0800500A

**Scientific name:** *Brassica cretica* Lam.

**Synonym:** Brassica oleracea var. italica Plenck

**Common name:** broccoli.

**Drug:** aerial part with flowers.

**E / D ratio:** 25-30 / 1

**Concentration in sulforaphane:** 0.3-0.5%

**Extraction solvent:** water.

**Supporting excipient:** maltodextrin.

**Origin of the drug:** Italy.

**Country of production of the product:** Italy.

**Production plant:** Evra srl Benefit Company - Lauria (PZ).

**Organoleptic characteristics:** greenish granular powder.

**Suggested dosage:** 500-1000 mg per day.

**Solubility:** soluble in water.

**Particle size:** 90% through 250-500 µ; <10% through 200 µ.

**Compaction density:** about 0.4 g / ml.

**Loss on drying (105 ° C x 3 h):** 5% max.

**Heavy metals:** Pb <3 ppm; Cd <1 ppm; Hg <0.1 ppm.

**Solvent residue:** compliant with Dir. 32/2009 / EC.

**Pesticides:** compliant with Reg. 396/2005 / CE and subsequent modifications.

**Polycyclic aromatic hydrocarbons:** compliant with Reg. 1933/2015 / EC.

**Aflatoxins:** Aflatoxin B1 <5 ppb Total aflatoxins (B1, B2, G1, G2) <10 ppb.

**Total bacterial load (TAMC):** 50000 CFU / g max.

**Total yeasts and molds (TYMC):** 500 CFU / g max.

**Pathogens:** Salmonella absent / 25 g; E. coli absent / 1 g.

**Enterobacteriaceae:** 100 CFU / g max.

Non-irradiated product.

It does not contain GMOs (Reg. 1829 and 1830/2003 / EC).

It does not contain traces of BSE / TSE or products of animal origin.

**Melamine:** compliant with Reg. 594/2012 / EC.

It does not contain any of the allergens included in Annex II of Reg. 1169/2011 / EC.

Product free from ethylene oxide residues.

**Storage:** in a cool place, in the original containers, well closed, away from light, humidity and direct heat sources.

**Minimum shelf life:** 36 months from the date of production.

Product suitable for vegans.

EU food grade certified product.

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*Brassica oleracea* is one of the most important vegetable plants of the *Brassicaceae* family consumed in human nutrition. Broccoli (var. *italica*) is one of the most widespread and commonly used cultivars, and thanks to its numerous recognized health properties, it is considered a super-food.

In fact, it contains a rich complex of biologically-active compounds wide-ranging in chemical nature: vitamins, carotenoids, flavonoids, phenolic acids, trace elements and, above all, a group of sulfur molecules (glucosinolates), precursors of metabolites which are formed by enzymatic bioactivation both in the plant, following cell lysis, as well as in the gastro-intestinal tract of mammals, including humans. The origin of the plant is uncertain, even though there is knowledge of the cultivation and consumption of wild cabbage which could be the same broccoli, or a very similar variety, since pre-Christian times. It is believed that as a wild species it was originally widespread in the coastal areas of Spain, France, the English islands and some parts of present-day Germany; the *italica* variety was probably domesticated over 2,000 years ago in the south of the peninsula, where indigenous sub-variants persist today.

We have evidence of its use as a food-medicine already among the ancient Greeks and Romans, with citations in Pythagoras, Diogenes, Pliny the Elder, and Cato. Cato recommended its use to prevent disease and increase longevity; the Romans consumed large quantities of it during banquets, as they believed that cabbage and cauliflower could prevent drunkenness.

In the Middle Ages, poultices of the fresh leaves of various species of cabbage were used as topical treatments, while in the 1700s it was customary to carry abundant stocks of cabbage and broccoli on ships to prevent scurvy (the vitamin C content of these vegetables is significant).

The modern nutraceutical interest arises from many observational studies correlating constant consumption of broccoli and other brassicaceae with protection against various forms of cancer and with a lower incidence of cardiovascular diseases, diabetes and neuro-degenerative diseases; broccoli has a very powerful detoxifying action, directed at the main endogenous enzymatic mechanisms responsible for detoxification from xenobiotics.

**Broccox®** is a soluble granular dry extract of broccoli standardized to 0.3-0.5% sulforaphane, the compound to which the most important health effects of the vegetable have been attributed.

**Scientific name:** *Brassica cretica* Lam. sin. *Brassica oleracea* var. *italica* Plenck.

**Family:** Brassicaceae (Cruciferae).

**Common name:** broccoli.

**Drug:** aerial part with flowers.

**Origin of the drug:** Italy.

**Country of production of the extract:** Italy.

**Production plant:** EVRA srl Benefit Company - Lauria (PZ).

**Claim (DM 10.08.2018):** Antioxidant. Regular functionality of the cardiovascular system. Digestive function. Joint function.

**Additional warning (DM 10.08.2018):** do not use in case of thyroid dysfunction.

## THE PHYTOCOMPLEX OF BROCCOLI.

The secondary metabolites of greatest interest are glucosinolates, a class of sulfur molecules structurally consisting of a  $\beta$ -thioglucose unit linked to an aglycone derived from methionine, an aromatic amino acid or a branched amino acid [1]. In broccoli, the most abundant of these is glucoraphanin (80.5% of total glucosinolates) followed by glucobrassicin (7.8%) and 1- and 4-methoxy-glucobrassicin (both around 3.8%) [2]. Other compounds of the class are: glucoiberin, glucoalyxin, gluconapine, progoinin, gluconastrutin. Glucosinolates as such are devoid of health effects and should be considered as pro-drugs that release a series of compounds including isothiocyanates (by the action of myrosinase) and nitriles (by ESP, Epithio Specifiers Proteins). Sulforaphane is generated from glucoraphanin, considered the most important metabolite and the most studied isothiocyanate of all. Indole-3-carbinol, produced from glucobrassicin, although less concentrated than sulforaphane, is the subject of equally intense research, especially for its potential applications as an anticancer molecule. The concentration of glucosinolates decreases from the seeds, to the sprouts, to the fresh vegetable ready for consumption.

Broccoli also contains important quantities of polyphenols that synergize the action of isothiocyanates: flavonoids (especially glycosylated flavanols: quercetin, myricetin and kaempferol), phenolic acids (some of these are found as acylated derivatives of flavanols: p-coumaric acid, caffeic, ferulic and synapic) and lignans. The concentrations of carotenoids (lutein above all), vitamin C and B vitamins, vitamin K1 (phylloquinone) and trace elements are also relevant. Among the latter, selenium should be mentioned, which is abundant thanks to the plant's ability to selectively accumulate it from the soil in the form of Se-methyl-amino acids.

## BIOACTIVATION OF GLUCOSINOLATES.

Glucosinolates are inactive metabolites that the plant accumulates in the vacuoles in the form of potassium salts; when broccoli tissues are subjected to cell lysis (by mechanical action or thermal stress) the glucosinolates are exposed to the action of myrosinase, a  $\beta$ -thioglucosidase that hydrolyzes the thio-sugar unit, releasing the aglycones. These are unstable and spontaneously transform into isothiocyanates or, to a lesser extent, into nitriles and epithionitriles by the action of ESP (fig. 1). The bioactivation of glucosinolates to isothiocyanates also occurs by the intestinal flora which contains an active isoform of myrosinase; there is, however, a considerable intra- and inter-individual variability in the activity of the enzyme and the bioconversion of glucoraphanin by the oral route varies from 10 to 40% of the dose; vice versa, the sulforaphane administered in the form of standardized extract is absorbed and metabolized for as much as 70-90%, being able to fully carry out its numerous activities on cellular targets [3]. Unfortunately, however, the poor stability of isothiocyanate is an important limitation to consider in the development of effective nutraceutical formulations.

Various studies have shown that the concentration of sulforaphane in the food matrix depends (in addition to the classic factors that determine the natural variability of phytocomplexes) also on the ways in which the vegetable is prepared for human consumption: the maximum dietary intake is obtained by consuming raw broccoli; steam cooking preserves a good fraction of the precursor by inactivating myrosinase, while boiling (especially for several minutes) causes the loss of a significant fraction of the active ingredients which, due to their water solubility, end up in cooking water.



**Fig. 1:** bioactivation of glucosinolates by myrosinase.

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**THE GLUCOSINOLATES IN BROCCOLI PROTECT THE CARDIO-VASCULAR SYSTEM.**

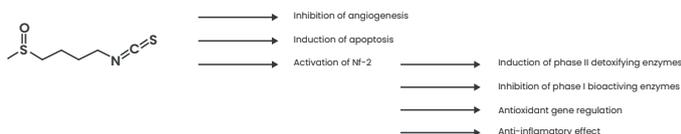


**SULFORAPHANE AND BROCCOLI-DERIVED ISOTHIOCYANATES HAVE CHEMOPREVENTIVE EFFECTS.**

- induce phase I and II enzymes inactivating toxic xenobiotics
- are indirect antioxidants (they activate Nrf-2 and the endogenous defense systems against redox stress)
- they are anti-apoptotic and anti-angiogenic
- they alleviate chronic inflammation

A significant amount of literature, especially observational studies, in vitro and pre-clinical, has shown that sulforaphane and isothiocyanates released from broccoli glucosinolates (with the synergy of the other components of the phytochemical complex) can have preventive effects in the induction and promotion of some neoplastic pathologies. Encouraging results in this direction have emerged from in vitro studies: in breast cancer, including the triple-negative type, in which sulforaphane is able to inhibit the stem cells that feed tumor proliferation and are not attacked by anti-neoplastic drugs [4]; in ovarian tumors, synergizing cisplatin therapy [5]; in bladder cancer and prostate cancer [6-7]; in lung [8] and colon [9] cancer lines.

One of the recognized mechanisms of action is the induction of phase II enzymes (in particular UGT-1 A) responsible for the detoxification of carcinogenic xenobiotic compounds. In fact, sulforaphane is a molecule with pleiotropic action capable of inducing the Nuclear Factor erythroid 2 related factor (Nrf2) which, in turn, regulates the transcription of hundreds of genes coding for proteins, enzymes and other factors involved in the processes of detoxification, resistance to oxidative stress and regulation of the cell cycle. Nrf2 is bound as an inactive form



to KEAP-1 (Kelch-like ECH-associated protein 1) acting as a repressor; sulforaphane releases it and allows its translocation into the nucleus, where Nrf2 binds to the Antioxidant Responsive Element (ARE), triggering the cellular defensive cascade which includes the activation of:  $\gamma$ -glutamylcysteine synthetase (GGCS), NADH-quinone reductase (NQO1), glutathione transferase (GST), glucuronosyl transferase (UGT), epoxide hydrolase and other detoxifying enzymes and cytoprotective proteins [10-11]. Some enzymes of phase I metabolism, on the other hand, are inhibited, including: CYP1A1, CYP2B1/2 and CYP3A4, i.e. the main activators of pro-carcinogenic molecules (for example, polycyclic aromatic hydrocarbons or aromatic amines). In this way, sulforaphane prevents the formation of DNA adducts and the consequent mutations [12].

In addition to this, sulforaphane regulates dozens of cell signaling pathways, especially pro-apoptotic and anti-inflammatory, therefore in an unfavorable direction to neoplastic proliferation: it inhibits the anti-apoptosis factor Bcl-2 while inducing pro-apoptotic ones such as BAX, cytochrome-C and caspase 3; it deactivates Akt and NF- $\kappa$ B, which promote inflammation and cell proliferation; it inhibits histone deacetylase (HDAC), causing the arrest of the cell cycle in G2M [13-14]. Sulforaphane is also a potent inhibitor of angiogenesis (causes down-regulation of VEGF and other angiogenic factors) and cell migration (by inhibition of MMP matrix metalloproteases), two very important mechanisms for the anticancer effects of broccoli and its extracts, also in potentially preventing metastatic processes [15].

**Fig. 2: Main mechanisms of the antitumor action of sulforaphane.**

In the context of many mechanistic and animal studies, few intervention studies have been performed on humans; most are aimed at understanding the pharmacokinetics of glucosinolates and isocyanates which, as already noted, have considerable intra- and inter-individual variability. One of the first published works on the chemopreventive effect of broccoli was conducted in China, in the province of Qidong, an area with a high incidence of hepatocarcinoma due to excessive exposure to food aflatoxins and air pollution with high con-

centrations of polycyclic aromatic hydrocarbons. The study included two groups of 100 subjects: one took a broccoli sprout tea containing 400  $\mu$ mol of glucoraphanin for 2 weeks and the other a placebo drink. In the subjects of the experimental group there was a statistically significant reduction vs placebo in the urinary elimination of aflatoxin-DNA adducts and phenanthrene activation metabolites, confirming the preventive potential of broccoli towards chemical carcinogenesis mechanisms [16]. In a subsequent RCT by the same team, 291

subjects from the same geographical area received a broccoli sprout drink (40  $\mu\text{mol}$  sulforaphane + 600  $\mu\text{mol}$  glucoraphanin) for 12 weeks; the treatment resulted in a significant increase vs placebo in the excretion of glutathione-conjugates of benzene (+ 61%) and acrolein (+ 23%) considered two ubiquitous carcinogenic pollutants [17].

Another work evaluated on 65 subjects the ability of sulforaphane to induce detoxifying enzymes in the upper respiratory tract after taking homogenized broccoli sprouts with a standardized concentration of this active ingredient. The levels of mRNA coding for phase II enzymes were measured in cells taken from nasal washing, before and after taking the preparation in incremental quantities. Broccoli dose-dependently increases the expression of glutathione-S-transferase M1 (GSTM1), glutathione-S-transferase P1 (GSTP1), NADPH quinone oxidoreductase (NQO1) and heme oxygenase-1 (HO-1) resulting in control of cellular oxidative stress and inflammation [18].

In subjects at high risk of prostate cancer and under active clinical surveillance, a gene expression profile was carried out to evaluate any changes induced by the intake of broccoli with the diet, for 6 or 12 months. The introduction of this vegetable in the daily diet leads to favorable transcriptional modifications in various cell signaling circuits that are altered by inflammation and can facilitate carcinogenesis of prostate tissue [20].

### THE GLUCOSINOLATES IN BROCCOLI PROTECT THE CARDIO-VASCULAR SYSTEM.

- reduce oxidative stress and vascular inflammation
- regulate the plasma lipid profile
- have anti-hypertensive effect

Pre-clinical and clinical evidence is also available regarding the favorable effects of broccoli on the health of the cardiovascular system. This mainly depends on the antioxidant and anti-inflammatory action of sulforaphane and other isothiocyanates that are generated from glucosinolates.

In spontaneously hypertensive rats, the addition of dried broccoli sprouts to the diet (glucoraphanin = 27.3  $\mu\text{mol}$  / g) reduced redox stress, blood pressure and inflammation markers in the kidney and central nervous system, in a significant way compared to the control animals that had not taken the vegetable.

A pilot phase I clinical study included 12 smokers (6 males and 6 females) who consumed 100 g per day of fresh broccoli sprouts evaluating oxidative stress markers and lipid content before and after treatment, specifically: plasma cholesterol, amino acids, NK cell activity, plasma concentrations of Q10, phosphatidylcholine hydroperoxide, 8-isoprostane and 8-hydroxy-2-deoxyguanosine. All subjects had a reduction in cholesterol (LDL and total) and oxidative stress markers; females also showed increases in HDL-cholesterol [19]. 81 diabetic patients at cardiovascular risk were randomized to take 10 g of powdered broccoli sprouts, 5 g of the same preparation or a placebo for 10 days daily. The group taking the higher dose showed a significant reduction in plasma triglycerides, OX-LDL / LDL ratio and AIP (Atherogenic Index of Plasma) compared to placebo and the lower dose group, as well as a significant increase in HDL cholesterol [21]. Another 12-week dietary intervention compared the intake of 400 g of broccoli high in glucoraphanin with the same serving of standard product and pea protein (as a control): in this case there were no significant changes in the parameters of cardiovascular risk among subjects in the treatment and control groups; however, those who took broccoli with a high content of glucoraphanin improved their metabolism by optimizing the integration between  $\beta$ -oxidation of fatty acids and the cycle of tricarboxylic acids [22].

### EFFECTS OF CONSUMING BROCCOLI SPROUTS RICH IN SULFORAPHANE IN SUBJECTS WITH TYPE II DIABETES.

- reduction of blood glucose, insulinemia, inflammatory markers and oxidative stress

Four intervention studies have shown favorable effects after taking broccoli sprouts in patients with type II diabetes. In one such study, 81 diabetics were randomized to take 10 g or 5 g of powdered sprouts with a standardized concentration of sulforaphane for 4 weeks (providing 225 and 112  $\mu\text{mol}$  of active, respectively) or a corresponding placebo. At the end of the study period the subjects who took the greatest amount of powder improved their plasma insulin concentration and HOMA-IR ( $p = 0.05$  due to the treatment effect) [23]. In another work with the same experimental design, the inflammatory markers before and after treatment (again 4 weeks) were measured: PCR, TNF $\alpha$  and IL-6. The CRP (Protein-C-Reactive) decreased statistically significantly both in the group that had taken 10 g of powder (-20.5%) and in that which had taken 5 g (- 16.4%). TNF $\alpha$  and IL-6 showed a decreasing trend in both experimental groups, although without reaching statistical significance [24].

### BROCCOLI CAN HELP PATIENTS WITH GASTRITIS AND HELICOBACTER PYLORI-POSITIVE GERD.

- antimicrobial action
- anti-inflammatory action on the gastric mucosa

Broccoli glucosinolates have demonstrated broad spectrum antimicrobial effects in some in vitro tests by inhibiting the replication of cultures of *Helicobacter pylori*, *Salmonella*, *Shigella*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa* and *Cryptococcus neoformans*.

The role of *Helicobacter pylori* in the genesis of gastric neoplasms is well defined: preclinical research has shown that sulforaphane administered at a dose of 1.33 mg (equal to a human-use dose of about 100 mg) is able to eradicate the bacterium in mice transplanted with infected human mucosa [25]. Yanaka et al. have also shown that the intake of broccoli sprouts (6  $\mu\text{mol}$  of glucoraphanin / g) by female mice with stomachs colonized by *H. pylori* has a clear anti-inflammatory effect by reducing the expression of IL-1 $\beta$  and TNF $\alpha$  as well as preventing gastric atrophy. In animals with Nrf-2 knock-out gene these effects are not evident, outlining (once again) the importance of this regulatory factor in the pharmacological outcome of sulforaphane. The same study included 48 *H. pylori* positive patients randomized to take broccoli sprouts or alfalfa (control group). The experimental group took 70 g of product containing 6  $\mu\text{mol}$  glucoraphanin / g for 8 weeks.

Broccoli improves several markers of colonization and gastric inflammation: the urease concentrations detected with the breath test, the anti-*H. pylori* antigens, the concentrations of pepsinogen I and II. Broccoli and its glucosinolates could, therefore, have a role in controlling the infection and in preventing some related neoplasms [26]. These results were confirmed by two other clinical studies in infected patients in which sulforaphane showed bactericidal activity.

### BROCCOLI AND SULFORAPHANE HAVE ALSO SHOWN EFFICACY IN OTHER CLINICAL CONTEXTS:

- cognitive decline and neuro-degeneration
- upper respiratory tract infections
- body weight control
- Gilbert's syndrome
- age-related macular degeneration
- rheumatoid arthritis

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