

# Sulforaphane Prevents Colitis-associated Cancer by Inducing Phase II Enzymes Activity of Liver Detoxification

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## **Abstract**

Ulcerative colitis (UC) is a kind of Inflammatory Bowel Disease (IBD) characterized by chronic inflammation that causes ulceration of the colonic mucosa and extends proximally from the rectum into the colon. In patients with prolonged and extensive colitis involving the entire organ, the risk for colorectal cancer is increasing. Consumption of cruciferous vegetables reduces the risk of cancer such as colorectal cancer by reducing early stage of inflammation due to its phytonutrien compounds. Sulforaphane is an organosulfur compound classified as an isothiocyanate that can prevent UC and colorectal cancer. Sulforaphane induces phase II enzyme and inhibit enzymes involved in carcinogenesis. Sulforaphane may also offer special protection to those with colon cancer susceptible genes.

**Keywords:** IBD, colitis ulcerative, sulforaphane, cruciferous vegetables

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## ***Sulforafan Mencegah Kanker yang Berkaitan dengan Kolitis Melalui Induksi Aktivitas Enzim Fase II dari Detoksifikasi Hati***

### **Abstrak**

Kolitis Ulserativa (KU) termasuk dalam golongan Inflammatory Bowel Disease (IBD) dan merupakan suatu penyakit inflamasi kronik yang terbatas pada kolon distal dan rektum. Pada pasien KU yang berkepanjangan dan meluas dapat menyebabkan terjadinya kanker kolorektal. Konsumsi sayuran golongan "cruciferous" telah diketahui mengandung fitonutrien dapat mencegah terjadinya berbagai macam kanker termasuk kanker kolorektal. Sulforafan dihasilkan dari senyawa isothiosianat yang berperan dalam mekanisme pencegahan terjadinya kanker kolorektal. Sulforafan menginduksi enzim fase II di hepar yang berperan dalam menghambat enzim-enzim yang berperan dalam karsinogenesis. Sulforafan juga memberikan perlindungan terhadap gen-gen yang "susceptible" terhadap kanker kolorektal.

**Kata kunci:** IBD, kolitis ulserativa, sulforafan, "cruciferous"

### **Background**

Ulcerative colitis (UC) is a chronic inflammatory disease that causes ulceration of the colonic mucosa and extends proximally from the rectum into the colon.<sup>1</sup> UC affects 1.4 billion people in the United States and approximately 5% of patients with UC develop colon cancer. In patients with prolonged and extensive colitis involving the entire organ, the risk for colorectal cancer approaches 20%.<sup>2</sup> Ulcerative colitis is incurable but it can be well controlled and even prevented.<sup>3</sup>

Inflammation is a complex reaction of the tissue organ caused by injury agents such as bacteria and free radicals. There are two types of inflammations; acute inflammation and chronic inflammation. Chronic inflammation has emerged as an important risk factor for cancer. Twenty percent of all cancers are

estimated due to chronic inflammation.<sup>4</sup> One of the best examples of the association between chronic inflammation and cancer is found in the heightened predisposition for colorectal cancer of patients suffering from UC and Crohn's disease, the major forms of inflammatory bowel disease (IBD).<sup>5</sup>

Edible plants in the family *Brassicaceae* are termed Cruciferous vegetable. Consumption of cruciferous vegetables reduces the risk of colorectal cancer by reducing early stage of inflammation. Cruciferous vegetables, especially broccoli contains phytonutrients sulforaphane, which has significant anti-cancer effects.<sup>6</sup> Sulforaphane is an organosulfur compound classified as an isothiocyanate. Sulforaphane induces phase II enzyme and inhibits the enzymes involved in carcinogenesis. Sulforaphane may also offer special

protection to those with colon cancer susceptible genes such as NF- $\kappa$ B.<sup>7</sup>

Liver detoxification occurs in two general phases: phase I and phase II. Phase I enzymes work in concert with phase II enzymes to get rid of carcinogens. When phase II enzymes are "switched on" by certain compounds in the diet, the body becomes more able to detoxify the carcinogens produced by phase I enzymes. Phase II enzymes can attack the carcinogens directly or render them inert and they are then excreted.<sup>8</sup> It is proposed that sulforaphane in broccoli prevents colitis associated cancer by inducing phase II enzymes activity.<sup>9</sup>

### Inflammatory Bowel Disease

IBD is thought to result from inappropriate and ongoing activation of the mucosal system driven by the presence of normal luminal flora.<sup>10</sup> IBD usually take on a relapsing remitting course. The prevalence of IBD is highest in North America, Northern Europe and United Kingdom with the average number of cases ranging from 100 to 200 cases per 100,000 persons. The two major subtypes of IBD are Crohn's disease and ulcerative colitis.<sup>11</sup>

UC is a chronic inflammation that involves only the mucosal layer, limited to the colon and rectum and ascends proximally. Chronic inflammation of the intestine is closely related with colorectal cancer. Clinical manifestation in patients with UC is tenesmus, diarrhea, abdominal pain, and rectal bleeding.<sup>12</sup>

### Broccoli

Broccoli is a plant of the Cabbage family, Brassicaceae (formerly Cruciferae). It is classified as the Italica Cultivar Group. The most distinctive characteristic of broccoli is that the tissue contains high levels of glucosinolates.<sup>13</sup> Glucosinolates are beta-thioglucoside-N-hydroxysulfates and are primarily found in *cruciferous* vegetables (cabbage, broccoli, brussels sprouts, cauliflower). Glucoraphanin is glucosinolate precursor and also known as 4-methylsulfinylbutyl glucosinolate. Through catalytic mediation of myrosinase ( $\beta$ -thioglucodase), which is released upon physical damage of plant cells especially during cutting and chewing, glucosinolates are hydrolyzed and then release the corresponding isothiocyanates such as sulforaphane.<sup>14</sup> One of these compounds is sulforaphane which has anticancer activities.<sup>13</sup> Despite all the benefits, when broccoli is boiled, glucosinolates are reduced because it is water soluble. The best method that gives no significant loss of total glucosinolates is steaming for less than 20 minutes. Eating broccoli just 3 to 5 servings can lower risk a cancer.<sup>15</sup>

Under low pH conditions, as in stomach, several condensation reaction of indole-3-carbinol occur, which result in the formation of 3,3-diindolylmethane as a major condensation product<sup>16</sup> and a potent modulator of the innate immune response with antiviral, antibacterial and anticancer activity.<sup>17</sup> Young broccoli sprouts and young cauliflower sprouts

are especially rich in glucoraphanin. have cancer chemopreventive activity but glucosinolates have lower anticancer activity than sulforaphane.<sup>6</sup>

### **Sulforaphane and Phase II Enzymes System**

Sulforaphane is an organosulfur compound, classified as isothiocyanate. Its molecular formula is  $C_6H_{11}NOS_2$ , and its molecular weight is 177,29 daltons. It is also known as 4-methylsulfinylbutyl isothiocyanate and (-)-1-isothiocyanato-4(R)-(methylsulfinyl) butane.<sup>22</sup> Sulforaphane has been extensively studied and shown to reduce the risk of colon, breast, prostate and other cancers in animal models<sup>8</sup>. Sulforaphane is an indirect antioxidant, which does not neutralize free radicals directly, but by inducing phase II enzymes.<sup>8,9</sup>

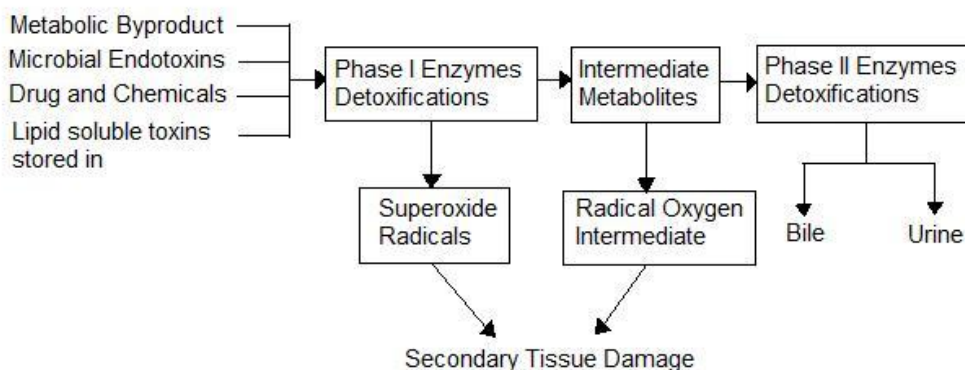
The body's first lines of defense against cancer are the phase I and phase II enzymes<sup>8</sup>. When a carcinogen enters the body, phase I enzymes are related with cytochrome P450 must often be activated. Phase I enzymes perform oxidations or reductions on the intermediate metabolite to prepare conjugation reaction by phase II enzymes.<sup>18</sup>

The phase II enzymes add another substance to the intermediate metabolite, this process is called conjugation and the substance is called conjugate. Phase II enzymes conjugate include amino acids, sugars, glutathione, methionine, sulfur, and acetyl Co-A.<sup>19</sup> A primary phase II detoxification process is a conjugation with glutathione. Glutathione is a

Sulforaphane and glucosinolates may tripeptide composed of three amino acids, cysteine, glutamic acid, and glycine.<sup>20</sup>

Figure shows phase II enzymes are important for protecting cells from DNA damage caused by carcinogens and reactive oxygen species (ROS). The result of this phase is a compound that is less toxic, water soluble, and easier for the body to eliminate.<sup>8</sup> If there are some problems with the phase II enzymes system, high risk of cancer will be present. Sulforaphane can also be used as a conjugate because it contains sulfur. Based on this, adding more sulforaphane in a conjugation process will produce more non toxic agents and also accelerate the process. The more increase conversion of intermediate metabolites to phase II enzymes, the more toxic agents in the body will be eliminated through the bile and urine. Unless quickly removed from the body by phase II enzymes system, the intermediate metabolites can cause widespread problems. Intermediate metabolites can cause damage of cell -even DNA damage- that can develops into carcinogenesis.<sup>21</sup>

Genes controlling phase II enzymes contain a specific sequence of DNA called an antioxidant response element (ARE), which play a role in increasing synthesis of conjugation substance and antioxidant enzymes.<sup>21,22</sup> Moreover, conjugation by sulfur can also be increased by supplemental sulfate, extra amounts of sulfur containing foods, and amino acids taurine and glutathione in the diet.<sup>22</sup>



**Figure** Phase II Enzymes System. Metabolic product, microbial endotoxin, drug and chemicals, and lipid soluble toxin enter the body and are processed into the phase I enzymes detoxification. In this phase, toxins have an electrical charge and they will change into intermediate metabolites. Phase II enzymes will add another substance to the intermediate metabolites to convert that metabolites into the less toxic and water soluble substance so that it is easier to eliminate them from the body through the bile and urine. In another way, if the toxins are overload, Phase I enzymes will produce superoxide radicals and therefore intermediate metabolites cannot be transformed to Phase II enzymes, but they will produce radical oxygen intermediate so it will cause a secondary tissue damage.<sup>20</sup>

Chronic inflammation of colon such as UC can cause colorectal cancer, and eating broccoli containing glucosinolates which are hydrolysed into sulforaphane could reduce inflammation in UC, so it can also reduce the risk or even prevent colorectal cancer.

## Conclusion

Broccoli (*Brassica oleraceae* var. *Italica*) potentially can be used as a prevention agent to cope with colitis-associated cancer. Sulforaphane in broccoli plays an important role in preventing cancer by inhibiting the biotransformation of non-carcinogenic into carcinogenic compounds and inducing detoxification by phase II enzymes which facilitate the removal of carcinogens from the body.

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