"Functional foods," "nutraceuticals," "designer foods" and "medicinal foods" are terms that describe foods, and key ingredients isolated from foods, that have non-nutritive or tertiary functional properties. Researchers, healthcare practitioners, laypersons, and the popular media use these words interchangeably. The purpose of this article is to present valid scientific information available on the physiologic actions of known constituents and combinations of constituents, as they naturally occur in "functional foods," highlighting their medicinal and nutritive mechanisms of action in the body.

Chemoprevention and the Crucifers

The scientific community continues to recognize and validate the considerable relationship between vegetable intake and cancer. Over 200 epidemiological studies show, with great consistency, that a low consumption of vegetables is directly associated with an increased risk of cancer (Table 1). Epidemiological studies also support the belief that dietary modification, through an increase in vegetable intake, could reduce the risk of cancer by 50% internationally. Specifically, researchers regard cruciferous vegetables, and particularly those that are members of the Brassica plant family, as critical elements in the risk reduction associated with vegetable intake and cancer. Further, in people under 56 years of age, cruciferous vegetable intake is inversely correlated with colon cancer incidence and comparatively among smokers the chemoprotective benefits of Brassica consumption are even greater. Van Poppel et al. examined 8 cohort studies and 74 case control studies that supported an inverse correlation between Brassica consumption and cancer risk. The association was found to be most consistent for lung, stomach, colon, and rectal cancers, and least consistent for prostatic, endometrial, and ovarian cancers. In studies examining total vegetable consumption an inverse association with cancer risk is also found, with the Brassicas showing the strongest effects as a subgroup. Brassicas also are low in fat, low in calories, and are potent sources of vitamins, minerals, fiber, and phytochemicals, all of which have been linked to cancer prevention.

Table 1 – Review of epidemiological studies demonstrating the relationship between vegetable consumption and cancer protection.

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Relative percentage of studies demonstrating cancer protection with high vegetable intake</th>
<th>Relative Median Risk Low vs. high consumption of vegetables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone-related</td>
<td>Breast: 57%</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Ovary/endometrium: 75%</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Prostate: 100%</td>
<td>1.3</td>
</tr>
<tr>
<td>Epithelial</td>
<td>Oral: 100%</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Lung: 98%</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Larynx: 100%</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>Esophagus: 93%</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Stomach: 89%</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Pancreas: 82%</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>Cervix: 88%</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Bladder: 60%</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>Colorectal: 57%</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous: 76%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Total: 75%</td>
<td>-</td>
</tr>
</tbody>
</table>

A discussion of the biochemical and physiologic implications of increasing one’s intake of cruciferous vegetables will follow. The term "chemoprevention," for the purpose of this research article, refers to the strategic approach of decreasing one’s susceptibility to carcinogenic factors through the administration of dietary chemicals, as introduced to the body within the matrix from which they originated (i.e., ingesting the whole vegetable vs. an isolated fraction). The rationale behind emphasizing the use of whole vegetables as opposed to an isolated fraction (considered a chemoprotective agent) is that the degree to which the protective effect of vegetables can be attributed to the nutritional or tertiary components, and to what extent indirect effects such as an equivalent reduction in fat consumption and associated increase in vitamin, fiber and carotenoid intake may be responsible for the protective effect, is not well defined. Nonetheless, the dietary approach of increasing one’s intake of cruciferous vegetables to defend oneself from cancer-causing agents has become widely recognized in the medical research community as a realistic and rational practice in the war against cancer.
Medicinal Properties in Whole Foods

Phase II Enzyme Inducers

Exposure to cruciferous vegetables (e.g., kale, Brussels sprouts, Chinese cabbage, bok choy, cabbage, turnips, collards, kohlrabi, rutabaga, cauliflower and broccoli) causes a coordinated metabolic induction of many of the Phase II liver detoxification enzymes that detoxify carcinogenic (cancer-causing) compounds from the body, thus reducing the susceptibility of cells to these substances. Glutathione transferases, NAD(P)H, quinone oxidoreductase, glucuronosyltransferase, and epoxide hydrolase are all Phase II enzymes that inactivate carcinogens.

Mechanisms of action of Phase II enzyme inducers

Phase II enzymes inactivate carcinogens in one of two ways: either through the destruction of the reactive centers of the compounds, or, more often, by conjugation with endogenous ligands, thereby counteracting the toxic properties associated with the carcinogen, and quickening their elimination from the body. Cruciferous vegetables contain water-soluble secondary metabolites referred to as glucosinolate compounds. Interestingly, the medicinal properties of glucosinolates are noted in the writings of Pythagoras and Hippocrates and at least 20 different compounds were identified by the 1980s. All cruciferous vegetables are believed to contain glucosinolates, but Brussels sprouts and broccoli have some of the highest levels.

The glucosinolates found in whole foods are converted by endogenous enzymes into isothiocyanates when they are chewed, crushed in the presence of water, or otherwise injured. This conversion is a natural defense response to predatory and other destructive influences. The tissue damage more specifically results in the release of the endogenous enzyme myrosinase, or thioglucosidase, which cleaves the glucoside bond.

\[
\text{S-3-D-CH}_2\text{H}_2\text{O}_4 \xrightarrow{\text{Mycrosinase}} \text{R-NC-S} + \text{Glucose + HSO}_4^- \\
\text{R-C} \quad \text{N-O-SO}_4^- \\
\text{Glucosinolate} \quad \text{Isothiocyanate}
\]

This results in an unstable intermediate which rearranges to release sulfate, isothiocyanates and other products. The isothiocyanates are the principal inducers of Phase II liver detoxification enzymes. Sulforaphane and sinigrin are two isothiocyanates that protect against, and oftentimes reduce, the severity of lung, colon, stomach, liver, and breast cancers. Sulforaphane supports the enzymatic activity that takes place in Phase I liver detoxification and assists the liver in carrying out the Phase II conjugation pathways. Sinigrin complements the activity of sulforaphane by also stimulating the Phase II detoxification system. In addition to supporting the liver detoxification system, sinigrin stimulates apoptosis, a process that naturally causes a damaged cell to fragment into membrane-bound particles that are then eliminated by phagocytosis. Organosulfur compounds such as dithiolethiones that are found in cruciferous vegetables are also considered putative chemopreventive agents via their effect on Phase II detoxification enzymes.

Glucosinolates commonly found in cruciferous vegetables

The most common glucosinolate compounds found in cruciferous vegetables, and more frequently in Brassica vegetables, are allylthiolalkyl glucosinolates, indole glucosinolates, and 3-hydroxalkyl glucosinolates. The 3-hydroxalkyl glucosinolates such as progoitrin give rise to oxazolidine-2-thione goitrin, which is a potent goitrogen, inhibiting iodine incorporation and thyroid formation. Hence, over-consumption of Brassica vegetables such as kale and cabbage can cause goiter in animals and in humans. However, broccoli does not contain significant quantities of these compounds.

Indole glucosinolates, including glucobrassicin, 4-hydroxyglucobrassicin, 1-hydroxyglucobrassicin, neoglucobrassicin, and 4-methoxyglucobrassicin, form unstable isothiocyanates when hydrolyzed by myrosinase. This reaction gives rise to compounds such as 3,3'-diindolylmethane, indole-3-acetonitrile and indole-3-carbinol. These compounds only represent weak inducers of Phase II detoxification enzymes, although as documented in most in-vivo studies with indole-3-carbinol, there is a reported chemoprotective role for this compound. It is important to note, however, that metabolic derivatives of indole glucosinolates also induce select cytochrome P-450 enzymes that can result in the formation of procarcinogens. The picture is not perfectly clear here, but what is known is that these derivatives simultaneously function as inducers of Phase I and Phase II enzymes.

The allylthiolalkyl glucosinolates, such as glucoraphanin, glucobrassicin and glucorucrin, form the isothiocyanates sulforaphane, iberin and erucin. These compounds are significant inducers of the Phase II detoxification enzymes, and they do not induce Phase I detoxification enzymes, as do the indole glucosinolates.

In summary, glucosinolates, which are not considered biologically active components in and of themselves, are the key compounds responsible for Phase II enzyme induction activity in cruciferous vegetables. The glucosinolates must undergo hydrolysis to isothiocyanates in order to demonstrate Phase II induction activity. Interestingly, the relative degree of potency of Phase II enzyme inducers is dependent upon multiple factors including cultivation techniques, handling and storage practices, and methods of food preparation that are independent of the relative concentration of glucosinolate compounds found in the sample. Also, with regard to Brassicas, there appears to be no net synthesis of Phase II inducers after sprouting and their concentration decreases as the plant grows. As a result, Brassica sprouts may contain 10-100 times the Phase II induction activity of mature plants. Indeed, extracts of broccoli sprouts have been shown to be more efficient at inhibiting rat tumorigenesis than extracts of mature plants. Conversely, mature broccoli contains significant amounts of indole compounds not found in sprouts that induce both Phase I and II detoxification enzymes. Glucosinolates are water-soluble, and hence it would be advisable to employ cooking techniques (such as steaming, stir frying, and rapid boiling with minimal water) to prevent excessive leaching of the isothiocyanate compounds.
Medicinal Properties in Whole Foods

urine in GSTM1 individuals. However, neither urinary nor serum isothiocyanate measurements were taken in the subjects, so other mechanisms cannot be ruled out. It is clear from the body of research available that consumption of higher levels of cruciferous vegetables is indicated for reducing the risk of some cancers.

Crucifers and cancer

Verhoeven et al.37 examined the results of seven cohort studies and 87 case-control studies on the association between Brassica vegetable consumption and cancer risk. In five of the cohort studies, Brassica consumption correlated inversely with the risk of certain cancers. The specific findings are summarized in Table 3.

Of the 87 case-control studies, 68 (78%) found a lower cancer risk associated with consumption of Brassica vegetables, although not all were significant and some applied only to one sex. The number of case-control studies in which at least one significant inverse relationship between Brassicas and cancer risk was found is shown in Table 4.

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Total Number of Studies</th>
<th>Number of studies showing a significant inverse association</th>
<th>Number of studies showing a significant positive association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>15</td>
<td>6 (40%)</td>
<td>0</td>
</tr>
<tr>
<td>Stomach</td>
<td>11</td>
<td>5 (45%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Rectum</td>
<td>10</td>
<td>4 (40%)</td>
<td>0</td>
</tr>
<tr>
<td>Lung</td>
<td>9</td>
<td>6 (67%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Although the percentage of case-control studies showing a significant inverse relationship between Brassica consumption and cancer risk is less than half in most cases, bear in mind that other variables known and unknown undoubtedly play a role in the relationship. Furthermore, only one study showed a positive correlation, suggesting that the inverse relationship between Brassica consumption and cancer is real and not simply an artifact of chance.

Because DNA damage is considered a pathogenic event in the initiation of many cancers,25 the urinary excretion of biomarkers of DNA damage serves as a potential indicator of cancer risk. An abundant and potentially mutagenic lesion caused by oxidative DNA damage is the incorporation of 8-oxo-7,8-dihydro-2-deoxyguanosine (8-oxodG) adducts into the DNA strand.26 Normal DNA repair mechanisms excise 8-oxodG, which is excised unchanged and independent of diet in the urine. Thus, the relative rate of excretion represents the integrated rate of oxidative DNA damage in the body.

Verheugen’s group38 investigated the hypothesis that dietary cruciferous vegetables result in a reduction of oxidative DNA damage in healthy, male, non-smoking humans. Ten volunteers consumed a diet containing 300 g of cooked, non-cruciferous vegetables (endive, French beans, peas, beets, fava beans, chicory and assorted other legumes and vegetables) per meal during a three-week run-in period. During the subsequent three-week intervention period, five of the volunteers continued on this diet (control group) while five others began consuming 300 g of cooked Brussels sprouts at the expense of 300 g of a glucoseoligosaccharide-free vegetable. 24-hour urine samples were collected at the end of the run-in and intervention periods. The Brussels sprouts caused no adverse effects as measured by several clinic-chemical parameters for liver, renal, thyroid, and blood-coagulation functions. During the run-in period, there was no difference in 8-oxodG excretions between the sprouts and cruciferous vegetable-free groups. Within the control group, there was no significant change in excretion between the run-in and the intervention period. By contrast, the 8-oxodG excretion decreased by 28% in the Brussels sprouts group during the intervention period.

Overview
These clinical results coupled with the results of earlier trials strongly suggest that cruciferous vegetables:

- Detoxify by upregulating detoxification enzymes
- Prevent oxidative cell and DNA damage
- Are chemoprotective against numerous types of cancer

About the author
Dr. Nick has studied and conducted research at Southwest College of Naturopathic Medicine and Health Sciences and the University of California, Los Angeles, and earned a Doctor of Naturopathic Medicine degree and a PhD degree in Nutrition. She graduated from UCLA with Latin and College honors and received distinguished honors from SCNM for her work in nutritional biochemistry, microbiology, homeopathy and botanical medicine.

She is Vice President of Research and Development at Longevity Through Prevention, Inc., a nutritional consulting

Trace Minerals International, Inc.

proudly announces its merger with

KING JAMES MEDICAL LABORATORY

Dr. Raymond Shambarger PhD, Laboratory Director
Dr. B. Blaunck-Busch PhD, Associate Director

Good Chemistry for Better Health

Elemental testing of hair, nails, urine, saliva, water & food.
We added hormonal and essential fatty acid analyses
and more. Call for our catalog.

27400 Center Ridge Rd, Suite 113
Cleveland, OH 44145-5656
Tel: 440-437-9101
email: info@traceical.com
Visit our website: www.traceical.com
continues to provide Analytical excellence and clinical support around the world

TOWNSEND LETTER FOR DOCTORS & PATIENTS – AUGUST/SEPTEMBER 2001
Medicinal Properties in Whole Foods

firm. Her expertise in nutritional medicine has earned her awards and grants to study in the United States and abroad. As a researcher, she identified and devised a method for measuring the effectiveness of nutritional formulations intracellularly on live cells using a chemiluminescent dye and molecular probe, and has a patent pending on her process (Optical Antioxidant Sensing Process™).

She is the author of numerous scientific documents that focus on validating the use of key nutrient combinations, primarily as they naturally occur in whole foods and herbs. She is a member of the American Medical Writers Association, the UCLA Alumni Scholar Association, the American Nutraceutical Association, the American Association of Naturopathic Physicians, and the American Holistic Health Association.

Correspondence:
Gina L. Nick, PhD, ND
Longevity Through Prevention, Inc.
P.O. Box 627
Brookfield, Wisconsin 53008 USA
888-299-2263
Email: dgrina@liponline.com

References