

# American Institute for Cancer Research 11th Annual Research Conference on Diet, Nutrition and Cancer

## Herbals, Cancer Prevention and Health<sup>1</sup>

Michael J. Wargovich,<sup>2</sup> Cynthia Woods, Destiny M. Hollis and Mary E. Zander

Division of Basic Research, South Carolina Cancer Center, Columbia, SC

**ABSTRACT** The use of herbs for medical benefit has played an important role in nearly every culture on earth. Herbal medicine was practiced by ancient cultures in Asia, Africa, Europe and the Americas. The recent popularity in use of herbals can be tied to the belief that herbs can provide some benefit over and above allopathic medicine and allow users to feel that they have some control in their choice of medications. The widespread use of herbs, either directly or as dietary supplements, has raised many scientific questions. Are herbal preparations safe? Do herbs interact with pharmaceutical medications to enhance or reduce their efficacy? The first interaction can be shown by the effects of St. John's Wort, a mild herbal antidepressant, and many commonly used medicines. St. John's Wort can induce the CYP3A family of activation enzymes through which ~50% of drugs are metabolized. This poses some risk of inadvertently reducing the half-life of such drugs as indinavir, cyclosporin and cyclophosphamide. On the other hand, herbal products may act in a pathway similar to pharmaceuticals yet without side effects. Natural anti-inflammatory compounds abound in the herbal world and are found in green tea, the spices turmeric and rosemary, feverfew and others. Because the use of nonsteroidal anti-inflammatory drugs (NSAID) is associated with a reduced risk for several cancers, it is at least plausible that natural NSAID should be explored for possible use as cancer preventives. *J. Nutr.* 131: 3034S-3036S, 2001.

**KEY WORDS:** • herbals • dietary supplements • cancer prevention • NSAID • herb-drug interactions

The use of herbs as medicines has played an important role in nearly every culture on earth, including Asia, Africa, Europe and the Americas. Recent surveys suggest that one in three Americans uses dietary supplements daily and the rate of usage is much higher in cancer patients (in some cases, up to 50% of patients treated in cancer centers) (1). Many of these supplements are herbal in nature. Among the many reasons cited by the general public for use of herbal medicines is the belief that botanicals will provide some measure of benefit over and above traditional allopathic medical approaches. There is also the sense that taking supplements will allow some measure of self-choice in medical care (2).

Herbal supplements are generally taken for two reasons, i.e., to alleviate symptoms of illness or to prevent illness. Examples of using herbal products for palliation include the widespread use of St. John's Wort (*Hypericum perforatum*) for relief of acute depression, the use of *Ginkgo biloba* for improvement in cognition and the use of *Echinacea* for relief of cold symptoms (3). In the second case, herbal products are taken specifically in the hopes of preventing disease or mitigating the effects of

risk for certain diseases. Examples include the consumption of green tea and other flavonoid-rich botanicals to take advantage of the natural antioxidants in them and the use of garlic because of the rich organosulfur compounds that have been shown, experimentally at least, to prevent cancer in animals (4,5). Many botanicals and some common dietary supplements are good sources of antioxidants and anti-inflammatory compounds. The latter, as we shall see, may have extraordinary utility in the prevention of colon and breast cancer.

As stated above, many in the general population take dietary supplements for palliation of symptomatic conditions. For example, St. John's Wort has been widely used in Europe, mainly in Germany, for relief of common depression (6). In a sense, St. John's Wort acts much like serotonin reuptake inhibitors, although the exact mechanism is not yet known. Some herbs used for palliation have more established mechanisms of action, as is the case for *Ginkgo biloba*. *Ginkgo* has been reported to have antioxidant properties and may be useful in the treatment and prevention of dementia and Alzheimer's disease (7). At least one hypothesis regarding Alzheimer's describes it as a disease predicated by oxidative damage (8). This damage may be ameliorated by *Ginkgo* supplements.

In the area of cancer prevention, herbs may act through several mechanisms to provide protection. Induction of phase I and phase II metabolic enzymes by herbal products is very common and may account for some of this activity. Garlic consumption and supplement use is widespread in Eastern and Western cultures (9). Garlic as well as several organosulfur

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<sup>2</sup> To whom correspondence should be addressed.  
E-mail: michael.wargovich@palmettohealth.org.

compounds derived from garlic show strong chemopreventive activity against experimentally induced cancers of the skin, esophagus, stomach, colon, liver, lung and mammary gland. Diallyl sulfide, one such compound in garlic, is an efficient inhibitor of the phase I enzyme cytochrome P<sub>450</sub> (CYP)<sup>3</sup> IIE1 (10). CYP2E1 is involved in the metabolic activation of several environmental and dietary carcinogens. Diallyl disulfide significantly increases a variety of phase II enzymes, including glutathione S-transferase, quinone reductase and UDP-glucuronosyltransferase, which are responsible for the detoxification of procarcinogens (11).

Activation of phase I and phase II enzymes, however, can lead to an important possible side effect of herbal supplements. For example, although St. John's Wort is widely used, it has been shown to induce the CYP3A family of activation enzymes, through which ~50% of modern medications also are metabolized, thus presenting the possibility of herb-drug interactions.

A type of herb-drug interaction that may be beneficial is the role of certain herbs in modulating the anti-inflammatory pathway. Anti-inflammatory drug use, especially use of non-steroidal anti-inflammatory drugs (NSAID), has been associated with reduced risk for colon and breast cancer (12,13). It is hypothesized that prostaglandins and potentially other eicosanoids could influence carcinogenesis through their effects on nuclear transcription sites and downstream gene products important in the control of cellular proliferation (14). Our laboratory has evaluated a number of commonly available over-the-counter and prescription NSAID in the rat aberrant crypt focus assay. Our findings suggest that most NSAID have chemopreventive effects in this colon cancer model (15). Nearly all NSAID modify preferentially one or both isoforms of the cyclooxygenase (COX) enzyme responsible for the production of prostaglandins, COX-1 and COX-2 (16). Strong inhibition of COX-1, whose products are involved in platelet aggregation, cytoprotection of the stomach lining and kidney function, leads to major side effects in humans, notably prolonged bleeding times and gastrointestinal ulcers (17). Although at least 10 published studies have documented a 50% reduction in risk for colon cancer based on "continuous" use of NSAID, the threat of ulceration precludes their use as chemopreventive agents by the general public, unless lower and safer doses of NSAID provide cancer preventive benefits (18). An alternative to this approach is to discover natural NSAID with similar efficacy but with a much wider safety margin. The number of herbals with potential anti-inflammatory activity is impressive. A partial listing of the most commonly used herbs with this property is shown in Table 1.

Compounds in green tea, milk thistle, red grapes and turmeric have been evaluated in animal carcinogenesis models with impressive results. In addition to their anti-inflammatory activity, the active substances in all four of these natural compounds are polyphenols, which are thought to be anticarcinogenic and antimutagenic (19,20). The catechins in green tea have been shown to reduce tumor multiplicity in the rat esophageal cancer model, as well as reduce the formation of premalignant lesions in the colon (aberrant crypt focus assay) (19,21). Additionally, tea compounds topically administered to mice before UV exposure significantly lowered skin tumors (22). Milk thistle's silymarin showed similar results in the SENCAR mouse skin tumorigenesis model. Resveratrol, found in the skins of grapes and in red wines, inhibited skin cancer

TABLE 1

Herbal sources of anti-inflammatory compounds

Common name	Botanical name
Blueberry	<i>Vaccinium myrtillus</i>
Devil's claw	<i>Harpagophytum procumbens</i>
Ginkgo	<i>Ginkgo biloba</i>
Ginger	<i>Zingiber officinale</i>
Green tea	<i>Camellia sinensis</i>
Milk thistle	<i>Silybum marianum</i>
Red grapes	<i>Vitis vinifera</i>
Stinging nettle	<i>Urtica dioica</i>
Turmeric	<i>Curcuma longa</i>
Willow bark	<i>Salix alba</i>
Yarrow	<i>Achillea millefolium</i>

in the two-stage mouse skin cancer model (23) and inhibited the neoplastic progression of altered mouse mammary glands in culture (24). Finally, curcumin, the active ingredient of the spice turmeric, has been shown to significantly inhibit the incidence and multiplicity of invasive and noninvasive colon adenocarcinomas as well as decrease colon tumor volume. This compound also decreased levels of prostaglandins and phospholipases (25). Furthermore, topical application of curcumin has been shown to inhibit tumor promotion in mouse skin (26).

Other sources of natural NSAID in Table 1 await similar investigations in animal models. One attractive characteristic of these herbal sources for possible future use in cancer prevention is their apparent wide safety margin in terms of toxicity compared with pharmaceutically based NSAID. Most natural herbals have been used for some time, yet there are few reports of adverse side effects in users. If natural NSAID are safe for common use, future cancer prevention protocols might involve the combination of herbal and pharmaceutical NSAID, which would allow usage of far-reduced doses of the pharmaceutically based NSAID. In a recent study, the combination of nettle leaf and the pharmaceutical NSAID diclofenac (reduced dose) was reported to be highly effective in treating patients with acute arthritis (27). Their relief responses were equivalent to the control group taking twice the amount of diclofenac. We eagerly await the first combined herbal-pharmaceutical anti-inflammatory experiments for the prevention of colon cancer.

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<sup>3</sup> Abbreviations used: COX, cyclooxygenase; CYP2E1, cytochrome P<sub>450</sub> IIE1; NSAID, nonsteroidal anti-inflammatory drugs.

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