Inflammation, Cancer, and Targets of Ginseng$^{1-3}$

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Abstract

Chronic inflammation is associated with a high cancer risk. At the molecular level, free radicals and aldehydes, produced during chronic inflammation, can induce deleterious gene mutation and posttranslational modifications of key cancer-related proteins. Other products of inflammation, including cytokines, growth factors, and transcription factors such as nuclear factor $\kappa B$, control the expression of cancer genes (e.g., suppressor genes and oncogenes) and key inflammatory enzymes such as inducible nitric oxide synthase and cyclooxygenase-2. These enzymes in turn directly influence reactive oxygen species and eicosanoid levels. The procancerous outcome of chronic inflammation is increased DNA damage, increased DNA synthesis, cellular proliferation, disruption of DNA repair pathways and cellular milieu, inhibition of apoptosis, and promotion of angiogenesis and invasion. Chronic inflammation is also associated with immunosuppression, which is a risk factor for cancer. Current treatment strategies for reactive species overload diseases are frequently aimed at treating or preventing the cause of the inflammation. Although these strategies have led to some progress in combating reactive species overload diseases and associated cancers, exposure often occurs again after eradication, treatment to eradicate the cause fails, or the treatment has long-term side effects. Therefore, the identification of molecules and pathways involved in chronic inflammation and cancer is critical to the design of agents that may help in preventing the progression of reactive species overload disease and cancer associated with disease progression. Here, we use ginseng as an example of an antiinflammatory molecule that targets many of the key players in the inflammation-to-cancer sequence.


Overall, chronic inflammation is bad for human health. Extensive laboratory and clinical evidence shows that chronic inflammation contributes to cancer (1). Information on the key molecules involved in inflammation-driven carcinogenesis is emerging. These molecules include nuclear factor $\kappa B$ (NF-$\kappa B$)$^{6}$; toll-like receptors; reactive oxygen and nitrogen species (RONS); cyclooxygenases (COXs); nitric oxide synthases (NOSs); pro-and antiinflammatory cytokines; metals; antioxidant enzymes; peroxisome proliferator-activated receptor ligands; kinases; growth factors; and the tumor suppressor proteins, p53 and retinoblastoma (pRB) proteins. Because we recently reviewed these key players in inflammation (1), here we present a summary table and figure (Table 1 and Fig. 1). All are potential targets for cancer chemoprevention and treatment. Many specific and general mediators of these targets have strong potential to be used as chemopreventive agents in inflammation-mediated carcinogenesis. Successful applications include the use of tumor necrosis factor-\(\alpha\) inhibitors (monoclonal antibodies) for Crohn disease (6) and interferon-\(\alpha\) for hepatitis (7). More general medicines that have consistently been found to inhibit many diseases associated with chronic inflammation (cancer, cardiovascular disease, diabetes) are nonsteroidal antiinflammatory drugs such as acetylsalicylic acid. A derivative, 5-acetylsalicylic acid, has been used with remarkable success in ameliorating inflammatory bowel disease (8). The mechanisms of 5-acetylsalicylic acid are not fully understood, but it inhibits COX weakly, activates apoptosis, inhibits proliferation and NF-$\kappa B$, scavenges RONS, and inhibits RON-associated base damage (1).

To this end, there are many natural food and herbal products that target the inflammatory cascade. These include red wine (9,10), raw fruits and vegetables (11,12), and fiber (13,14). Many others, such as green tea (15), curcumin (16), and garlic (17), have strong antiinflammatory properties. We have been
shown to decrease significantly with ginseng use include cancers preventive agent or adjuvant treatment. Some of the cancers believed to be most potent when harvested after 4–5 y of growth all forms have many beneficial properties (18,20,21). Ginseng is seng has the most potency but modern research has shown that steamed, and dried). Traditional medicine suggests that red ginseng (peeled and dried), or red ginseng (peeled, hundreds of years (19). Ginseng is prepared and used in several ways: as fresh ginseng (sliced and eaten, or brewed in a tea), toll-like receptor; VEGF, vascular endothelial growth factor. protein; PPAR, peroxisome proliferators activated receptor; RONS, reactive oxygen and nitrogen species; ROS, reactive oxygen species; TLR, Toll-like receptor.

Unconventional treatment: ginseng as a dietary supplement

 Several types of ginseng are found throughout the world, and all are part of the Araliaceae family, species in the genus Panax. The name ginseng comes from the Chinese words “Jen Sheng,” meaning “man-herb,” because of the humanoid shape of the root or rhizome of the plant, which is the part of the plant most commonly consumed. The name Panax means “all healing,” which describes the traditional belief that ginseng has properties to heal all aspects of the body. There are several different species of ginseng: 2 of the most commonly used are P. ginseng (Chinese ginseng) and P. quinquefolius (American ginseng) (18). P. ginseng has been used in the Orient for thousands of years, and P. quinquefolius has been used by Native Americans for hundreds of years (19). Ginseng is prepared and used in several ways: as fresh ginseng (sliced and eaten, or brewed in a tea), white ginseng (peeled and dried), or red ginseng (peeled, steamed, and dried). Traditional medicine suggests that red ginseng has the most potency but modern research has shown that all forms have many beneficial properties (18,20,21). Ginseng is believed to be most potent when harvested after 4–5 y of growth (22).

Studies indicate that ginseng has potential as a chemo-preventive agent or adjuvant treatment. Some of the cancers shown to decrease significantly with ginseng use include cancers of the pharynx, stomach, liver, pancreas, and colon (22,23). Mechanisms include inhibition of DNA damage (24), induction of apoptosis (25), and inhibition of cell proliferation (26). It is also becoming increasingly clear that ginseng has potent effects on the inflammatory cascade and may inhibit the inflammation-to-cancer sequence.

Ginseng targets the inflammatory players

There is evidence that ginseng has potent effects on key players in the inflammatory cascade (Fig. 1). For example, ginsan, a polysaccharide extracted from P. ginseng, showed inhibition of s, the p38 MAP kinase pathway, and NF-κB in vitro and inhibition of proinflammatory cytokines in vivo (27). The ginsenoside Rg3 was shown to inhibit phorbol ester–induced COX-2 and NF-κB induction (28). BST204, a fermented ginseng extract, can inhibit inducible NOS (iNOS) expression and subsequent nitric oxide production from lipopolysaccharide-stimulated RAW264.7 murine macrophages. In contrast, others showed that incubation of the same cells with P. ginseng showed a dose-dependent stimulation of iNOS (29). We are currently examining the effects of P. quinquefolius on nitric oxide production in both ANA-1 mouse macrophages and colon cells as a part of ongoing investigations into the potential for ginseng to inhibit colon cancer. We (25) recently showed that P. ginseng can inhibit chemically induced abberant crypt foci in mice. As mentioned, a cytokine storm is associated with active inflammation. It is therefore interesting to find that ginseng inhibits the lipopolysaccharide-induced production of tumor necrosis factor-α and other proinflammatory cytokines by cultured macrophages (30). Such an effect, therefore, may have a chemopreventive outcome.

Ginseng can also inhibit other mediators of the inflammation-to-carcinogenesis, such as matrix metalloproteases and kinase pathways (31). Recently it was also shown to activate peroxisome proliferator-activated receptor-γ (32) and transforming growth factor-β1 (33), which have the potential to inhibit the inflammation-to-cancer sequence (1). Finally, studies have found an effect of ginseng on key tumor suppressor proteins. For example, the ginsenoside Rs3 induces p53 and p21 (34) and other proapoptotic molecules (35). Ginseng can also

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**TABLE 1** Key players in the inflammation-to-cancer sequence

<table>
<thead>
<tr>
<th>Player</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>COX, cyclooxygenase</td>
<td>Inhibits inflammation</td>
</tr>
<tr>
<td>iNOS, inducible NOS</td>
<td>Produces nitric oxide</td>
</tr>
<tr>
<td>MMP, matrix metalloprotease</td>
<td>Targets extracellular matrix</td>
</tr>
<tr>
<td>NF-κB, nuclear factor-κB</td>
<td>Activates transcription factors</td>
</tr>
<tr>
<td>p53, p21</td>
<td>Induces cell cycle arrest</td>
</tr>
<tr>
<td>pRb, retinoblastoma protein</td>
<td>Inactivates tumor suppressor pathways</td>
</tr>
<tr>
<td>PPAR, peroxisome proliferators activated receptor</td>
<td>Regulates metabolism</td>
</tr>
</tbody>
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**Figure 1** The ubiquitous effects of ginseng on key players involved in the inflammation-to-cancer sequence. Abbreviations: COX, cyclooxygenase; MMP, matrix metalloprotease; NF-κB, nuclear factor-κB; NOS, nitric oxide synthase; pRb, retinoblastoma protein; PPAR, peroxisome proliferators activated receptor; RONS, reactive oxygen and nitrogen species; ROS, reactive oxygen species; TLR, Toll-like receptor.

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1. COX, cyclooxygenase; iNOS, inducible NOS; MMP, matrix metalloprotease; NF-κB, nuclear factor-κB; NOS, nitric oxide synthase; pRb, retinoblastoma protein; PPAR, peroxisome proliferators activated receptor; RONS, reactive oxygen and nitrogen species; ROS, reactive oxygen species; TLR, Toll-like receptor; VEGF, vascular endothelial growth factor.
cause the dephosphorylation and activation of the retinoblastoma tumor suppressor protein (36). The influence of various forms of ginseng on these molecules has the ultimate effect of stimulating apoptosis and inhibiting cell cycle progression. Overall, this is a good example of a natural herb that has ubiquitous properties that are conducive to stopping inflammatory-mediated carcinogenesis. Clinical studies on free radical overload diseases are warranted.

**Literature Cited**


