Nitric oxide as a target of complementary and alternative medicines to prevent and treat inflammation and cancer

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Abstract

Nitric oxide (NO) and associated reactive nitrogen species (RNS) are involved in many physiological functions. There has been an ongoing debate to whether RNS can inhibit or perpetuate chronic inflammation and associated carcinogenesis. Although the final outcome depends on the genetic make-up of its target, the surrounding microenvironment, the activity and localization of nitric oxide synthase (NOS) isoforms, and overall levels of NO/RNS, evidence is accumulating that in general, RNS drive inflammation and cancers associated with inflammation. To this end, many complementary and alternative medicines (CAMs) that work in chemoprevention associated with chronic inflammation, are inhibitors of excessive NO observed in inflammatory conditions. Here we review recent literature outlining a role of NO/RNS in chronic inflammation and cancer, and point toward NO as one of several targets for the success of CAMs in treating chronic inflammation and cancer associated with this inflammation.

Introduction

Several groups, including ourselves, have recently written reviews detailing our current knowledge of the role of NO/RNS in inflammation and carcinogenesis [1–4]. Although these reviews come to a general consensus that NO and RNS play paradoxical roles in carcinogenesis, they list the experimental studies in tabular form, which indicate approximately two out of three studies find NO potentiates inflammation and/or carcinogenesis. As also indicated in these and other reviews, final outcome depends on the experimental model, the genetic make-up of NO/RNS targets, the surrounding microenvironment, the activity and localization of NOS isoforms, and overall levels of NO/RNS. Regarding the latter issue of overall levels, although pathological levels of NO can have free radical scavenging properties, and drive apoptosis, a general finding is that these levels have pro-cancerous consequences [2], mechanistically by modifying bio-molecules such as DNA, proteins, and lipids.

The case for NO as a key modulator of inflammation and cancer

Reactive species overload diseases are associated with a high cancer risk [5]. The finding that inducible NOS (iNOS) expression is elevated in these diseases, points toward its pathological impact. Chronically elevated levels of NO/RNS leads to several chemical processes, including

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nitrination, nitrosylation, nitrosation, and oxidation. Chemical modification of cancer proteins can ultimately drive carcinogenesis, by causing dysfunction of such proteins. DNA base deamination, the formation of exocyclic-DNA adducts, and single and double-stranded breaks in DNA can also occur, increasing the risk of somatic mutation in cancer genes.

As mentioned, either pharmacologically, or molecular targeting iNOS, endothelial NOS (eNOS), or neuronal NOS (nNOS), or all three isoforms has a preventive effect on carcinogenesis in approximately two out of three published studies. NO/RNS as an exacerbator, or inhibitor of inflammation is also paradoxical. One can interpret the high NOS expression observed in reactive species overload diseases as either being a reactive protective mechanism, or a cause of the disease.

One argument that NO is protective against chronic inflammation is the finding that NO-releasing NSAIDs are successful in treating colitis and gastritis [6,7]. Mechanistically, this may be due to the cytotoxic effect of NO on lamina propria T-helper Type 1 cells [8]. Caution should be used, here, however, when extrapolating these positive outcomes in reactive species overload diseases to cancer associated with these diseases. Although high levels of NO can drive apoptosis of inflammatory cells, this may come at the risk of mutagenesis to by-standing epithelial cells [9]. On the basis of the available published literature, overall, NO/RNS promotes de novo tumorigenesis when associated with chronic inflammation, angiogenesis and growth of established solid tumors [4].

NO is not the only target for prevention and treatment of chronic inflammation

Although iNOS is easily induced and expressed in macrophages during host-defense mechanisms, many other cell types such as endothelial and epithelial cells have been shown to express iNOS. An increased level of constitutive and inducible NOS expression and/or activity is also observed in a variety of human cancers. Moreover, iNOS expression and/or nitrotyrosine accumulation, in the mucosa of patients with reactive species overloads diseases [including ulcerative colitis (UC), Helicobacter pylori–associated gastritis, viral hepatitis, Wilson’s Disease, hemochromatosis, and Barrett’s esophagus, [1]] indicate that NO production and peroxynitrite formation may be involved in the pathogenesis of these diseases, and thus predispose individuals to cancer.

With this body of evidence, it is intriguing to speculate targeting NO will prevent and treat chronic inflammation and cancers associated with chronic inflammation. This, however, does not take into account the complexity of the inflammatory micro-environment, and the plethora of molecules shown to play a key role in these diseases. We have recently reviewed these players [5,10]. Briefly, in addition to NO and nitric oxide synthases, these molecules include nuclear factor-kappa B (NF-κB); toll-like receptors (TLRs); reactive oxygen and nitrogen species (RONS); cyclooxygenases (COXs); pro- and anti-inflammatory cytokines; metals; antioxidant enzymes; peroxisome proliferator-activated receptor (PPAR) ligands; kinases; growth factors; and the tumor suppressor proteins, p53 and retinoblastoma (pRb) (Figure 1). All are potential targets for the prevention and treatment of chronic inflammation, cancer chemoprevention and cancer treatment.

Agents that target individual or multiple players in this cascade have been used with success in humans. These include the use of tumor necrosis factor-α (TNF- α) inhibitors (monoclonal antibodies) for Crohn’s disease and UC [11,12] and interferon-α (IFN-α) for hepatitis [13]. Some agents that target multiple players simultaneously have consistently been found to inhibit many diseases associated with chronic inflammation (cancer, cardiovascular disease, diabetes). These include non-steroidal anti-inflammatory drugs, such as acetylsalicylic acid. A derivative, 5-acetylsalicylic acid (5-ASA), has been used with remarkable success in ameliorating mild to moderate bouts of inflammatory bowel disease [14]. The mechanisms of 5-ASA are not fully
understood, but it inhibits COX-1 and COX-2 weakly, activates apoptosis, inhibits proliferation and NF-κB, scavenges RONS, and inhibits RON-associated base damage. Recently, it has been shown that simultaneous inhibition of COX-2 and iNOS protects from colitis in rats [15].

Research over the last few years has implicated NF-κB as a molecular node in the inflammation to cancer sequence. In un-stimulated conditions, NF-κB proteins bind to IkB. Upon stimulation, IkB proteins are phosphorylated and degraded through the proteasome. This releases NF-κB which then translocates to the nucleus and binds to its promoter elements (κB sites) and regulates the expression of many genes. Because (i) NF-κB is upregulated in reactive species overload diseases, and (ii) many of the genes targeted by NF-κB are involved in the inflammatory cascade (iNOS, COX-2, cytokines and matrix metalloproteinases), anti-apoptotic events (e.g. the pro-survival Bcl-2 homolog Bfl-1/A1) and cell cycle events (e.g. cyclin D1), it is emerging as one of the more promising targets in the chemoprevention of these diseases.

NF-κB is a target of many antioxidants associated with chemoprevention (e.g. NSAIDs, butyrate, curcumin, triterpenoids, gliotoxin and other sponge compounds, black tea, leptons, caffeic acid, resveratrol, quercetin, green tea). Therefore, its usefulness in taming high cancer risk, reactive species overload diseases has been shown indirectly. More direct genetic and pharmacological inhibition of the NF-κB pathway has been shown to inhibit experimental colitis [16,17]. Recent studies have shown NOD2 mutations - those that play a key role in Crohn’s disease - can lead to NF-κB activation [18]. This group also showed that the genetic deletion of a functional NF-κB pathway in epithelial cells protected from tumorigenesis associated with experimental colitis [16]. Deletion of functional NF-κB pathway in myeloid cells resulted in diminished activation (and thus propagation of inflammation) and reduced tumor size, indicating a protection from inflammatory-driven tumor progression. NF-κB inhibition has also been shown to protect from pancreatitis, cystitis and hepatitis progression to liver cancer (reviewed in: [5]). However, as others have pointed out [19], due to its importance in immune function, targeting NF-κB specifically for cancer chemoprevention might be impractical. To this end, targeting NF-κB for moderate inhibition in people with hyperactive immune systems (autoimmune diseases and high cancer risk reactive species overload diseases), while simultaneously targeting other key players in the inflammatory cascade (including NO), may have diverse and beneficial effects for chemoprevention. Overall, many of the CAMs showing promise in chemoprevention of high cancer risk, reactive species overload diseases, do just this.

**Dietary CAMs target NO, and other players in inflammation**

CAMs are a diverse group of health care practices and products that are not presently considered to be part of conventional medicine. One form of CAM is the use of natural food and herbal products to prevent and treat disease, and/or to maintain health. Although many of these products have been used for hundreds and even thousands of years, only recently have Western societies begun to appreciate the impact on human health and gain significant knowledge into their mechanism of action. As discussed, one reason for the successful use of CAMs to prevent and treat chronic inflammatory diseases is that they target key players in inflammation, including NO.

According to the National Center for Complementary and Alternative Medicine (NCCAM): “the CAM domain of biologically based practices includes, but is not limited to, botanicals, animal-derived extracts, vitamins, minerals, fatty acids, amino acids, proteins, prebiotics and probiotics [live bacteria (and sometimes yeasts) found in foods such as yogurt or in dietary supplements], whole diets, and functional foods”. This is clearly a large and diverse group, and covering the impact of each on disease prevention/treatment, and their mechanism of action is...
beyond the scope of this review. For purposes of the present discussion, we will focus on CAMs that have been used successfully on reactive species overload diseases (animal models and/or human), then explore the mechanism by which these CAMs work. Collectively, I hope to convince you that current evidence points toward their ability to work as anti-oxidants and target key players in inflammation. This includes, but is not exclusive to, NO and RNS.

Table 1 provides an overview of some CAMs that have been used successfully to prevent and/or treat reactive species overload diseases in animals and/or humans. A scan of the literature indicates many of these compounds target the players in chronic inflammation and the inflammation-to-cancer sequence. For example (there are many), aloe vera suppresses the release of pro-inflammatory cytokines from inflammatory cells [20]. Butyrate suppresses NF-kB activation [21]. There are many more published studies showing that the listed CAMs in Table 1 target key molecules in inflammation and the inflammation-to-cancer sequence. However, this review has a focus on NO and its pathway. We have reasoned that this pathway is key to chronic inflammation, but targeting this pathway alone (as with many molecules, including NF-kB) gives paradoxical results. Therefore, although we cite studies showing an effect of various CAMs on the NO pathway, in many cases these CAMs also diminish the activation of other pro-inflammatory molecules, or stimulate the activation of anti-inflammatory molecules. We submit that such ubiquitous effects that diminish the activation and/or expression of multiple pro-inflammatory players, but do not completely block individual players (or over-stimulate anti-inflammatory players) are key to the penultimate success of certain CAMs in the prevention and treatment of autoimmune and reactive species overload diseases.

The finding that many of the CAMs listed in Table 1 have been shown to reduce NO species gives further weight to the role of NO in chronic inflammation and carcinogenesis. For example, aloe has been shown to inhibit cytokine-induced iNOS expression, and nitric oxide accumulation in tumor cells [22]. Nitric oxide contributes to desipramine-induced hypotension in rats [23]. Interestingly, berberine chloride can also cause an increase in eNOS expression, but it inhibits iNOS expression [24]. The inhibition of iNOS expression by berberine in vivo has been confirmed in a more recent study in hepatocytes [25]. Additionally, berberine can inhibit cytokine/lipopolysaccharide induced iNOS expression in inflammatory cells, as can butyrate, caffeic acid, clericirome (a coumerin derivative), catalposide, curcumin, Artemisia asiatica, garlic, quercetin/quercitrin, ginkgo biloba, lactoferrin, leptin, linoletic acid, lycopene, omega-3 fatty acids, wogonin, rutin, resveratrol, selenium, black tea extracts, green tea extracts, vitamin E, Acanthopanax senticosus, cadmium, cannabinoids, alpha-lipoic acid, ginseng, silymarin, Sho-saiko-to (TJ-9), and astaxanthin [26–54]. Among many other examples, butyrate can also inhibit iNOS expression in colon cancer cells [55], and DA-6034 can inhibit iNOS expression in gastric cancer cells [56], giving some insight into their ability to protect against colitis and potentially gastritis, respectively. S-Adenosylmethionine, which protects against hepatitis, attenuates the induction of iNOS in the liver of lipopolysaccharide-treated rats and in cytokine-treated hepatocytes [57]. S-Adenosylmethionine also accelerates the re-synthesis of inhibitor kappa B alpha, blunts the activation of NF-kB and reduces the transactivation of the iNOS promoter [57]. Green tea does not only inhibit iNOS expression [58], but also directly scavenges NO [59], as do other CAMs [57,60], suggesting additional NO-related anti-inflammatory mechanisms.

The importance of NO in disease pathology so far is highlighted here by the clear and relatively consistent findings above that many of the CAMs listed in Table 1 can inhibit the induced expression of iNOS and NO production. We should mention, however, that this finding is consistent for induced expression in macrophages. In other cell types, CAMs can drive NO production [61], especially from eNOS in endothelial cells, which is indicative of their cardio-protective mechanisms [62–65]. Finally, in some cases CAMs can induce NO in unstimulated
macrophages [66]. For example, ginseng can induce iNOS in resting macrophages [67]; a finding consistent with the understanding that ginseng boosts immune cell function in healthy individuals. Therefore, many of these CAMs will have differing effects depending on whether they are used in healthy people, or people with autoimmune, reactive species overload diseases. In the former case, CAMs (e.g. ginseng) can stimulate immunity; in the latter case, CAMs (e.g. ginseng) inhibit an overactive immune system, as indicated by the ability to inhibit activated macrophages.

In some instances, the ability of CAMs to inhibit NO production leads to other cancer inhibitory effects. These inhibitory effects are sometimes independent (but complementary to) NO, and sometimes dependent on nitric oxide, due to its direct impact on cell growth and apoptosis. For example, curcumin can induce melanoma cell apoptosis and cell cycle arrest [68]. This was associated with the down-regulation of NF-κB activation, iNOS and DNA-dependent protein kinase catalytic subunit expression, and up-regulation of p53, p21(Cip1), p27(Kip1) and checkpoint kinase 2. Curcumin also down-regulated constitutive NOS activity in melanoma cells. Zheng et al. concuded that curcumin arrested cell growth at the G(2)/M phase and induced apoptosis in human melanoma cells by inhibiting NF-κB activation and thus depletion of endogenous nitric oxide.

We have described the ability of many CAMs shown to prevent and/or treat reactive species overload diseases, and have presented evidence that the prevention of NO/RNS is a mechanism. However, as mentioned, the other players in inflammation and the inflammation-to-cancer sequence are also targets of CAMs. Powerful evidence for this statement comes from studies with the CAMs emerging as the more potent, successful and consistent in treating multiple high cancer risk, reactive species overload diseases. These include curcumin, green tea, resveratrol, and quercetin. For example (Figure 1), in addition to NO inhibition, curcumin (a principal curcuminoid of the Indian curry spice turmeric) inhibits NF-κB [69], inflammatory cytokines [70–74], Cox-2 [75–77], matrix metalloproteinases [75,78], pro-survival kinase pathways [79], modulate TLR signaling [80], growth factor expression [81], induces p53 [82–84], and activates anti-inflammatory peroxisome proliferator-activated receptor-gamma [85]. Green tea catechins (Figure 1) activate wild-type p53 [86–89], and protect from p53 mutation [90]. They promote pRb hypophosphorylation and activation of this tumor suppressor protein [91]. They inhibit pro-inflammatory cytokines [92–94], NF-κB [95,96], Cox-2 [97–100], growth factors such as IGF-I [101], and MMPs such as MMP-7 [102] and MMP-9 [103].

As discussed above, green tea catechins inhibit iNOS [58,104–106] and scavenge NO [107] and other free radicals [59]. Interestingly, as with many CAMs, green tea (as well as resveratrol [108] and quercetin [109]) can induce eNOS in endothelial cells, indicative of their cardio-protective effects [108,110]. Finally, they modulate TLR signaling pathways [111] and activate anti-inflammatory peroxisome proliferator-activated receptors [112].

As with green tea [88,113], resveratrol (trans-3,5,4′-trihydroxystilbene), a compound found largely in the skins of red grapes, prevents DNA damage and induces apoptosis in a p53-dependent manner [114–116]. Interestingly, resveratrol can induce the expression of the p53 target, NAG-1 [non-steroidal anti-inflammatory (NSAID) drug-activated gene-1], a member of the transforming growth factor-beta superfamily, that has pro-apoptotic and antitumorigenesis activities [117]. Also similar to green tea, resveratrol prevents pRb hyperphosphorylation and thus the inactivation of this tumor suppressor protein. Resveratrol also inhibits MMP-2 [118] and MMP-9 [119,120], Cox-1 [121], Cox-2 [122–124], pro-inflammatory cytokines [125–127], NF-κB activation [123,124,128], and growth factors such as hepatocyte growth factor [129]. Finally, consistent with the its anti-inflammatory themed
effects, resveratrol can stimulate anti-inflammatory cytokines [130] as well as anti-inflammatory PPARs [131].

Quercetin is a flavonoid found in many foods such as apples, grapes, wines, onions, berries, teas, and brassica vegetables. It is also found in some potent CAMs, including Ginkgo biloba, St. John’s Wort, and Sambucus canadensis (Elder). Quercetin mediates the down-regulation of mutant p53 [132], and upregulation of wild-type p53 [133–136]. As with resveratrol, quercetin also induces NAG-1 in a p53-dependent manner [137]. It also causes hypophosphorylation and activation of pRb [138]. It inhibits pro-inflammatory cytokines [139–142], growth factor signaling [143], kinases [134,144,145], MMPs-1,-2, and -9 [144, 146]. The ability of quercetin to inhibit DNA damage [147] may be at least in part due to its ability to suppress Cox-2 [147–150] and NF-κB [139–141,147,150–153].

**Concluding remarks**

I have made the case that NO remains a viable candidate target for the prevention and/or treatment of radical species overload diseases, and associated cancers. However, due to the paradoxical behavior of NO, and other nodes in the inflammation-to-cancer sequence (including NF-κB), an approach that is worth further consideration and exploration is the targeting of multiple players in the cascade. CAMs have been used for thousands of years, and we are beginning to understand the mechanisms. One key mechanism of many is their anti-oxidant properties, and their ability to target multiple inflammation players simultaneously. Perhaps cocktails made up of key active components of CAMs, or synthetic drugs that partially block many of the key players (aspirin is one of these) will prove to be beneficial in treating the millions of people world-wide with autoimmune and high cancer risk, reactive species overload diseases.

**Acknowledgements**

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**References**


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232. Finley JW, Davis CD. Selenium (Se) from high-selenium broccoli is utilized differently than selenite, selenate and selenomethionine, but is more effective in inhibiting colon carcinogenesis. Biofactors 2001;14:191–196. [PubMed: 11568456]


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Fig. 1.
Popular and powerful CAMs target many key players in inflammation.
### Table 1
CAMs that protect against reactive species overload diseases

<table>
<thead>
<tr>
<th>Compound(s)</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Colitis</td>
<td>[154]</td>
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<tr>
<td>Aloe vera + ubiquinol</td>
<td>[154]</td>
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<tr>
<td>Antidepressants (desipramine)</td>
<td>[155]</td>
</tr>
<tr>
<td>Berberine chloride</td>
<td>[156]</td>
</tr>
<tr>
<td>Butyrate</td>
<td>[157–159]</td>
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<tr>
<td>Caffeic acid phenethyl ester</td>
<td>[160]</td>
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<tr>
<td>Catalposide</td>
<td>[161]</td>
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<tr>
<td>Cladosiphon okamuranus Tokida</td>
<td>[162]</td>
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<tr>
<td>Cloricromene</td>
<td>[163]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>[164–171]</td>
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<tr>
<td>DA-9601 (standardized extract of Artemisia asiatica)</td>
<td>[172]</td>
</tr>
<tr>
<td>* DA-6034 (a flavonoid derivative)</td>
<td>[173]</td>
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<tr>
<td>Diammonium Glycyrrhizinate</td>
<td>[174]</td>
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<tr>
<td>Fructo-oligosaccharide</td>
<td>[175]</td>
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<tr>
<td>* Galanin</td>
<td>[176,177]</td>
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<tr>
<td>* Garlic</td>
<td>[178–180]</td>
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<tr>
<td>Ginkgo biloba</td>
<td>[181,182]</td>
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<tr>
<td>Ghrelin</td>
<td>[183]</td>
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<tr>
<td>Gliotoxin</td>
<td>[184]</td>
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<tr>
<td>Glutamine</td>
<td>[185]</td>
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<tr>
<td>Goat milk Oligosaccharides</td>
<td>[186]</td>
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<tr>
<td>* Green tea catechins</td>
<td>[187–191]</td>
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<tr>
<td>IDS 30 (stinging nettle extract)</td>
<td>[192]</td>
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<tr>
<td>* Inositol compounds</td>
<td>[193,194]</td>
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<tr>
<td>Iron chelators</td>
<td>[195]</td>
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<tr>
<td>* Lactoferrin</td>
<td>[196–198]</td>
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<tr>
<td>Lactulose</td>
<td>[199]</td>
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<tr>
<td>Leptin</td>
<td>[200]</td>
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<td>* Linoleic acid</td>
<td>[201–203]</td>
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<tr>
<td>Low-alkaloid tobacco</td>
<td>[204]</td>
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<tr>
<td>* Lycopene</td>
<td>[200,205]</td>
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<tr>
<td>Lysed E. coli</td>
<td>[206]</td>
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<tr>
<td>Morin</td>
<td>[207]</td>
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<tr>
<td>Nicotine</td>
<td>[208]</td>
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<tr>
<td>Nanocrystalline silver</td>
<td>[209]</td>
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<tr>
<td>* Omega-3 fatty acids</td>
<td>[210]</td>
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<td>[199,211–214]</td>
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<tr>
<td>Paeonol</td>
<td>[215]</td>
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<tr>
<td>* Probiotics</td>
<td>[216–218]</td>
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<tr>
<td>* (Bifidobacterium lactis, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus reuteri, Lactobacillus fermentum, Lactobacillus plantarum 299V and Lactobacillus salivarius Ls-33)</td>
<td>[219–221]</td>
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<td>[222]</td>
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<td>Compound(s)</td>
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<td>* Quercetin</td>
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<tr>
<td>Quercitrin</td>
<td>[224]</td>
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<tr>
<td>* Resveratrol</td>
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<td>* Rutoside</td>
<td>[167,229]</td>
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<tr>
<td>Saccharomyces boulardii</td>
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<tr>
<td>* Selenium</td>
<td>[231,232]</td>
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<tr>
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<td>Thearubigin ( * black tea extract)</td>
<td>[235–237]</td>
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<td>Traditional chinese medicines **</td>
<td>[238]</td>
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<td>Trimetazidine</td>
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<td>UR-1505</td>
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<tr>
<td>* Ursodiol</td>
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<td>* Vitamin A</td>
<td>[244,245]</td>
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<tr>
<td>Vitamin C</td>
<td>[246]</td>
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<tr>
<td>* Vitamin D</td>
<td>[247]</td>
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<tr>
<td>* Vitamin E</td>
<td>[231,248]</td>
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<td>* Copper chelators</td>
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<td>DL-alpha-lipoic acid</td>
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<td>* Glycyrrhizin (from liquorice root)</td>
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<td>Kangxian baogan decoction</td>
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<td>Punicalagin and punicalin</td>
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<td>*Phyllanthus</td>
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<td>[254]</td>
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<tr>
<td>*Selenium</td>
<td>[289–291]</td>
</tr>
<tr>
<td>Silibinin</td>
<td>[292]</td>
</tr>
<tr>
<td>Silymarin</td>
<td>[293]</td>
</tr>
<tr>
<td>Sodium fusidate</td>
<td>[294]</td>
</tr>
<tr>
<td>*TJ-9 (Sho-saikō-to)</td>
<td>[295,296]</td>
</tr>
<tr>
<td>*Ursodiol</td>
<td>[297]</td>
</tr>
<tr>
<td>*Vitamin E</td>
<td>[298,299]</td>
</tr>
<tr>
<td>*Vitamin K</td>
<td>[300]</td>
</tr>
<tr>
<td>Whey protein</td>
<td>[301]</td>
</tr>
<tr>
<td>Zinc</td>
<td>[302]</td>
</tr>
<tr>
<td><strong>Gastritis</strong></td>
<td></td>
</tr>
<tr>
<td>Acupuncture</td>
<td>[303]</td>
</tr>
<tr>
<td>Antioxidant cocktail (selenium, β-carotene, and vitamins A, C and E)</td>
<td>[304]</td>
</tr>
<tr>
<td>Astaxanthin</td>
<td>[305]</td>
</tr>
<tr>
<td>*Curcumin</td>
<td>[306,307]</td>
</tr>
<tr>
<td>DA-9601</td>
<td>[308,309]</td>
</tr>
<tr>
<td>*Garlic</td>
<td>[310–312]</td>
</tr>
<tr>
<td>*Green tea catechins</td>
<td>[313–316]</td>
</tr>
<tr>
<td>*Iron chelators</td>
<td>[195,317]</td>
</tr>
<tr>
<td>Kampo</td>
<td>[318]</td>
</tr>
<tr>
<td>Moxibustion</td>
<td>[303]</td>
</tr>
<tr>
<td>*Rebamipide</td>
<td>[319,320]</td>
</tr>
<tr>
<td>Red wine</td>
<td>[314]</td>
</tr>
<tr>
<td>TJ-15</td>
<td>[321]</td>
</tr>
<tr>
<td><strong>Pancreatitis</strong></td>
<td></td>
</tr>
<tr>
<td>Black tea (Camellia sinensis)</td>
<td>[322]</td>
</tr>
<tr>
<td>*Curcumin</td>
<td>[323–325]</td>
</tr>
<tr>
<td>DA-9601</td>
<td>[326,327]</td>
</tr>
<tr>
<td>Eicosapentaenoic acid (Omega-3 fatty acids)</td>
<td>[328]</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>[330]</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>[331]</td>
</tr>
<tr>
<td>*Green tea catechins</td>
<td>[332–334]</td>
</tr>
<tr>
<td>Iron chelators</td>
<td>[335]</td>
</tr>
<tr>
<td>Lactobacillus plantarum</td>
<td>[336]</td>
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<tr>
<td>Leptin</td>
<td>[337]</td>
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<tr>
<td>Ligustrazine</td>
<td>[338]</td>
</tr>
<tr>
<td>*Melatonin/L-tryptophan</td>
<td>[339,340]</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>[341–343]</td>
</tr>
<tr>
<td>Compound(s)</td>
<td>Reference</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>TJ-10</td>
<td>[344]</td>
</tr>
<tr>
<td>TJ-45</td>
<td>[345]</td>
</tr>
<tr>
<td>Ursodiol</td>
<td>[346]</td>
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<tr>
<td>Vitamin E</td>
<td>[347]</td>
</tr>
<tr>
<td>Zinc</td>
<td>[348]</td>
</tr>
<tr>
<td><strong>Esophagitis/Barrett’s Esophagitis</strong></td>
<td>[349,350]</td>
</tr>
<tr>
<td>* Green tea catechins</td>
<td>[351,352]</td>
</tr>
<tr>
<td>Harmaline</td>
<td>[353]</td>
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<tr>
<td>Inositol compounds</td>
<td>[354]</td>
</tr>
<tr>
<td>Rutin</td>
<td>[353]</td>
</tr>
<tr>
<td>Thioprole/thiazolidine-4-carboxylic acid</td>
<td>[355]</td>
</tr>
<tr>
<td><strong>Prostatitis</strong></td>
<td>[356]</td>
</tr>
<tr>
<td>Cernilton (pollen extract)</td>
<td></td>
</tr>
<tr>
<td>* Green tea catechins</td>
<td>[351,357–359]</td>
</tr>
<tr>
<td>Kampo medicines</td>
<td>[360]</td>
</tr>
<tr>
<td>* Lycopene</td>
<td>[361,362]</td>
</tr>
<tr>
<td>Quercetin</td>
<td>[363]</td>
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<tr>
<td>Saw palmetto</td>
<td>[364]</td>
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<tr>
<td>* Soy</td>
<td>[365–367]</td>
</tr>
<tr>
<td><strong>Cystitis</strong></td>
<td>[368,369]</td>
</tr>
<tr>
<td>* Garlic</td>
<td></td>
</tr>
<tr>
<td>Green tea catechins</td>
<td>[370]</td>
</tr>
<tr>
<td>Quercetin</td>
<td>[371]</td>
</tr>
<tr>
<td>Uro-Vaxom (E. coli extract)</td>
<td>[372]</td>
</tr>
<tr>
<td>* Vitamin D or analogues</td>
<td>[373,374]</td>
</tr>
</tbody>
</table>

* Indicates there is animal and/or human evidence that this CAM protects from cancer or metastases in that organ.

** Traditional Chinese medicinal herbs for enema consisted of Huangqi (astragalus), Dahuang (caulis fibraureae), Huangbai (cortex phellodendri), Wubeizi (galla chinensis) and Baiji (rhizoma bletillae), mixed with 1g crude drug per milliliter by Medicament Section of Shanghai Tongji Hospital.