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**File: ■ Antioxidant Supplements
■ Gastrointestinal Diseases
■ Inflammatory Bowel Disease**

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RE: Review Documents Clinical Evidence for Usefulness of Some Antioxidant Supplements in Inflammatory Bowel Conditions

Khan I, Samson SE, Grover AK. Antioxidant supplements and gastrointestinal diseases: a critical appraisal. *Med Princ Pract.* 2017;26(3):201-217.

Some gastrointestinal (GI) diseases, including irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) (subdivided into Crohn's disease [CD] and ulcerative colitis [UC]), are thought to result in part from oxidative stress. Antioxidant supplements are often used to treat and manage symptoms. The authors searched the Medline electronic database for studies of antioxidants and the diseases listed, as well as celiac disease (CLD). Initial searches using different terms yielded 372 and 340 reports, most from in vitro or in vivo studies. Eighty human studies were found, none on CLD.

The authors devoted more than 10 pages to reviewing the literature on the GI tract. [Note: This is highly unusual and usually found only in book chapters.] In the 80 human studies, allopurinol (a drug and not related to the article's title), a xanthine oxidase inhibitor, was tested in combination with sulfasalazine or steroid (prednisone) in IBD and UC, increasing the immunosuppressive metabolite 6-thioguanine nucleotide (6-TGN) more than monotherapy and leading to better relapse rates. Combination therapy with another drug (again off focus), mesalamine, was not as successful in UC as in IBD.

Boswellia (*Boswellia serrata*, Burseraceae), used in Ayurvedic and European traditional medicines, showed benefit against collagenous colitis in one of two studies. A double-blind, randomized controlled trial (RCT) found boswellia beneficial in CD but less so than mesalamine, again, a drug. In juvenile CD, a small study found a product containing boswellia with other ingredients useful in maintaining long-term remission. In patients with UC for six weeks or longer, boswellia extract was more effective than sulfasalazine in maintaining remission.

Curcumin, the active ingredient of the widely used spice turmeric (*Curcuma longa*, Zingiberaceae), inhibits inflammatory pathways and is well tolerated. A randomized, partially blinded study with 207 patients with IBS who took turmeric extract for eight weeks reported benefits for both low-dose and high-dose turmeric but did not include a placebo group. In two RCTs, combined therapy with curcumin and mesalamine was superior to mesalamine alone. In two open studies with adult and pediatric patients who had UC or CD, curcumin alone was of marginal efficacy.

Chamomile (*Matricaria chamomilla* syn. *M. recutita*, Asteraceae) flowers contain antioxidant and anti-inflammatory compounds including bisabolol, chamazulene, apigenin, and luteolin. Two RCTs in patients with UC found a preparation of chamomile, myrrh (*Commiphora* spp., Burseraceae), and coffee (*Coffea arabica*, Rubiaceae) charcoal as effective as mesalamine. Wormwood (*Artemisia absinthium*, Asteraceae) and related species also contain antioxidants. A small RCT reported that wormwood extracts reduced or eliminated the need for steroids in patients with CD. An open study also had positive results. However, both were small and of short duration. Peppermint (*Mentha × piperita*, Lamiaceae) contains antioxidants including rosmarinic acid, eriocitrin, luteolin, and terpenes. Seven studies examined peppermint in IBS, finding only marginal efficacy but no reported adverse events (AEs).

Other antioxidants subjected to limited study, which were considered to have insufficient evidence of benefit, include aloe vera (*Aloe vera*, Asphodelaceae), andrographis (*Andrographis paniculata*, Acanthaceae), bilberry (*Vaccinium myrtillus*, Ericaceae), red or chili pepper (*Capsicum annuum*, Solanaceae), carnosine, ferrous fumarate, green tea (*Camellia sinensis*, Theaceae), kiwi (*Actinidia deliciosa*, Actinidiaceae) fruit, mastic gum (from mastic tree [*Pistacia lentiscus*, Anacardiaceae]), *N*-acetyl cysteine, oxpentifylline, pomegranate (*Punica granatum*, Lythraceae), psyllium (*Plantago ovata*, Plantaginaceae), resveratrol, superoxide dismutase, and tormentil (*Potentilla erecta*, Rosaceae).

Omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) occur in fish oil and in flax (*Linum usitatissimum*, Linaceae) and hemp (*Cannabis sativa*, Cannabaceae) seeds. [Note: Omega-6s are essential fatty acids, but are highly inflammatory.] For CD, UC, and IBS, PUFAs have been tested in combination with other ingredients and/or in small and/or poorly controlled studies. In an RCT, mesalamine controlled remission in pediatric patients with CD, but 95% relapsed within one year. Adjunct therapy with omega-3s reduced the rate to 61%. In a multicenter RCT study on CD, relapse rates were about the same with or without omega-3 supplementation. In another study, enteric-coated PUFA capsules helped patients with CD maintain remission better than placebo. In a small, crossover RCT, patients with UC taking prednisone or sulfasalazine reported significant benefits with omega-3 supplementation. In another, omega-3 improved the oxidative status of patients with UC taking sulfasalazine; yet another found that omega-3 had some benefits against UC but was less effective than sulfasalazine. No AEs were reported in any of the PUFA studies discussed.

Chinese medicine and Ayurveda offer medications that may be useful in GI diseases. From the former, *léi gōng téng* (*Tripterygium wilfordii*, Celastraceae), rich in antioxidant polyphenols, performed better than azathioprine, mesalamine, or sulfasalazine against CD. Sample sizes were small in the four trials reported. *Léi gōng téng* has male anti-fertility effects that were not monitored in these studies. In two studies on UC, multiherbal medicines were significantly efficacious. One, an RCT in patients with ulcerative proctitis using the Chinese formulation *xilei san* given by enema, saw improvement within 14 days; after six months, the remission rate was 81.8% with *xilei san* compared to 16.7% with placebo. Overall improvements were noted in several parameters. An open study used an Ayurvedic medicine containing bael (*Aegle marmelos*, Rutaceae) and bacopa (*Bacopa monnieri*, Plantaginaceae) along with a cluster fig (*Ficus racemosa* syn. *F. glomerata*, Moraceae) enema. While patients could keep using steroids or sulfasalazine as needed, after four weeks they had such significant improvement in symptoms that they stopped taking the drugs. Sample size in these trials was small. The review says that "marginal" benefits of other multiherb

preparations have been reported in IBS or UC; some of these studies report clinically meaningful benefits, but study sizes are small.

Lack of uniformity in disease diagnosis, etiology, and pathophysiology has led researchers to use many indices to monitor effects of antioxidant therapies in these GI maladies, some quite subjective. Studies identified were also quite heterogeneous in their adherence to Cochrane criteria for clinical trials. Most did not comment on the quality of antioxidants used, which may vary substantially depending on many factors. The authors devised a rating system for reported substance efficacy and study quality to help readers choose substances for further exploration.

Also, boswellia, *léi gōng téng*, omega-3s, and chamomile should be considered as adjunct therapy with current medicines, and clinical trials of combined therapy are recommended. Studies on promising antioxidants should be replicated, including those using Chinese and Ayurvedic formulas. Finally, they note that although there is scant evidence for benefits of some antioxidants studied, such as peppermint, there were also no AEs.

—*Mariann Garner-Wizard*

Referenced article can be accessed at <https://www.karger.com/Article/FullText/468988>.

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