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Black raspberries for prevention of aerodigestive tract cancers

Our laboratory has investigated the ability of different formulations of black raspberries (brb) to prevent the development of aerodigestive tract cancers. Preclinical studies have shown protective effects of dietary freeze-dried black raspberries against oral, esophageal and colon cancer in animals. Mechanistically, the berries inhibited tumor development in these sites by reducing abnormal cell proliferation, angiogenesis and inflammation, and by increasing apoptosis in carcinogen-treated premalignant tissues. Gene expression changes in these tissues correlated with the cellular events associated with tumor inhibition. Promising preclinical results have led to clinical evaluations in cancer patients or in patients at increased risk for cancer development. The initial clinical study in humans was a phase i trial in which freeze-dried brbs were administered to humans at a dose known to be chemopreventive in animal models. The berries were found to be well tolerated, however, the uptake of both brb anthocyanins and ellagic acid into blood was less than 1% of the administered dose. Thus, berries are most effective in tissues where localized absorption is possible. With this in mind, different formulations of brbs have been evaluated for their effects on preneoplastic lesions or cancers of the human oral cavity, esophagus and colon. These are follows: 1. Oral cavity: topical application of a brb gel to dysplastic lesions (oral leukoplakia) caused histologic regression associated with improved histologic grade and reduced loss of heterozygosity at tumor suppressor gene loci, as well as protective modulation of genes linked to RNA processing and growth factor recycling. 2. Esophagus: in patients with Barrett's esophagus, oral consumption of brbs increased tissue levels of GST-pi and decreased urinary 8-isoprostane, a marker of lipid peroxidation and oxidative stress. There was little effect on lesion size. 3. Colon: in colorectal cancer patients, brb consumption inhibited cancer cell proliferation and angiogenesis (new blood vessel formation) and caused demethylation of tumor suppressor genes associated with the Wnt signaling pathway. In patients with familial adenomatous polyposis, brb suppositories inhibited rectal polyp progression and improved plasma cytokine profiles. 4. Stomach: because we have found recently that an extract of brbs inhibits the growth of *Helicobacter pylori,* there is an ongoing trial to evaluate the effects of brbs on stomach cancer. Common themes across studies support that berries are anti-proliferative, anti-inflammatory, reduce oxidative stress and restore tumor suppressive activity.

Recent Publications

1. Stoner G D et al. (2005) Pharmacokinetics of anthocyanins and ellagic acid in healthy volunteers fed freeze-dried black raspberries daily for 7 days. J. Clin. Pharmacol. 45(10):1153-1164.
2. Wang L S et al. (2011) Modulation of genetic and epigenetic biomarkers of colorectal cancer in humans by black raspberries: a phase I pilot study. Clinical Cancer Res. 17(3):598-610.
3. Mallery S et al. (2014) Freeze-dried black raspberry gel induces clinical and histologic regression and reduces loss of heterozygosity events in premalignant oral intraepithelial lesions. Clin. Cancer Res. 20(7):1910-1924.
4. Wang L S et al. (2014) A Phase 1b study of the effects of black raspberries on rectal polyps in patients with familial adenomatous polyposis. Cancer Prev. Res. 7(7):666-674.
5. Kresty L A, Mallery S R and Stoner G D (2017) Black raspberries in cancer clinical trials: past, present and future. J. Berry Res. 6(2):251-261.

Biography

Gary D Stoner completed his PhD at the University of Michigan (USA) in 1970, conducted Post-doctoral studies at the University of California-San Diego and, in 1992, joined the Department of Preventive Medicine at Ohio State University as Lucius Wing Chair in Cancer Etiology and Prevention. He has chaired the NIH Chemo/Dietary Prevention and the ACS Nutrition and Environment Study Sections. He is Professor of Medicine at the Medical College of Wisconsin and is conducting additional clinical trials of berries for the prevention of esophagus and colon cancer. He has more than 300 peer-reviewed publications, 55 book chapters and has edited 4 books.

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