

JOURNAL
ABSTRACTS

Fucoxanthin

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Antioxidant activity of carotenoids is suggested to be one of the factors for their disease preventing effects. Marine carotenoids fucoxanthin and its two metabolites, fucoxanthinol and halocynthiaxanthin, have been shown to exhibit several biological effects. The antioxidant activities of these three carotenoids were assessed in vitro with respect to radical scavenging and singlet oxygen quenching abilities. The 1,1-diphenyl-2-picrylhydrazyl radical scavenging activity of fucoxanthin and fucoxanthinol was higher than that of halocynthiaxanthin, with the effective concentration for 50% scavenging (EC 50) being 164.60, 153.78, and 826.39 microM, respectively. 2,2'-Azinobis-3-ethylbenzo thizoline-6-sulphonate radical scavenging activity of fucoxanthinol (EC 50, 2.49 microM) was stronger than that of fucoxanthin (EC 50, 8.94 microM). Hydroxyl radical scavenging activity as measured by the chemiluminescence technique showed that the scavenging activity of fucoxanthin was 7.9 times higher than that by fucoxanthinol, 16.3 times higher than that by halocynthiaxanthin, and 13.5 times higher than that by alpha-tocopherol. A similar trend was observed when the hydroxyl radical scavenging was assessed by the electron spin resonance (ESR) technique. ESR analysis of the superoxide radical scavenging activity also showed the superiority of fucoxanthin over the other two carotenoids tested. Singlet oxygen quenching ability of the three carotenoids was lower than that of beta-carotene, with quenching rate constants (k_Q, x10¹⁰ M⁻¹ s⁻¹) being 1.19, 1.81, 0.80, and 12.78 for fucoxanthin, fucoxanthinol, halocynthiaxanthin, and beta-carotene, respectively. The higher radical scavenging activity of fucoxanthin and fucoxanthinol compared with halocynthiaxanthin is assumed to be due to presence of the allenic bond.

J Agric Food Chem. 2007 Oct 17;55(21):8516-22

FUCOXANTHIN, A NATURAL CAROTENOID, INDUCES G1 ARREST AND GADD45 GENE EXPRESSION IN HUMAN CANCER CELLS.

BACKGROUND: Although the antitumor effects of fucoxanthin are known, the precise mechanism of action has yet to be elucidated. **MATERIALS AND METHODS:** HepG2 and DU145 cells were used for these investigations. The effect of fucoxanthin on gene expression was assayed using a DNA microarray system. Northern blot and/or quantitative RT-PCR were carried out to confirm any changes in gene expression. The effect of fucoxanthin on cell cycle progression was analyzed using flow cytometry. RNA interference experiments were employed for the GADD45 gene. **RESULTS:** Fucoxanthin markedly induced GADD45A, a cell cycle-related gene, in HepG2 and DU145 cells. Concomitant G1 arrest, but not apoptosis, was observed in both cell types following treatment with fucoxanthin. The introduction of siRNA against GADD45A partially perturbed the induction of G1 arrest by fucoxanthin in both cell types. **CONCLUSION:** Fucoxanthin induced G1 arrest in HepG2 and DU145 cells. GADD45A may be involved in fucoxanthin-induced G1 arrest.

In Vivo. 2007 Mar-Apr;21(2):305-9

DIETARY COMBINATION OF FUCOXANTHIN AND FISH OIL ATTENUATES THE WEIGHT GAIN OF WHITE ADIPOSE TISSUE AND DECREASES BLOOD GLUCOSE IN OBESE/DIABETIC KK-A^y MICE.

Fucoxanthin is a marine carotenoid found in edible brown seaweeds. We previously reported that dietary fucoxanthin attenuates the weight gain of white adipose tissue (WAT) of diabetic/obese KK- A(y) mice. In this study, to evaluate the antiobesity and antidiabetic effects of fucoxanthin and fish oil, we investigated the effect on the WAT weight, blood glucose, and insulin levels of KK- A(y) mice. Furthermore, the expression level of uncoupling protein 1 (UCP1) and adipokine mRNA in WAT were measured. After 4 weeks of feeding, 0.2% fucoxanthin in the diet markedly attenuated the gain of WAT weight in KK- A(y) mice with increasing UCP1 expression compared with the control mice. The WAT weight of the mice fed 0.1% fucoxanthin and 6.9% fish oil was also significantly lower than that of the mice fed fucoxanthin alone. In addition, 0.2% fucoxanthin markedly decreased the blood glucose and plasma insulin concentrations in KK- A(y) mice. The mice fed with the combination diet of 0.1% fucoxanthin and fish oil also showed improvements similar to that of 0.2% fucoxanthin. Leptin and tumor necrosis factor (TNF α) mRNA expression in WAT were significantly down-regulated by 0.2% fucoxanthin. These results suggest that dietary fucoxanthin

decreases the blood glucose and plasma insulin concentration of KK- A(y) along with down-regulating TNF α mRNA. In addition, the combination of fucoxanthin and fish oil is more effective for attenuating the weight gain of WAT than feeding with fucoxanthin alone.

J Agric Food Chem. 2007 Sep 19;55(19):7701-6

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Biochim Biophys Acta. 2004 Nov 18;1675

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Cancer Lett. 2005 Mar 18;220(1):75-84

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Comp Biochem Physiol C Toxicol Pharmacol. 2006 Jan-Feb;142(1-2):53-9

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Comp Biochem Physiol C Toxicol Pharmacol. 2006 Jan-Feb;142(1-2):53-9

PROBIOTICS FOR PREVENTION OF RECURRENT VULVOVAGINAL CANDIDIASIS: A REVIEW.

Vulvovaginal candidiasis (VVC) is a common infection affecting the quality of life of many women. Probiotics have been investigated as possible agents for the prevention of recurrences of VVC. We reviewed the available literature. In some studies the development of VVC was associated with either a low number of lactobacilli in the vagina or with the presence of H₂O₂-non-producing vaginal lactobacilli, although there are a few studies not supporting these statements. In addition, *in vitro* studies have shown that lactobacilli can inhibit the growth of *Candida albicans* and/or its adherence on the vaginal epithelium. The results of some clinical trials support the effectiveness of lactobacilli, especially *Lactobacillus acidophilus*, *Lactobacillus rhamnosus* GR-1 and *Lactobacillus fermentum* RC-14, administered either orally or intravaginally in colonizing the vagina and/or preventing the colonization and infection of the vagina by *C. albicans*, while the results of a small number of clinical trials do not corroborate these findings. Nevertheless, most of the relevant clinical trials had methodological problems such as small sample size, no control group (placebo) and included women without confirmed recurrent VVC, and thus they are not reliable for drawing definitive conclusions. Thus, the available evidence for the use of probiotics for prevention of recurrent VVC is limited. However, the empirical use of probiotics may be considered in women with frequent recurrence of VVC (more than three episodes per year), especially for those who have adverse effects from or contraindications for the use of antifungal agents, since adverse effects of probiotics are very rare. In any case women should be clearly informed about the unproven usefulness of probiotics for this purpose. In conclusion, despite the promising results of some studies, further research is needed to prove the effectiveness of probiotics in preventing the recurrences of VVC and to allow their wide use for this indication.

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PROBIOTIC LACTOBACILLUS DOSE REQUIRED TO RESTORE AND MAINTAIN A NORMAL VAGINAL FLORA.

Forty-two healthy women were randomized to receive one of three encapsulated *Lactobacillus rhamnosus* GR-1 plus *Lactobacillus fermentum* RC-14 probiotic dosage regimens or *L. rhamnosus* GG by mouth each day for 28 days. However, the vaginal flora, assessed by Nugent scoring, was only normal in 40% of the cases, and 14 patients had asymptomatic bacterial vaginosis. Treatment with *L. rhamnosus* GR-1/*L. fermentum* RC-14 once and twice daily correlated with a healthy vaginal flora in up to 90% of patients, and 7/11 patients with bacterial vaginosis converted to normal or intermediate scores within 1 month. Ingestion of *L. rhamnosus* GG failed to have an effect. This study confirms the potential efficacy of orally administered lactobacilli as a non-chemotherapeutic means to restore and maintain a normal urogenital flora, and shows that over 10(8) viable organisms per day is the required dose.

FEMS Immunol Med Microbiol. 2001 Dec;32(1):37-41

PROBIOTICS AND PREBIOTICS: EFFECTS ON DIARRHEA.

Probiotics have preventive as well as curative effects on several types of diarrhea of different etiologies. Prevention and therapy (or alleviation) of diarrhea have been successfully investigated for numerous dietary probiotics to establish probiotic properties and to justify health claims (the medicinal use of probiotic food and the therapy of gastrointestinal diseases itself may not be advertised under current food laws). Other probiotic microorganisms (e.g., *Lactobacillus rhamnosus* GG, *L. reuteri*, certain strains of *L. casei*, *L. acidophilus*, *Escherichia coli* strain Nissle 1917, and certain bifidobacteria and enterococci (*Enterococcus faecium* SF68) as well as the probiotic yeast *Saccharomyces boulardii* have been investigated with regard to their medicinal use, either as single strains or in mixed-culture probiotics. However, the effects on humans have been assessed mainly in smaller ($n < 100$) randomized, controlled clinical studies or in open label trials, but large intervention studies and epidemiological investigations of long-term probiotic effects are largely missing. Perhaps with the exception of nosocomial diarrhea or antibiotic-associated diarrhea, the results of these studies are not yet sufficient to give specific recommendations for the clinical use of probiotics in the treatment of diarrhea.

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DIETARY MODIFICATION OF ATOPIC DISEASE: USE OF PROBIOTICS IN THE PREVENTION OF ATOPIC DERMATITIS.

The increased prevalence of atopic diseases, atopic dermatitis, allergic rhinitis, and asthma has been described as an epidemic. New approaches in the fight against allergic diseases are called for, the target being the persistence of the atopic T helper 2-skewed immune responder pattern beyond infancy. Atopic dermatitis, the earliest of these conditions, might act as a portal for the development of IgE-mediated atopic manifestations. Abundant evidence implies that specific strains selected from the healthy gut microbiota exhibit powerful antipathogenic and anti-inflammatory capabilities, and several targets for the probiotic approach have emerged in atopic dermatitis: degradation/structural modification of enteral antigens, normalization of the properties of aberrant indigenous microbiota and of gut barrier functions, regulation of the secretion of inflammatory mediators, and promotion of the development of the immune system. Better understanding of the effects of different probiotic strains and deeper insight into the mechanisms of the heterogeneous manifestations of atopic disease are needed for the validation of specific strains carrying anti-allergic potential.

Curr Allergy Asthma Rep. 2004 Jul;4(4):270-5

AUGMENTATION OF ANTIMICROBIAL METRONIDAZOLE THERAPY OF BACTERIAL VAGINOSIS WITH ORAL PROBIOTIC LACTOBACILLUS RHAMNOSUS GR-1 AND LACTOBACILLUS REUTERI RC-14: RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL.

This study enrolled 125 premenopausal women diagnosed with bacterial vaginosis (BV) by presence of vaginal irritation, discharge and 'fishy' odor, and Nugent criteria and detection of sialidase enzyme. The subjects were treated with oral metronidazole (500 mg) twice daily from days 1 to 7, and randomized to receive oral Lactobacillus rhamnosus GR-1 (1 x 10⁹) and Lactobacillus reuteri RC-14 (1 x 10⁹) or placebo twice daily from days 1 to 30. Primary outcome was cure of BV as determined by normal Nugent score, negative sialidase test and no symptoms or signs of BV at day 30. A total of 106 subjects returned for 30-day follow-up, of which 88% were cured in the antibiotic/probiotic group compared to 40% in the antibiotic/placebo group (p<0.001). Of the remaining subjects, 30% subjects in the placebo group and none in the probiotic group had BV, while 30% in the placebo and 12% in the probiotic group fell into the intermediate category based upon Nugent score, sialidase result and clinical findings. High counts of Lactobacillus sp. (>10⁵ CFU/ml) were recovered from the vagina of 96% probiotic-treated subjects compared to 53% controls at day 30. In summary, this study showed efficacious use of lactobacilli and antibiotic in the eradication of BV in black African women.

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COMPREHENSIVE REVIEW OF CONVENTIONAL AND NON-CONVENTIONAL METHODS OF MANAGEMENT OF RECURRENT VULVOVAGINAL CANDIDIASIS.

Recurrent vulvovaginal candidiasis (VVC) is a condition what causes women a great deal of discomfort, inconvenience, and sometimes has psychological sequelae.(1) This condition is notoriously difficult to manage. Conventional management is generally favoured by medical practitioners. Some practitioners prefer not to offer other options because of significant possible side-effects and the lack of research supporting alternative treatments. There are many studies and much available information surrounding uncomplicated VVC, including two systematic reviews.(2,3) In the area of recurrent VVC however, quality conclusive studies are scarce, and recurrent VVC is featured infrequently in randomised controlled trials (RCTs). Systematic reviews that strongly support a particular pharmacological method of conventional management of recurrent VVC over another are absent from medical literature. Recommendations are largely formed on the basis of scanty RCTs and expert opinion. There is even less conclusive evidence in the area of alternative therapies; yet despite this, anecdotally many practitioners (both alternative and mainstream) continue to advocate certain treatments in the absence of any reliable cure that can be confidently prescribed. As the use of methods other than mainstream medicine becomes more widespread, it is important to be aware of both conventional and non-conventional management of recurrent vulvovaginal candidiasis. Practitioners need to ascertain their patient's preference and treatment history. It is difficult to find comprehensive literature assessing both approaches. Giving women the most up-to-date and relevant information, and different management options, is essential in allowing them to make informed decisions. This review critically assesses both mainstream and less conventional approaches in the management of recurrent VVC.

Aust N Z J Obstet Gynaecol. 2007 Aug;47(4):262-72

NUCLEIC ACID-BASED DIAGNOSIS OF BACTERIAL VAGINOSIS AND IMPROVED MANAGEMENT USING PROBIOTIC LACTOBACILLI.

Bacterial vaginosis (BV) is a common condition in women that represents an imbalance of the vaginal microflora, lactobacilli depletion, and excess growth of mainly anaerobic Gram-negative pathogens. Diagnosis is made using a series of tests or a Gram stain of a vaginal smear. Treatment with antibiotics is quite effective, but recurrences are common. A study of 55 vaginal samples from 11 postmenopausal women showed the presence of BV by the Gram stain-based Nugent scoring system, and polymerase chain reaction-denaturing gradient gel electrophoresis showed that Bacteroides or Prevotella species were the most common isolates recovered (24 of 25), with Escherichia coli, Staphylococcus aureus, and Streptococcus agalactiae also found in some samples. In one case, only Gardnerella vaginalis was found. These findings illustrate that BV remains common even

among otherwise healthy women, but it is not caused solely by either *Gardnerella* or *Mobiluncus*. Use of a FemExam system (Cooper Surgical, Shelton, CT), based upon elevated pH and trimethylamine levels, to screen vaginal smears from 59 healthy women showed poor correlation with the Gram stain method. A randomized, placebo-controlled trial of these subjects showed that the lactobacilli-dominant microbiota was restored in subjects with BV but not in controls, following 2 months of daily oral intake of *Lactobacillus rhamnosus* GR-1 and *Lactobacillus fermentum* RC-14. These studies show that nucleic acid-based methods are effective at identifying bacteria responsible for BV. If such methods could be used to develop a commercially available, self-use kit, women would be much better placed to take control of their own health, for example, using medicinal food or dietary supplement products such as the clinically proven probiotic strains *L. rhamnosus* GR-1 and *L. fermentum* RC-14.

J Med Food. 2004 Summer;7(2):223-8

TREATMENT OF BACTERIAL VAGINOSIS: A COMPARISON OF ORAL METRONIDAZOLE, METRONIDAZOLE VAGINAL GEL, AND CLINDAMYCIN VAGINAL CREAM.

BACKGROUND. Treatment options for bacterial vaginosis are numerous. The purpose of this study was to compare the efficacy of oral metronidazole, metronidazole vaginal gel, and clindamycin vaginal cream for the treatment of bacterial vaginosis using traditional clinical and laboratory methods, as well as a new DNA probe test. We also determined the percentage of patients receiving each treatment who developed posttreatment vaginal candidiasis, a potential complication of treating bacterial vaginosis. **METHODS.** One hundred one women in whom bacterial vaginosis was diagnosed by standard criteria were randomly assigned to receive: oral metronidazole 500 mg twice daily for 1 week, 0.75% metronidazole vaginal gel 5 g twice daily for 5 days, or 2% clindamycin vaginal cream 5 g once daily for 7 days. Women with coexisting vulvovaginal candidiasis or vaginal trichomoniasis were excluded. Tests of cure by vaginal saline wet prep and potassium hydroxide microscopic examinations, Gram's stain, pH and DNA probe tests for *Gardnerella vaginalis* and *Candida* species were scheduled 7 to 14 days following treatment. **RESULTS.** There were no statistically significant differences in cure rates for oral metronidazole (84.2%), metronidazole vaginal gel (75.0%), or clindamycin vaginal cream (86.2%) ($\chi^2 = 1.204$, $df = 2$, $P = .548$) using traditional clinical and laboratory criteria. Cure rates were lower based on DNA testing, indicating that *Gardnerella vaginalis* may remain after a clinical cure. This would explain cases of recurrent disease. Posttreatment vulvovaginal candidiasis was experienced by 12.5% of subjects treated with oral metronidazole, 14.8% of subjects treated with clindamycin vaginal cream, and 30.4% of subjects treated with metronidazole vaginal gel ($\chi^2 = 2.607$, $df = 2$, $P = .272$). **CONCLUSIONS.** Oral metronidazole, metronidazole vaginal gel, and clindamycin vaginal cream achieved nearly equivalent cure rates for the treatment of bacterial vaginosis. Patients treated with these agents experienced similar rates of posttreatment vulvovaginal candidiasis, but those using the intravaginal products reported being more satisfied with the treatment.

J Fam Pract. 1995 Nov;41(5):443-9

ITRACONAZOLE VS FLUCONAZOLE FOR THE TREATMENT OF UNCOMPLICATED ACUTE VAGINAL AND VULVOVAGINAL CANDIDIASIS IN NONPREGNANT WOMEN: A METAANALYSIS OF RANDOMIZED CONTROLLED TRIALS.

In this metaanalysis of randomized controlled trials (RCTs) we aimed to compare the in vivo and in vitro activity and the safety of per os itraconazole and fluconazole treatment of uncomplicated acute vaginal/vulvovaginal candidiasis in nonpregnant women. We used PubMed, Scopus, Web of Science, and Cochrane Library to identify the studies that were relevant to our metaanalysis RCTs. Six RCTs were included in this study that comprised 1092 enrolled patients with signs and symptoms of vaginal/vulvovaginal candidiasis that was confirmed by microscopy and/or microbiologic cultures that were obtained from the ectocervix and/or vaginal fundus. Overall, there was no difference between itraconazole and fluconazole regarding clinical cure and improvement at the first and second scheduled visit assessments (pooled odds ratio [OR], 0.94 [95% CI, 0.6-1.48] and 1.09 [95% CI, 0.68-1.75], respectively), mycologic cure at the first and second scheduled visit assessments (OR, 0.73 [95% CI, 0.31-1.7] and 0.71 [95% CI, 0.49-1.03], respectively), withdrawal of patients because of severe adverse events (OR, 0.72 [95% CI, 0.16-3.32]), and adverse events noted from the nervous and digestive systems (OR, 1.07 [95% CI, 0.42-2.73] and 1.84 [95% CI, 0.3-11.27], respectively). In conclusion, effectiveness and safety of oral itraconazole and fluconazole in the treatment of acute uncomplicated vaginal/vulvovaginal candidiasis are similar.

Am J Obstet Gynecol. 2007 Dec 7

A DELICATE BALANCE: RISK FACTORS FOR ACQUISITION OF BACTERIAL VAGINOSIS INCLUDE SEXUAL ACTIVITY, ABSENCE OF HYDROGEN PEROXIDE-PRODUCING LACTOBACILLI, BLACK RACE, AND POSITIVE HERPES SIMPLEX VIRUS TYPE 2 SEROLOGY.

BACKGROUND: The etiology of bacterial vaginosis (BV) is poorly understood, but better definition of the risk factors associated with its acquisition should improve our understanding of this complex disease entity. **METHODS:** A longitudinal cohort study of young sexually active women was conducted to identify variables associated with BV acquisition. Seven hundred seventy-three women without BV at enrollment were followed at 4-month intervals for 1 year. At each visit, demographic and behavioral interview

data, a vaginal smear for the Gram stain diagnosis of BV, and a serum sample for detection of herpes simplex virus type 1 (HSV-1) and HSV-2 type-specific antibodies were collected. RESULTS: The overall incidence of BV acquisition was 36 cases/100 woman-years

(223 acquisitions of BV during 619 woman-years of follow-up). Acquisition of BV was independently associated with black race, cigarette smoking, vaginal intercourse, receptive anal sex before vaginal intercourse, sex with an uncircumcised male partner, lack of vaginal H₂O₂-producing lactobacilli, and the detection of HSV-2 serum antibodies at the visit before BV acquisition. Longitudinal analyses revealed that HSV-2 serum antibodies were independently associated with loss of H₂O₂-producing lactobacilli. CONCLUSIONS: Our findings suggest that multiple and diverse risk factors can contribute to BV acquisition. They also illustrate why a more complete understanding of BV pathogenesis and the formulation of effective BV prevention strategies have been elusive. Further work will be needed to determine the specific effects of HSV-2 infection on vaginal flora composition and the acquisition of BV.

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