



Probiotic Agents and Infectious Diseases: A Modern Perspective on a Traditional Therapy

Alvarez-Olmos MI, Oberhelman RA

***Clin Infect Dis.* 2001 Jun 1;32(11):1567-76**

There is an increasing scientific and commercial interest in the use of beneficial microorganisms, or "probiotics," for the prevention and treatment of disease. The microorganisms most frequently used as probiotic agents are lactic-acid bacteria such as *Lactobacillus rhamnosus* GG (LGG), which has been extensively studied in recent literature. Multiple mechanisms of action have been postulated, including lactose digestion, production of antimicrobial agents, competition for space or nutrients, and immunomodulation. We have reviewed recent studies of probiotics for the treatment and control of infectious diseases. Studies of pediatric diarrhea show substantial evidence of clinical benefits from probiotic therapy in patients with viral gastroenteritis, and data on LGG treatment for *Clostridium difficile* diarrhea appear promising. However, data to support use of probiotics for prevention of traveler's diarrhea are more limited. New research suggests potential applications in vaccine development and prevention of sexually transmitted diseases. Further studies are needed to take full advantage of this traditional medical approach and to apply it to the infectious diseases of the new millennium.

Suppressive Effect of *Lactobacillus gasseri* OLL 2716 (LG21) on *Helicobacter pylori* Infection in Humans

Sakamoto I, Igarashi M, Kimura K, Takagi A, Miwa T, Koga Y

***J Antimicrob Chemother.* 2001 May;47(5):709-10**

To examine the efficacy of *Lactobacillus gasseri* OLL2716 (LG21) as a probiotic for *Helicobacter pylori* in humans, 31 subjects infected with the bacterium ingested yogurt containing LG21 daily for an 8 week period. The [(13)C]urea breath test and assays of serum pepsinogens revealed a significant improvement following LG21 treatment. LG21 was thus determined to be effective in both suppressing *H. pylori* and reducing gastric mucosal inflammation.

Systemic Immunity-Enhancing Effects in Healthy Subjects Following Dietary Consumption of the Lactic Acid Bacterium *Lactobacillus rhamnosus* HN001

Sheih YH, Chiang BL, Wang LH, Liao CK, Gill HS

***J Am Coll Nutr.* 2001 Apr;20(2 Suppl):149-56**

Objective: To determine the effects of the probiotic lactic acid bacterium, *Lactobacillus rhamnosus* HN001, on natural cellular immunity when delivered orally in normal low-fat milk (LFM) or lactose-hydrolyzed low-fat milk (LFM-LH).

Design: A three stage, pre-post intervention trial, spanning nine weeks.

Setting: Taipei Medical College Hospital, Taipei, Taiwan.

Subjects: Fifty-two healthy middle-aged and elderly volunteers (17 males, 35 females; median age 63.5, range 44-80).

Interventions: Stage 1 (run-in diet): 25 g/200 mL reconstituted LFM powder, twice daily for 3 weeks. Stage 2 (probiotic intervention): LFM or LFM-LH, supplemented with 10(9) CFUs/g *L. rhamnosus* HN001 in each case, for 3 weeks. Stage 3 (wash-out): LFM for 3 weeks.

Measures Of Outcome: In vitro phagocytic capacity of peripheral blood polymorphonuclear (PMN) leukocytes; in vitro tumoricidal activity of natural killer (NK) leukocytes.

Results: Immunological responses were unaffected by the run-in diet of LFM alone. In contrast, the relative proportion of PMN cells showing phagocytic activity increased by 19% and 15%, respectively, following consumption of HN001 in either LFM or LFM-LH; the relative level of NK cell tumor killing activity increased by 71% and 147%. In most cases these levels declined following cessation, but remained above baseline.

Conclusions: Dietary consumption of *L. rhamnosus* HN001, in a base of low-fat milk or lactose-hydrolyzed low-fat milk, appears to enhance systemic cellular immune responses and may be useful as a dietary supplement to boost natural immunity.

Microecology, Bacterial Vaginosis and Probiotics: Perspectives for Bacteriotherapy

Famularo G, Pieluigi M, Coccia R, Mastroiacovo P, Simone CD

***Med Hypotheses*. 2001 Apr;56(4):421-30**

Probiotics enriched in lactobacilli have been proposed as an effective and alternative tool to antibiotics for the treatment of bacterial vaginosis. The protective role of H₂O₂-producing lactobacilli has been strongly emphasized, but no clear-cut correlation appears to link the metabolic characteristics of administered lactobacilli with the clinical impact of probiotic therapy. On account of our review of basic mechanisms involved in bacterial vaginosis, we suggest that lactobacilli with an elevated arginine deiminase activity could have a greater therapeutic potential than strains producing only H₂O₂. Preliminary results from our laboratory have demonstrated that treatment with probiotics containing arginine deiminase-positive lactobacilli improves clinical symptoms and is paralleled by a significant decline of polyamine levels in vaginal microenvironment. This is of outstanding interest due to the central role of polyamines in the pathogenesis of bacterial vaginosis. We should critically rethink, against this perspective, the use of probiotics for the treatment of affected women. Copyright 2001 Harcourt Publishers Ltd.

Screening of Intestinal Microflora for Effective Probiotic Bacteria

O'Sullivan DJ

***J Agric Food Chem*. 2001 Apr;49(4):1751-60**

Increasing consumer awareness of health-promoting intestinal bacteria has fueled the addition of viable probiotic bacteria as functional ingredients in certain foods. However, to effectively market the enhanced attributes of these foods, the added probiotic bacteria need to have scientific credibility. The scientific rationale for using many of the strains of probiotic bacteria currently on the market is weak. Furthering the current understanding of what features a bacterium needs to have for effective probiotic functionality will enable the selection of strains with a more credible scientific rationale. To screen for effective strains, one must understand the microbial diversity in the intestines of healthy individuals. The advent of molecular tools has greatly enhanced our ability to accomplish this. These tools comprise genetic fingerprinting, specific probes, molecular speciation, and techniques for the in situ analysis of specific microbial groups in the intestine. This review will detail these scientific approaches and how their impact will improve criteria for selection of probiotic bacteria.

Probiotics in Primary Prevention of Atopic Disease: A Randomised Placebo-Controlled Trial

Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E

***Lancet*. 2001 Apr 7;357(9262):1076-9**

Comment in:

***Lancet*. 2001 Apr 7;357(9262):1057-9**

Background: Reversal of the progressive increase in frequency of atopic disease would be an important breakthrough for health care and wellbeing in western societies. In the hygiene hypothesis this increase is attributed to reduced microbial exposure in early life. Probiotics are cultures of potentially beneficial bacteria of the healthy gut microflora. We assessed the effect on atopic disease of *Lactobacillus* GG (which is safe at an early age and effective in treatment of allergic inflammation and food allergy).

Methods: In a double-blind, randomised placebo-controlled trial we gave *Lactobacillus* GG prenatally to mothers who had at least one first-degree relative (or partner) with atopic eczema, allergic rhinitis, or asthma, and postnatally for 6 months to their infants. Chronic recurring atopic eczema, which is the main sign of atopic disease in the first years of life, was the primary endpoint. **FINDINGS:** Atopic eczema was diagnosed in 46 of 132 (35%) children aged 2 years. Asthma was diagnosed in six of these children and allergic rhinitis in one. The frequency of atopic eczema in the probiotic group was half that of the placebo group (15/64 [23%] vs 31/68 [46%]; relative risk 0.51 [95% CI 0.32-0.84]). The number needed to treat was 4.5 (95% CI 2.6-15.6).

Interpretations: *Lactobacillus* GG was effective in prevention of early atopic disease in children

at high risk. Thus, gut microflora might be a hitherto unexplored source of natural immunomodulators and probiotics, for prevention of atopic disease.

Probiotic Activities of *Lactobacillus casei* Rhamnosus: In Vitro Adherence to Intestinal Cells and Antimicrobial Properties

Forestier C, De Champs C, Vatoux C, Joly B

***Res Microbiol.* 2001 Mar;152(2):167-73**

The interest of probiotics as remedies for a broad number of gastrointestinal and other infectious diseases has gained wide interest over the last few years, but little is known about their underlying mechanism of action. In this study, the probiotic activities of a human isolate of *Lactobacillus casei* subsp. *rhamnosus* strain (Lcr35) were investigated. Using intestinal Caco-2 cell line in an in vitro model, we demonstrated that this strain exhibited adhesive properties. The inhibitory effects of Lcr35 organisms on the adherence of three pathogens, enteropathogenic *Escherichia coli* (EPEC), enterotoxigenic *E. coli* (ETEC) and *Klebsiella pneumoniae*, were determined. A decrease in the number of adhering pathogens was observed, using either preincubation, postincubation or coincubation of the pathogens with Lcr35. Moreover, the antibacterial activities of cell-free Lcr35 supernatant was examined against nine human pathogenic bacteria, ETEC, EPEC, *K. pneumoniae*, *Shigella flexneri*, *Salmonella typhimurium*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis* and *Clostridium difficile*. The growth of all strains was inhibited, as measured by determining the number of viable bacteria over time, but no bactericidal activity was detected in this in vitro assay. Together, these findings suggest that this probiotic strain could be used to prevent colonization of the gastrointestinal tract by a large variety of pathogens.

Efficacy of *Lactobacillus* GG in Prevention of Nosocomial Diarrhea in Infants

Szajewska H, Kotowska M, Mrukowicz JZ, Armanska M, Mikolajczyk W

***J Pediatr.* 2001 Mar;138(3):361-5**

Objective: Nosocomial diarrhea is a major problem in pediatric hospitals worldwide. We evaluated the efficacy of orally administered *Lactobacillus* GG (LGG) in the prevention of this disease in young children. **STUDY**

Design: Eighty-one children aged 1 to 36 months who were hospitalized for reasons other than diarrhea were enrolled in a double-blind trial and randomly assigned at admission to receive LGG (n = 45) at a dose of 6 x 10⁹ colony-forming units or a comparable placebo (n = 36) twice daily orally for the duration of their hospital stay.

Results: LGG reduced the risk of nosocomial diarrhea (> or =3 loose or watery stools/24 h) in comparison with placebo (6.7% vs 33.3%; relative risk: 0.2; [95% CI: 0.06-0.6]; number needed to treat: 4 [95% CI: 2-10]). The prevalence of rotavirus infection was similar in LGG and placebo groups (20% vs 27.8%, respectively; relative risk: 0.72; 95% CI: 0.33-1.56). However, the use of LGG compared with placebo significantly reduced the risk of rotavirus gastroenteritis (1/45 [2.2%] vs 6/36 [16.7%], respectively; relative risk: 0.13; 95% CI: 0.02-0.79; number needed to treat: 7; 95% CI: 3-40).

Conclusions: Prophylactic use of LGG significantly reduced the risk of nosocomial diarrhea in infants, particularly nosocomial rotavirus gastroenteritis.

Adherence of Probiotic Bacteria to Human Intestinal Mucus in Healthy Infants and During Rotavirus Infection

Juntunen M, Kirjavainen PV, Ouweland AC, Salminen SJ, Isolauri E

***Clin Diagn Lab Immunol.* 2001 Mar;8(2):293-6**

The concentration of fecal mucin and the adhesion of specific probiotics and their combinations in the intestinal mucus of infants during and after rotavirus diarrhea and in healthy children were determined. Mucus was prepared from fecal samples from 20 infants during and after rotavirus diarrhea and from 10 healthy age-matched children. Mucin concentration was determined, and the adhesion of five probiotics-*Lactobacillus rhamnosus* GG, *Lactobacillus casei* Shirota, *Lactobacillus paracasei* F19, *Lactobacillus acidophilus* LA5, and *Bifidobacterium lactis* Bb12-and their combinations was tested in vitro. The mean concentrations of fecal mucin during and after rotavirus diarrhea, 15.2 and 14.1 mg/g, were comparable to that in healthy children, 14.9 mg/g. The adherence of probiotics ranged from 1 to 34% in healthy subjects as indicated for the

following strains: *L. rhamnosus* GG, 34%; *B. lactis* Bb12, 31%; *L. acidophilus* LA5, 4%; *L. paracasei* F19, 3%; and *L. casei* Shirota, 1% ($P = 0.0001$). The distinctive pattern of probiotic adherence was not influenced by rotavirus diarrhea. The adhesion of Bb12 in the presence of GG increased from 31 to 39% in healthy infants ($P = 0.018$) and in episodes of diarrhea increased from 26 to 44% ($P = 0.001$). Rotavirus diarrhea does not decrease the production of fecal mucin or with respect to the adhesion of probiotic bacteria tested in vitro. Combination of specific probiotic strains may enhance adherence in a synergistic manner. Optimal clinical application of these interactions may offer novel therapeutic guidelines for the treatment and prevention of gastrointestinal infections.

Oral Probiotics Can Resolve Urogenital Infections

Reid G, Bruce AW, Fraser N, Heinemann C, Owen J, Henning B
***FEMS Immunol Med Microbiol.* 2001 Feb;30(1):49-52**

We report the first clinical evidence that probiotic lactobacilli can be delivered to the vagina following oral intake. In 10 women with a history of recurrent yeast vaginitis, bacterial vaginosis (BV) and urinary tract infections, strains *Lactobacillus rhamnosus* GR-1 and *Lactobacillus fermentum* RC-14 suspended in skim milk and given twice daily for 14 days, were recovered from the vagina and identified by morphology and molecular typing within 1 week of commencement of therapy. In six cases of asymptomatic BV or intermediate BV (based upon Nugent scoring) was resolved within 1 week of therapy.

Probiotic Agents to Protect the Urogenital Tract Against Infection

Reid G

***Am J Clin Nutr.* 2001 Feb;73(2 Suppl):437S-443S**

The urogenital microflora of a healthy woman comprises approximately 50 species of organisms, which differ in composition according to reproductive stages and exposure to several factors, including antibiotics and spermicides. Infections are very common with > 300 million cases of urinary tract infections, bacterial vaginosis, and yeast vaginitis worldwide per annum. At the time of infection in the bladder and vagina, the urogenital flora is often dominated by the infecting pathogens, in contrast with healthy phases when indigenous organisms dominate. Premenopausal women have a flora of mostly lactobacilli, and certain properties of these strains, including adhesive ability and production of acids, bacteriocins, hydrogen peroxide, and biosurfactants, appear important in conferring protection to the host. Efforts to artificially restore an unbalanced flora with the use of probiotics have met with mixed results but research aimed at selecting scientifically based strains could well provide a reliable alternative treatment and preventive regimen to antibiotics in the future.

Prophylactic and Therapeutic Uses of Probiotics: A Review

Kopp-Hoolihan L

***J Am Diet Assoc.* 2001 Feb;101(2):229-38; quiz 239-41**

Probiotics, live microbial food supplements that beneficially affect the host by improving its intestinal microbial balance, are quickly gaining interest as functional foods in the current era of self-care and complementary medicine. Microbes have been used for years in food and alcoholic fermentations and relatively recently have undergone scientific scrutiny to examine their purported health benefits. Some of the claims for which research supports a beneficial effect of probiotic consumption include: improving intestinal tract health, enhancing the immune system, synthesizing and enhancing the bioavailability of nutrients, reducing symptoms of lactose intolerance, decreasing the prevalence of allergy in susceptible individuals, and reducing risk of certain cancers. The mechanisms by which probiotics exert their effects are largely unknown, but may involve modifying gut pH, antagonizing pathogens through production of antimicrobial and antibacterial compounds, competing for pathogen binding and receptor sites as well as for available nutrients and growth factors, stimulating immunomodulatory cells, and producing lactase. Selection criteria, efficacy, food and supplement sources and safety issues around probiotics are reviewed. Nutrition professionals can provide a tremendous service by helping clients overcome negative perceptions of all bacteria and, when appropriate, by developing individualized dietary plans to take advantage of the benefits probiotics may confer.

Probiotics and Safety

Ishibashi N, Yamazaki S

***Am J Clin Nutr.* 2001 Feb;73(2 Suppl):465S-470S**

Bacterial species that have traditionally been regarded as safe are used in probiotics; the main strains used include lactic acid bacteria and bifidobacteria that inhabit the intestinal tracts of humans and animals. However, reports of frequent isolation of bacteria used in probiotics from infection sources in recent years have raised much debate over the safety of probiotics. This article describes the status quo of isolation of probiotic bacteria from infections and reviews each of the factors that have to be addressed in assessing the safety of probiotics, namely pathogenicity, infectivity, toxicity, and intrinsic properties of the bacteria. Monoassociation with *Bifidobacterium longum* in gnotobiotic mice as a method to assess safety with respect to infection, and translocation and immune responses as a result of the monoassociation are also described.

Protection From Gastrointestinal Diseases With the Use of Probiotics

Marteau PR, de Vrese M, Cellier CJ, Schrezenmeir J

***Am J Clin Nutr.* 2001 Feb;73(2 Suppl):430S-436S**

Probiotics are nonpathogenic microorganisms that, when ingested, exert a positive influence on the health or physiology of the host. They can influence intestinal physiology either directly or indirectly through modulation of the endogenous ecosystem or immune system. The results that have been shown with a sufficient level of proof to enable probiotics to be used as treatments for gastrointestinal disturbances are 1) the good tolerance of yogurt compared with milk in subjects with primary or secondary lactose maldigestion, 2) the use of *Saccharomyces boulardii* and *Enterococcus faecium* SF 68 to prevent or shorten the duration of antibiotic-associated diarrhea, 3) the use of *S. boulardii* to prevent further recurrence of *Clostridium difficile*-associated diarrhea, and 4) the use of fermented milks containing *Lactobacillus rhamnosus* GG to shorten the duration of diarrhea in infants with rotavirus enteritis (and probably also in gastroenteritis of other causes). Effects that are otherwise suggested for diverse probiotics include alleviation of diarrhea of miscellaneous causes; prophylaxis of gastrointestinal infections, which includes traveler's diarrhea; and immunomodulation. Trials of gastrointestinal diseases that involve the ecosystem are currently being performed, eg, *Helicobacter pylori* infections, inflammatory bowel disease, and colon cancer.

Protective Role of Probiotics and Prebiotics in Colon Cancer

Wollowski I, Rechkemmer G, Pool-Zobel BL

***Am J Clin Nutr.* 2001 Feb;73(2 Suppl):451S-455S**

Ingestion of viable probiotics or prebiotics is associated with anticarcinogenic effects, one mechanism of which is the detoxification of genotoxins in the gut. This mechanism was shown experimentally in animals with use of the rat colon carcinogen 1,2-dimethylhydrazine and by determining endpoints that range from tumorigenesis to induction of DNA damage. Because of the complexity of cancer initiation, cancer progression, and the exposure of cancer in the gut, many types of interactions may be envisaged. Notably, some of our newer studies showed that short-lived metabolite mixtures isolated from milk that was fermented with strains of *Lactobacillus bulgaricus* and *Streptococcus thermophilus* are more effective in deactivating etiologic risk factors of colon carcinogenesis than are cellular components of microorganisms. Ingestion of prebiotics results in a different spectrum of fermentation products, including the production of high concentrations of short-chain fatty acids. Gut flora, especially after the ingestion of resistant starch, induces the chemopreventive enzyme glutathione transferase pi in the colon of the rat. Together, these factors lead to a reduced load of genotoxic agents in the gut and to an increased production of agents that deactivate toxic components. Butyrate is one such protective agent and is associated with lowering cancer risk. It was recently shown that butyrate may inhibit the genotoxic activity of nitrosamides and hydrogen peroxide in human colon cells. In humans, the ingestion of probiotics leads to the excretion of urine with low concentrations of components that are genotoxic in human colon cells and high concentrations of components that induce oxidized DNA bases.

Probiotics--Compensation for Lactase Insufficiency

de Vrese M, Stegelmann A, Richter B, Fenselau S, Laue C, Schrezenmeir J
***Am J Clin Nutr.* 2001 Feb;73(2 Suppl):421S-429S**

Yogurt and other conventional starter cultures and probiotic bacteria in fermented and unfermented milk products improve lactose digestion and eliminate symptoms of intolerance in lactose maldigesters. These beneficial effects are due to microbial beta-galactosidase in the (fermented) milk product, delayed gastrointestinal transit, positive effects on intestinal functions and colonic microflora, and reduced sensitivity to symptoms. Intact bacterial cell walls, which act as a mechanical protection of lactase during gastric transit, and the release of the enzyme into the small intestine are determinants of efficiency. There is a poor correlation between lactose maldigestion and intolerance; in some studies, low hydrogen exhalation without significant improvement of clinical symptoms was observed. Probiotic bacteria, which by definition target the colon, normally promote lactose digestion in the small intestine less efficiently than do yogurt cultures. They may, however, alleviate clinical symptoms brought about by undigested lactose or other reasons.

Quality Assurance Criteria for Probiotic Bacteria

Tuomola E, Crittenden R, Playne M, Isolauri E, Salminen S
***Am J Clin Nutr.* 2001 Feb;73(2 Suppl):393S-398S**

Acid and bile stability and intestinal mucosal adhesion properties are among the criteria used to select probiotic microbes. The quality control of probiotic cultures in foods traditionally has relied solely on tests to ensure that an adequate number of viable bacteria are present in the products throughout their shelf lives. Viability is an important factor, but not the only criterion for quality assurance. To be effective, probiotic strains must retain the functional health characteristics for which they were originally selected. Such characteristics include the ability to survive transit through the stomach and small intestine and to colonize the human gastrointestinal tract. In vitro test protocols can be readily adopted to examine the maintenance of a strain's ability to tolerate acidic conditions, survive and grow in the presence of bile, and metabolize selective substrates. Molecular techniques are also available to examine strain stability. Adhesion characterization may be an important quality-control method for assessing gut barrier effects. Adhesion has been related to shortening the duration of diarrhea, immunogenic effects, competitive exclusion, and other health effects. Adhesion properties should be carefully monitored, including adhesion to intestinal cells (eg, Caco-2) and human intestinal mucus. This article outlines the types of in vitro testing that can be used to ensure quality control of functional probiotic strains.

Probiotics in Foods Not Containing Milk or Milk Constituents, With Special Reference to *Lactobacillus plantarum* 299v

Molin G.

***Am J Clin Nutr.* 2001 Feb;73(2 Suppl):380S-385S**

Lactic acid fermentation is the simplest and safest way of preserving food and has probably always been used by humans. Species such as *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Lactobacillus paracasei*, *Lactobacillus acidophilus*, and *Lactobacillus salivarius* are common in the human mucosa, from the mouth to the rectum. In food, *L. paracasei* and *L. rhamnosus* are usually associated with dairy products whereas *L. plantarum* is found in fermented foods of plant origin. A probiotic food product containing no milk constituent was launched in Sweden in 1994. The product is a lactic acid fermented oatmeal gruel that is mixed in a fruit drink. It contains approximately 5×10^{10} colony-forming units of *L. plantarum* 299v/L. The strain *L. plantarum* 299v originates from the human intestinal mucosa and has been shown in rats to decrease translocation, improve mucosal status, improve liver status, improve the immunologic status of the mucosa, and reduce mucosal inflammation. In humans, *L. plantarum* 299v can increase the concentration of carboxylic acids in feces and decrease abdominal bloating in patients with irritable bowel disease. It can also decrease fibrinogen concentrations in blood. Should probiotics be administered through foods, the probiotic organism must remain vigorous in the food until consumption and the food must remain palatable, ie, the food carrier and the organism must suit each other. *L. plantarum* 299v not only affects the bacterial flora of the intestinal mucosa but may also regulate the host's immunologic defense. The mechanisms involved need to be clarified.

Effect of Lactobacillus GG Supplementation on Antibiotic-Associated Gastrointestinal Side Effects During Helicobacter pylori Eradication Therapy: A Pilot Study

Armuzzi A, Cremonini F, Ojetto V, et al

***Digestion.* 2001;63(1):1-7**

Background: One-week triple therapy is currently regarded as the reference of anti-Helicobacter pylori treatment. However, antibiotic-associated gastrointestinal side effects are among the major pitfalls of such regimens. Probiotic supplementation may be regarded as a therapeutic tool to prevent or reduce these troublesome drug-related manifestations. **AIM:** To determine whether the addition of the probiotic Lactobacillus GG to an anti-H. pylori standard triple therapy could help to prevent or minimize the occurrence of gastrointestinal side effects.

Methods: One hundred and twenty healthy asymptomatic subjects screened positive for H. pylori infection and deciding to receive eradication therapy were randomized either to 1-week pantoprazole (40 mg b.i.d.), clarithromycin (500 mg b.i.d.), tinidazole (500 mg b.i.d.) or to the same regimen supplemented with Lactobacillus GG for 14 days. Patients filled in validated questionnaires during follow-up to determine the type and severity of side effects and to judge overall tolerability.

Results: Bloating, diarrhea and taste disturbances were the most frequent side effects during the eradication week and were significantly reduced in the Lactobacillus GG-supplemented group (RR = 0.4, CI 0.2-0.8; RR = 0.3, CI 0.1-0.8; RR = 0.3, CI 0.1-0.7, respectively). The same pattern was observed throughout the follow-up period. Overall assessment of treatment tolerability showed a significant trend in favor of the Lactobacillus GG-supplemented group (p = 0.03).

Conclusions: Lactobacillus GG supplementation beneficially affects H. pylori therapy-related side effects and overall treatment tolerance. Copyright 2001 S. Karger AG, Basel

Lactobacillus plantarum Reduces Infection of Pancreatic Necrosis in Experimental Acute Pancreatitis

Mangiante G, Colucci G, Canepari P, et al

***Dig Surg.* 2001;18(1):47-50**

Background: Infection is the commonest cause of death in acute pancreatitis. Early reduction of commensal flora (particularly Lactobacillus species) and, at the same time, overgrowth of Enterobacteriaceae, especially Escherichia coli, have recently been described during acute pancreatitis. Lactobacillus plantarum has been shown to be effective in reducing the egress of endotoxin and microbial translocation in several experimental models such as chemically induced hepatitis and ulcerative colitis. **Aim:** The aim of the study was to determine whether L. plantarum 299v (Lp 299v) is capable of effectively reducing microbial translocation in experimental pancreatitis. **Methods:** Acute pancreatitis was induced by isolation and ligation of the biliopancreatic duct in Lewis rats weighing 250-350 g. The animals were divided into 3 groups: group A, sham operation; group B, induction of pancreatitis and no further treatment, and group C, induction of pancreatitis + daily administration by gavage of a 5-ml/day suspension of Lp 299v at 0.5-1.0 x 10⁹ bacteria/ml for 8 days, 4 days before and 4 days after induction of pancreatitis. All animals were sacrificed after 96 h. Histological studies and microbiological analyses were performed. **Results:** At sacrifice, 40/55 animals showed signs of severe pancreatitis. Since acute pancreatitis was the specific disease investigated, only these animals were subjected to further study. In group B, we found pathogenic micro-organisms in the mesenteric lymph nodes in 14/20 animals and in the pancreatic tissue in 10/20. The bacterial flora consisted predominantly of E. coli, Enterococcus faecalis, Pseudomonas and Proteus species. In contrast, when the animals were kept under an 'umbrella' of Lp 299v, growth of E. faecalis or E. coli were detected only in 4/20 mesenteric lymph node cultures and in 3/20 pancreatic tissue cultures. **Conclusions:** Lp 299v is effective in reducing microbial translocation in experimental pancreatitis. Treatment with probiotic bacteria seems to be a promising alternative to antibiotic therapy. Copyright 2001 S. Karger AG, Basel

Probiotic Therapy and Functional Foods for Prevention of Urinary Tract Infections: State of the Art and Science.

Reid G

***Curr Infect Dis Rep.* 2000 Dec;2(6):518-522**

In the past year, interest has heightened in the potential for probiotics to prevent urinary tract infection (UTI). Mainly, this has been due to concerns about antibiotic resistance and recognition of the scientific efficacy of probiotics. The critical factors in any successful application of probiotics to patient care are the scientific basis for selecting probiotic strains and clinical verification that they are effective against the recurrence of UTI. Three strains--Lactobacillus rhamnosus GR-1 and Lactobacillus fermentum B-54 and RC-14--have been shown to colonize the vagina and act as a barrier to the ascension of uropathogens into the bladder. Their ability to produce growth and adhesion antagonists against urogenital pathogens is clinically important, because these appear to be important mechanisms of action. Probiotic therapy has been shown to be safe, but too few reliable products are on the market, and none are yet available for use against UTI. Given the right strains and delivery system, probiotic therapy could provide the first new UTI-prevention system in 40 years, and may help in the management of recurrent UTI.

Probiotics in the Treatment of Diarrheal Diseases

Reid G

Curr Infect Dis Rep. 2000 Feb;2(1):78

Infections of the gastrointestinal tract are a major health problem worldwide, and many result in death, especially in the Third World. The approach to treatment and prevention of these infections has revolved around antibiotic administration for many years, but the emergence of multidrug-resistant pathogens is forcing people to look at alternatives to antibiotics. For more than 100 years, probiotic remedies (viable organisms that benefit the host by improving the microbial balance) have been used to fight infection. Now, substantial scientific and clinical evidence indicates that certain well-selected probiotic organisms can reduce the risk and duration of diarrhea.

Vinegar: Medicinal Uses and Antiglycemic Effect

Vinegar folklore is as colorful as it is practical. Legend states that a courtier in Babylonia (c. 5000 BC) "discovered" wine, formed from unattended grape juice, leading to the eventual discovery of vinegar and its use as a food preservative. Hippocrates (c. 420 BC) used vinegar medicinally to manage wounds. Hannibal of Carthage (c. 200 BC), the great military leader and strategist, used vinegar to dissolve boulders that blocked his army's path. Cleopatra (c. 50 BC) dissolved precious pearls in vinegar and offered her love potion to Anthony. Sung Tse, the 10th century creator of forensic medicine, advocated hand washing with sulfur and vinegar to avoid infection during autopsies. Based on the writings of US medical practitioners dating to the late 18th century, many ailments, from dropsy to poison ivy, croup, and stomachache, were treated with vinegar,^[1] and, before the production and marketing of hypoglycemic agents, vinegar "teas" were commonly consumed by diabetics to help manage their chronic ailment. This review examines the scientific evidence for medicinal uses of vinegar, focusing particularly on the recent investigations supporting vinegar's role as an antiglycemic agent. Epidemiologic studies and clinical trials were identified by a MEDLINE title/abstract search with the following search terms: vinegar, glucose; vinegar, cancer; or vinegar, infection. All relevant randomized or case-control trials were included in this review.

Vinegar: Medicinal Uses and Antiglycemic Effect

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Abstract

Vinegar folklore is as colorful as it is practical. Legend states that a courtier in Babylonia (c. 5000 BC) "discovered" wine, formed from unattended grape juice, leading to the eventual discovery of vinegar and its use as a food preservative. Hippocrates (c. 420 BC) used vinegar medicinally to manage wounds. Hannibal of Carthage (c. 200 BC), the great military leader and strategist, used vinegar to dissolve boulders that blocked his army's path. Cleopatra (c. 50 BC) dissolved precious pearls in vinegar and offered her love potion to Anthony. Sung Tse, the 10th century creator of forensic medicine, advocated hand washing with sulfur and vinegar to avoid infection during autopsies. Based on the writings of US medical practitioners dating to the late 18th century, many ailments, from dropsy to poison ivy, croup, and stomachache, were treated with vinegar,^[1] and, before the production and marketing of hypoglycemic agents, vinegar "teas" were commonly consumed by diabetics to help manage their chronic ailment. This review examines the scientific evidence for medicinal uses of vinegar, focusing particularly on the recent investigations supporting vinegar's role as an antiglycemic agent. Epidemiologic studies and clinical trials were identified by a MEDLINE title/abstract search with the following search terms: vinegar, glucose; vinegar, cancer; or vinegar, infection. All relevant randomized or case-control trials were included in this review.

Readers are encouraged to respond to George Lundberg, MD, Editor of *MedGenMed*, for the editor's eye only or for possible publication via email: glundberg@medscape.net

Vinegar Production

Vinegar, from the French *vin aigre*, meaning "sour wine," can be made from almost any fermentable carbohydrate source, including wine, molasses, dates, sorghum, apples, pears, grapes, berries, melons, coconut, honey, beer, maple syrup, potatoes, beets, malt, grains, and whey. Initially, yeasts ferment the natural food sugars to alcohol. Next, acetic acid bacteria (*Acetobacter*) convert the alcohol to acetic acid. Commercial vinegar is produced by either fast or slow fermentation processes. For the quick methods, the liquid is oxygenated by agitation and the bacteria culture is submerged permitting rapid fermentation. The slow methods are generally used for the production of the traditional wine vinegars, and the culture of acetic acid bacteria grows on the surface of the liquid and fermentation proceeds slowly over the course of weeks or months. The longer fermentation period allows for the accumulation of a nontoxic slime composed of yeast and acetic acid bacteria, known as the *mother* of vinegar. Vinegar eels (nematoda *Turbatrix acetii*) feed on these organisms and occur in naturally fermenting vinegar.^[2] Most manufacturers filter and pasteurize their product before bottling to prevent these organisms from forming. After opening, *mother* may develop in stored vinegar; it is considered harmless and can be removed by filtering. Many people advocate retaining the *mother* for numerous, but unsubstantiated, health effects.

The chemical and organoleptic properties of vinegars are a function of the starting material and the fermentation method. Acetic acid, the volatile organic acid that identifies the product as vinegar, is responsible for the tart flavor and pungent, biting odor of vinegars. However, acetic acid should not be considered synonymous with vinegar. The US Food and Drug Administration (FDA) states that diluted acetic acid is not vinegar and should not be added to food products customarily expected to contain vinegar.^[3] Other constituents of vinegar include vitamins, mineral salts, amino acids, polyphenolic compounds (eg, gallic acid, catechin, caffeic acid, ferulic acid), and nonvolatile organic acids (eg, tartaric, citric, malic, lactic).^[4,5]

In the United States, vinegar products must contain a minimum of 4% acidity.^[6] European countries have regional standards for vinegar produced or sold in the area. White distilled vinegars are generally 4% to 7% acetic acid whereas cider and wine vinegars are 5% to 6% acetic acid. Specialty vinegars are grouped as herbal or fruit vinegars. Herbal vinegars consist of wine vinegars or white distilled vinegars, which may be seasoned with garlic, basil, tarragon, cinnamon, clove, or nutmeg. Fruit vinegars are wine and white vinegars sweetened with fruit or fruit juice to produce a characteristic sweet-sour taste. Traditional vinegars are produced from regional foods according to well-established customs. The balsamic vinegar of Modena, Italy, is made from the local white Trebbiano grapes, which are harvested as late as possible, fermented slowly, and concentrated by aging in casks of various woods. Traditional rice wine vinegars are produced in Asia, coconut and cane vinegars are common in India and the Philippines, and date vinegars are popular in the Middle East.

Medicinal Uses of Vinegar

Anti-infective Properties

The use of vinegar to fight infections and other acute conditions dates back to Hippocrates (460-377 BC; the father of modern medicine), who recommended a vinegar preparation for cleaning ulcerations and for the treatment of sores. Oxymel, a popular ancient medicine composed of honey and vinegar, was prescribed for persistent coughs by Hippocrates and his contemporaries, and by physicians up to modern day.^[7] The formulation of oxymel was detailed in the *British Pharmacopoeia* (1898) and the *German Pharmacopoeia* (1872), and, according to the *French Codex* (1898), the medicine was prepared by mixing virgin honey, 4 parts, with white wine vinegar, 1 part, concentrating and clarifying with paper pulp.^[8]

Recent scientific investigations clearly demonstrate the antimicrobial properties of vinegar, but mainly in the context of food preparation.^[9-12] Experts advise against using vinegar preparations for treating wounds.^[13] At concentrations nontoxic to fibroblasts and keratinocytes ($\leq 0.0025\%$), acetic acid solutions were ineffective at inhibiting the growth of *Escherichia coli*, group D *Enterococcus*, or *Bacteroides fragilis* bacteria, and only slightly effective at inhibiting the growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa* bacteria.^[13] Similarly, experts caution against using vinegar as a household disinfectant against human pathogens because chemical disinfectants are more effective.^[14,15] However, undiluted vinegar may be used effectively for cleaning dentures, and, unlike bleach solutions, vinegar residues left on dentures were not associated with mucosal damage.^[16]

Although investigations have demonstrated the effectiveness of diluted vinegar (2% acetic acid solution at pH 2) for the treatment of ear infections (otitis externa, otitis media, and granular myringitis),^[17,18] the low pH of these solutions may irritate inflamed skin and damage cochlear outer hair cells.^[19] Immediate vinegar application at the site of jellyfish stings is practiced at various coastal locations around the world^[20,21] because vinegar deactivates the nematocysts. However, hot-water immersion is considered the most efficacious initial treatment for jellyfish envenomation because the venom is deactivated by heat.^[22,23]

In the popular media, vinegar is commonly recommended for treating nail fungus, head lice, and warts, yet scientific support for these treatment strategies is lacking. Takano-Lee and colleagues^[24] demonstrated that, of 7 home remedies tested, vinegar was the least effective for eliminating lice or inhibiting the hatching of eggs. Scattered reports suggest that the successive topical application of highly concentrated acetic acid solutions (up to 99%) alleviated warts,^[25,26] presumably due to the mechanical destruction of wart tissue. One treatment protocol, however, required local anesthesia, excision, and rapid neutralization at the site of application, thus limiting its use by the lay public.

Although not a treatment modality, vinegar washes are used by midwives in remote, poorly resourced locations (eg, Zimbabwe and the Amazon jungle) to screen women for the human papilloma virus infection.^[27,28] Contact with acetic acid causes visual alterations of the viral lesions permitting rapid detection of infection with 77% sensitivity^[29] and the option of immediate treatment with cryotherapy.

Cardiovascular Effects

Kondo and colleagues^[30] reported a significant reduction in systolic blood pressure (approximately 20 mm Hg) in spontaneously hypertensive (SHR) rats fed a standard laboratory diet mixed with either vinegar or an acetic acid solution (approximately 0.86 mmol acetic acid/day for 6 weeks) as compared with SHR rats fed the same diet mixed with deionized water. These observed reductions in systolic blood pressure were associated with reductions in both plasma renin activity and plasma aldosterone concentrations (35% to 40% and 15% to 25% reductions in renin activity and aldosterone concentrations, respectively, in the experimental vs control SHR rats). Others have reported that vinegar administration (approximately 0.57 mmol acetic acid, orally) inhibited the renin-angiotensin system in nonhypertensive Sprague-Dawley rats.^[31]

Trials investigating the effects of vinegar ingestion on the renin-angiotensin system have not been conducted in humans, and there is no scientific evidence that vinegar ingestion alters blood pressure in humans. In their report, Kondo and colleagues^[30] speculated that dietary acetic acid promoted calcium absorption and thereby downregulated the renin-angiotensin system.^[32] In the rat model, acetic acid administration enhanced calcium absorption and retention^[33]; moreover, in humans, calcium absorption in the distal colon was enhanced by acetate.^[34] Clearly, much work is needed to establish whether vinegar ingestion alters calcium absorption and/or blood pressure regulation in humans.

Whether chronic vinegar ingestion affects other risk factors for cardiovascular disease in humans is not known. Hu and colleagues^[35] reported a significantly lower risk for fatal ischemic heart disease among participants in the Nurses' Health Study who consumed oil-and-vinegar salad dressings frequently (5-6 times or more per week) compared with those who rarely consumed them (multivariate RR: 0.46; CI: 0.27-0.76, *P* for trend = .001). Frequent consumption of mayonnaise or other creamy salad dressings was not significantly associated with risk for ischemic heart disease in this population (multivariate RR: 0.84; CI: 0.50-1.44, *P* for trend = .44). The study authors contend that because oil and vinegar dressings are a major dietary source of dietary alpha-linolenic acid, an antiarrhythmic agent, alpha-linolenic acid may potentially be the beneficial ingredient of this food.^[35] Yet, creamy, mayonnaise-based salad dressings are also rich in alpha-linolenic acid and did not show the same risk benefit as the oil and vinegar dressings.

Antitumor Activity

In vitro, sugar cane vinegar (Kibizu) induced apoptosis in human leukemia cells,^[36] and a traditional Japanese rice vinegar (Kurosu) inhibited the proliferation of human cancer cells in a dose-dependent manner.^[37] An ethyl acetate extract of Kurosu added to drinking water (0.05% to 0.1% w/v) significantly inhibited the incidence (-60%) and multiplicity (-50%) of azoxymethane-induced colon carcinogenesis in male F344 rats when compared with the same markers in control animals.^[38] In a separate trial, mice fed a rice-shochu vinegar-fortified feed (0.3% to 1.5% w/w) or control diet were inoculated with sarcoma 180 (group 1) or colon 38 (group 2) tumor cells (2×10^6 cells subcutaneously).^[39] At 40 days post-inoculation, vinegar-fed mice in both experimental groups had significantly smaller tumor volumes when compared with their control counterparts. A prolonged life span due to tumor regression was also noted in the mice ingesting rice-shochu vinegar as compared with controls, and in vitro, the rice-shochu vinegar stimulated natural killer cell cytotoxic activity.^[39]

The antitumor factors in vinegar have not been identified. In the human colonic adenocarcinoma cell line Caco-2, acetate treatment, as well as treatment with the other short-chain fatty acids (SCFA) n-butyrate and propionate, significantly prolonged cell doubling time, promoted cell differentiation, and inhibited cell motility.^[40] Because bacterial fermentation of dietary fiber in the colon yields the SCFA, the investigators concluded that the antineoplastic effects of dietary fiber may relate in part to the formation of SCFA. Others have also documented the antineoplastic effects of the SCFA in the colon, particularly n-butyrate.^[41] Thus, because acetic acid in vinegar deprotonates in the stomach to form acetate ions, it may possess antitumor effects.

Vinegars are also a dietary source of polyphenols,^[6] compounds synthesized by plants to defend against oxidative stress. Ingestion of polyphenols in humans enhances in vivo antioxidant protection and reduces cancer risk.^[42] Kurosu vinegar is particularly rich in phenolic compounds, and the in-vitro antioxidant activity of an ethyl acetate extract of Kurosu vinegar was similar to the antioxidant activity of alpha-tocopherol (vitamin E) and significantly greater than the antioxidant activities of other vinegar extracts, including wine and apple vinegars.^[43] Kurosu vinegar extracts also suppressed lipid peroxidation in mice treated topically with H₂O₂-generating chemicals.^[43] Currently, much interest surrounds the role of dietary polyphenols, particularly from fruits, vegetables, wine, coffee, and chocolate, in the prevention of cancers as well as other conditions including cardiovascular disease^[44]; perhaps vinegar can be added to this list of foods and its consumption evaluated for disease risk.

Epidemiologic data, however, is scarce and unequivocal. A case-control study conducted in Linzhou, China, demonstrated that vinegar ingestion was associated with a decreased risk for esophageal cancer (OR: 0.37).^[45] However, vinegar ingestion was associated with a 4.4-fold greater risk for bladder cancer in a case-control investigation in Serbia.^[46]

Blood Glucose Control

The antiglycemic effect of vinegar was first reported by Ebihara and Nakajima^[47] in 1988. In rats, the blood glucose response to a 10% corn starch load was significantly reduced when coadministered with a 2% acetic acid solution.^[45] In healthy human subjects, although the glucose response curve was not significantly altered, the area under the insulin response curve following the ingestion of 50 g sucrose was reduced 20% when coadministered with 60 mL strawberry vinegar.^[47] Several years later, Brighenti and colleagues^[48] demonstrated in normoglycemic subjects that 20 mL white vinegar (5% acetic acid) as a salad dressing ingredient reduced the glycemic response to a mixed meal (lettuce salad and white bread containing 50 g carbohydrate) by over 30% ($P < .05$). Salad dressings made from neutralized vinegar, formulated by adding 1.5 g sodium bicarbonate to 20 mL white vinegar, or a salt solution (1.5 g sodium chloride in 20 mL water) did not significantly affect the glycemic response to the mixed meal.^[48] Separate placebo-controlled trials have corroborated the meal-time, antiglycemic effects of 20 g vinegar in healthy adults.^[49-51]

While compiling a glycemic index (GI) table for 32 common Japanese foods, Sugiyama and colleagues^[52] documented that the addition of vinegar or pickled foods to rice (eg, sushi) decreased the GI of rice by 20% to 35%. In these trials, healthy fasted subjects ingested the reference and test foods, each containing 50 g carbohydrate, on random days, and the food GI was calculated using the areas under the 2-hour blood glucose response curves. In the vinegar-containing foods, the amount of acetic acid was estimated to be 0.3-2.3 g, an amount similar to that found in 20 g vinegar (approximately 1 g). Ostman and colleagues^[53] reported that substitution of a pickled cucumber (1.6 g acetic acid) for a fresh cucumber (0 g acetic acid) in a test meal (bread, butter, and yogurt) reduced meal GI by over 30%^[53] in healthy subjects.

Recently, the antiglycemic property of vinegar was demonstrated to extend to individuals with marked insulin resistance or type 2 diabetes.^[54] In this crossover trial, individuals with insulin resistance ($n = 11$, fasting insulin concentrations greater than 20 mU/mL) or with diagnosed type

2 diabetes ($n = 10$) consumed a vinegar test drink (20 g vinegar, 40 g water, 1 tsp saccharine) or placebo immediately before the consumption of a mixed meal (87 g total carbohydrate). In the insulin-resistant subjects, vinegar ingestion reduced postprandial glycemia 64% as compared with placebo values ($P = .014$) and improved postprandial insulin sensitivity by 34% ($P = .01$). In individuals with type 2 diabetes, vinegar ingestion was less effective at reducing mealtime glycemia (-17%, $P = .149$); however, vinegar ingestion was associated with a slight improvement in postprandial insulin sensitivity in these subjects (+19%, $P = .07$).^[54] The lack of a significant effect of vinegar on mealtime glycemia in the type 2 diabetics may be related to the use of venous blood sampling in this trial. Greater within-subject variation in glucose concentrations are noted for venous blood as compared with capillary blood; moreover, the concentration of glucose in venous blood is lower than that in capillary blood. Thus, capillary blood sampling is preferred for determining the glycemic response to food.^[55]

The marked antiglycemic effect of vinegar in insulin-resistant subjects is noteworthy and may have important implications. Multicenter trials have demonstrated that treatment with antiglycemic pharmaceuticals (metformin or acarbose) slowed the progression to diabetes in high-risk individuals^[56,57]; moreover, because these drugs improved insulin sensitivity, the probability that individuals with impaired glucose tolerance would revert to a normal, glucose-tolerant state over time was increased.^[57]

In healthy subjects, Ostman and colleagues^[58] demonstrated that acetic acid had a dose-response effect on postprandial glycemia and insulinemia. Subjects consumed white bread (50 g carbohydrate) alone or with 3 portions of vinegar containing 1.1, 1.4, or 1.7 g acetic acid. At 30 minutes post-meal, blood glucose concentrations were significantly reduced by all concentrations of acetic acid as compared with the control value, and a negative linear relationship was calculated between blood glucose concentrations and the acetic acid content of the meal ($r = -0.47$, $P = .001$). Subjects were also asked to rate feelings of hunger/satiety on a scale ranging from extreme hunger (-10) to extreme satiety (+10) before meal consumption and at 15-minute intervals after the meal. Bread consumption alone scored the lowest rating of satiety (calculated as area under the curve from time 0-120 minutes). Feelings of satiety increased when vinegar was ingested with the bread, and a linear relationship was observed between satiety and the acetic acid content of the test meals ($r = 0.41$, $P = .004$).^[58]

In a separate trial, healthy adult women consumed fewer total calories on days that vinegar was ingested at the morning meal.^[50] In this trial, which used a blinded, randomized, placebo-controlled, crossover design, fasting participants consumed a test drink (placebo or vinegar) followed by the test meal composed of a buttered bagel and orange juice (87 g carbohydrate). Blood samples were collected for 1 hour after the meal. At the end of testing, participants were allowed to follow their normal activities and eating patterns the remainder of the day, but they were instructed to record food and beverage consumption until bedtime. Vinegar ingestion, as compared with placebo, reduced the 60-minute glucose response to the test meal (-54%, $P < .05$) and weakly affected later energy consumption (-200 kilocalories, $P = .111$). Regression analyses indicated that 60-minute glucose responses to test meals explained 11% to 16% of the variance in later energy consumption ($P < .05$).^[50] Thus, vinegar may affect satiety by reducing the mealtime glycemic load. Of 20 studies published between 1977 and 1999, 16 demonstrated that low-glycemic index foods promoted postmeal satiety and/or reduced subsequent hunger.^[59]

It is not known how vinegar alters meal-induced glycemia, but several mechanisms have been proposed. Ogawa and colleagues examined the effects of acetic acid and other organic acids on disaccharidase activity in Caco-2 cells.^[60] Acetic acid (5 mmol/L) suppressed sucrase, lactase, and maltase activities in concentration- and time-dependent manners as compared with control values, but the other organic acids (eg, citric, succinic, L-malic, and L-lactic acids) did not suppress enzyme activities. Because acetic acid treatment did not affect the de-novo synthesis of the sucrase-isomaltase complex at either the transcriptional or translational levels, the investigators concluded that the suppressive effect of acetic acid likely occurs during the

posttranslational processing of the enzyme complex.^[60] Of note, the lay literature has long proclaimed that vinegar interferes with starch digestion and should be avoided at meal times.^[61]

Several investigations examined whether delayed gastric emptying contributed to the antiglycemic effect of vinegar. Using noninvasive ultrasonography, Brighenti and colleagues^[50] did not observe a difference in gastric emptying rates in healthy subjects consuming bread (50 g carbohydrate) in association with acetic acid (ie, vinegar) vs sodium acetate (ie, vinegar neutralized by the addition of sodium bicarbonate); however, a significant difference in post-meal glycemia was noted between treatments with the acetic acid treatment lowering glycemia by 31.4%. In a later study, Liljeberg and Bjorck^[62] added paracetamol to the bread test meal to permit indirect measurement of the gastric emptying rate. Compared with reference values, postmeal serum glucose and paracetamol concentrations were reduced significantly when the test meal was consumed with vinegar. The results of this study should be carefully considered, however, because paracetamol levels in blood may be affected by food factors and other gastrointestinal events. In rats fed experimental diets containing the indigestible marker polyethylenglycol and varying concentrations of acetic acid (0, 4, 8, 16 g acetic acid /100 g diet), dietary acetic acid did not alter gastric emptying, the rate of food intake, or glucose absorption.^[63]

Safety of Vinegar

Vinegar's use as a condiment and food ingredient spans thousands of years, and perhaps its use can be labeled safe by default. Yet there are rare reports in the literature regarding adverse reactions to vinegar ingestion. Inflammation of the oropharynx and second-degree caustic injury of the esophagus and cardia were observed in a 39-year-old woman who drank 1 tablespoon of rice vinegar in the belief it would dislodge a piece of crab shell from her throat.^[64] (The use of vinegar in these situations is a popular Chinese folk remedy.) Her symptoms resolved spontaneously after several days. Esophageal injury by vinegar is likely very rare but deserves notice. Chronic inflammation of the esophagus is a cancer risk; but, as reported previously,^[45] vinegar use was inversely related to risk for cancer of the esophagus.

The unintentional aspiration of vinegar has been associated with laryngospasm and subsequent vasovagal syncope that resolved spontaneously.^[65] Hypokalemia was observed in a 28-year-old woman who had reportedly consumed approximately 250 mL apple cider vinegar daily for 6 years.^[66] Although speculative, the hypokalemia was attributed to elevated potassium excretion related to the bicarbonate load from acetate metabolism.

These complications attributed to vinegar ingestion are isolated occurrences, but with the increased interest in vinegar as adjunct therapy in diabetes, carefully controlled trials to examine potential adverse effects of regular vinegar ingestion are warranted.

Summary

For more than 2000 years, vinegar has been used to flavor and preserve foods, heal wounds, fight infections, clean surfaces, and manage diabetes. Although vinegar is highly valued as a culinary agent, some varieties costing \$100 per bottle, much scrutiny surrounds its medicinal use. Scientific investigations do not support the use of vinegar as an anti-infective agent, either topically or orally. Evidence linking vinegar use to reduced risk for hypertension and cancer is equivocal. However, many recent scientific investigations have documented that vinegar ingestion reduces the glucose response to a carbohydrate load in healthy adults and in individuals with diabetes. There is also some evidence that vinegar ingestion increases short-term satiety. Future investigations are needed to delineate the mechanism by which vinegar alters postprandial glycemia and to determine whether regular vinegar ingestion favorably influences glycemic control as indicated by reductions in hemoglobin A1c. Vinegar is widely

available; it is affordable; and, as a remedy, it is appealing. But whether vinegar is a useful adjunct therapy for individuals with diabetes or prediabetes has yet to be determined.

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Vinegar: Medicinal Uses and Antiglycemic Effect

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Abstract

Vinegar folklore is as colorful as it is practical. Legend states that a courtier in Babylonia (c. 5000 BC) "discovered" wine, formed from unattended grape juice, leading to the eventual discovery of vinegar and its use as a food preservative. Hippocrates (c. 420 BC) used vinegar medicinally to manage wounds. Hannibal of Carthage (c. 200 BC), the great military leader and strategist, used vinegar to dissolve boulders that blocked his army's path. Cleopatra (c. 50 BC) dissolved precious pearls in vinegar and offered her love potion to Anthony. Sung Tse, the 10th century creator of forensic medicine, advocated hand washing with sulfur and vinegar to avoid infection during autopsies. Based on the writings of US medical practitioners dating to the late 18th century, many ailments, from dropsy to poison ivy, croup, and stomachache, were treated with vinegar,^[1] and, before the production and marketing of hypoglycemic agents, vinegar "teas" were commonly consumed by diabetics to help manage their chronic ailment. This review examines the scientific evidence for medicinal uses of vinegar, focusing particularly on the recent investigations supporting vinegar's role as an antiglycemic agent. Epidemiologic studies and clinical trials were identified by a MEDLINE title/abstract search with the following search terms: vinegar, glucose; vinegar, cancer; or vinegar, infection. All relevant randomized or case-control trials were included in this review.

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Vinegar Production

Vinegar, from the French *vin aigre*, meaning "sour wine," can be made from almost any fermentable carbohydrate source, including wine, molasses, dates, sorghum, apples, pears, grapes, berries, melons, coconut, honey, beer, maple syrup, potatoes, beets, malt, grains, and whey. Initially, yeasts ferment the natural food sugars to alcohol. Next, acetic acid bacteria (*Acetobacter*) convert the alcohol to acetic acid. Commercial vinegar is produced by either fast or slow fermentation processes. For the quick methods, the liquid is oxygenated by agitation and the bacteria culture is submerged permitting rapid fermentation. The slow methods are generally used for the production of the traditional wine vinegars, and the culture of acetic acid bacteria grows on the surface of the liquid and fermentation proceeds slowly over the course of weeks or months. The longer fermentation period allows for the accumulation of a nontoxic slime composed of yeast and acetic acid bacteria, known as the *mother* of vinegar. Vinegar eels (nematoda *Turbatrix acetii*) feed on these organisms and occur in naturally fermenting vinegar.^[2] Most manufacturers filter and pasteurize their product before bottling to prevent these organisms from forming. After opening, *mother* may develop in stored vinegar; it is considered harmless and can be removed by filtering. Many people advocate retaining the *mother* for numerous, but unsubstantiated, health effects.

The chemical and organoleptic properties of vinegars are a function of the starting material and the fermentation method. Acetic acid, the volatile organic acid that identifies the product as

vinegar, is responsible for the tart flavor and pungent, biting odor of vinegars. However, acetic acid should not be considered synonymous with vinegar. The US Food and Drug Administration (FDA) states that diluted acetic acid is not vinegar and should not be added to food products customarily expected to contain vinegar.^[3] Other constituents of vinegar include vitamins, mineral salts, amino acids, polyphenolic compounds (eg, galic acid, catechin, caffeic acid, ferulic acid), and nonvolatile organic acids (eg, tartaric, citric, malic, lactic).^[4,5]

In the United States, vinegar products must contain a minimum of 4% acidity.^[6] European countries have regional standards for vinegar produced or sold in the area. White distilled vinegars are generally 4% to 7% acetic acid whereas cider and wine vinegars are 5% to 6% acetic acid. Specialty vinegars are grouped as herbal or fruit vinegars. Herbal vinegars consist of wine vinegars or white distilled vinegars, which may be seasoned with garlic, basil, tarragon, cinnamon, clove, or nutmeg. Fruit vinegars are wine and white vinegars sweetened with fruit or fruit juice to produce a characteristic sweet-sour taste. Traditional vinegars are produced from regional foods according to well-established customs. The balsamic vinegar of Modena, Italy, is made from the local white Trebbiano grapes, which are harvested as late as possible, fermented slowly, and concentrated by aging in casks of various woods. Traditional rice wine vinegars are produced in Asia, coconut and cane vinegars are common in India and the Philippines, and date vinegars are popular in the Middle East.

Medicinal Uses of Vinegar

Anti-infective Properties

The use of vinegar to fight infections and other acute conditions dates back to Hippocrates (460-377 BC; the father of modern medicine), who recommended a vinegar preparation for cleaning ulcerations and for the treatment of sores. Oxymel, a popular ancient medicine composed of honey and vinegar, was prescribed for persistent coughs by Hippocrates and his contemporaries, and by physicians up to modern day.^[7] The formulation of oxymel was detailed in the *British Pharmacopoeia* (1898) and the *German Pharmacopoeia* (1872), and, according to the *French Codex* (1898), the medicine was prepared by mixing virgin honey, 4 parts, with white wine vinegar, 1 part, concentrating and clarifying with paper pulp.^[8]

Recent scientific investigations clearly demonstrate the antimicrobial properties of vinegar, but mainly in the context of food preparation.^[9-12] Experts advise against using vinegar preparations for treating wounds.^[13] At concentrations nontoxic to fibroblasts and keratinocytes ($\leq 0.0025\%$), acetic acid solutions were ineffective at inhibiting the growth of *Escherichia coli*, group D *Enterococcus*, or *Bacteroides fragilis* bacteria, and only slightly effective at inhibiting the growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa* bacteria.^[13] Similarly, experts caution against using vinegar as a household disinfectant against human pathogens because chemical disinfectants are more effective.^[14,15] However, undiluted vinegar may be used effectively for cleaning dentures, and, unlike bleach solutions, vinegar residues left on dentures were not associated with mucosal damage.^[16]

Although investigations have demonstrated the effectiveness of diluted vinegar (2% acetic acid solution at pH 2) for the treatment of ear infections (otitis externa, otitis media, and granular myringitis),^[17,18] the low pH of these solutions may irritate inflamed skin and damage cochlear outer hair cells.^[19] Immediate vinegar application at the site of jellyfish stings is practiced at various coastal locations around the world^[20,21] because vinegar deactivates the nematocysts. However, hot-water immersion is considered the most efficacious initial treatment for jellyfish envenomation because the venom is deactivated by heat.^[22,23]

In the popular media, vinegar is commonly recommended for treating nail fungus, head lice, and warts, yet scientific support for these treatment strategies is lacking. Takano-Lee and colleagues^[24] demonstrated that, of 7 home remedies tested, vinegar was the least effective for

eliminating lice or inhibiting the hatching of eggs. Scattered reports suggest that the successive topical application of highly concentrated acetic acid solutions (up to 99%) alleviated warts,^[25,26] presumably due to the mechanical destruction of wart tissue. One treatment protocol, however, required local anesthesia, excision, and rapid neutralization at the site of application, thus limiting its use by the lay public.

Although not a treatment modality, vinegar washes are used by midwives in remote, poorly resourced locations (eg, Zimbabwe and the Amazon jungle) to screen women for the human papilloma virus infection.^[27,28] Contact with acetic acid causes visual alterations of the viral lesions permitting rapid detection of infection with 77% sensitivity^[29] and the option of immediate treatment with cryotherapy.

Cardiovascular Effects

Kondo and colleagues^[30] reported a significant reduction in systolic blood pressure (approximately 20 mm Hg) in spontaneously hypertensive (SHR) rats fed a standard laboratory diet mixed with either vinegar or an acetic acid solution (approximately 0.86 mmol acetic acid/day for 6 weeks) as compared with SHR rats fed the same diet mixed with deionized water. These observed reductions in systolic blood pressure were associated with reductions in both plasma renin activity and plasma aldosterone concentrations (35% to 40% and 15% to 25% reductions in renin activity and aldosterone concentrations, respectively, in the experimental vs control SHR rats). Others have reported that vinegar administration (approximately 0.57 mmol acetic acid, orally) inhibited the renin-angiotensin system in nonhypertensive Sprague-Dawley rats.^[31]

Trials investigating the effects of vinegar ingestion on the renin-angiotensin system have not been conducted in humans, and there is no scientific evidence that vinegar ingestion alters blood pressure in humans. In their report, Kondo and colleagues^[30] speculated that dietary acetic acid promoted calcium absorption and thereby downregulated the renin-angiotensin system.^[32] In the rat model, acetic acid administration enhanced calcium absorption and retention^[33]; moreover, in humans, calcium absorption in the distal colon was enhanced by acetate.^[34] Clearly, much work is needed to establish whether vinegar ingestion alters calcium absorption and/or blood pressure regulation in humans.

Whether chronic vinegar ingestion affects other risk factors for cardiovascular disease in humans is not known. Hu and colleagues^[35] reported a significantly lower risk for fatal ischemic heart disease among participants in the Nurses' Health Study who consumed oil-and-vinegar salad dressings frequently (5-6 times or more per week) compared with those who rarely consumed them (multivariate RR: 0.46; CI: 0.27-0.76, *P* for trend = .001). Frequent consumption of mayonnaise or other creamy salad dressings was not significantly associated with risk for ischemic heart disease in this population (multivariate RR: 0.84; CI: 0.50-1.44, *P* for trend = .44). The study authors contend that because oil and vinegar dressings are a major dietary source of dietary alpha-linolenic acid, an antiarrhythmic agent, alpha-linolenic acid may potentially be the beneficial ingredient of this food.^[35] Yet, creamy, mayonnaise-based salad dressings are also rich in alpha-linolenic acid and did not show the same risk benefit as the oil and vinegar dressings.

Antitumor Activity

In vitro, sugar cane vinegar (Kibizu) induced apoptosis in human leukemia cells,^[36] and a traditional Japanese rice vinegar (Kurosu) inhibited the proliferation of human cancer cells in a dose-dependent manner.^[37] An ethyl acetate extract of Kurosu added to drinking water (0.05% to 0.1% w/v) significantly inhibited the incidence (-60%) and multiplicity (-50%) of azoxymethane-induced colon carcinogenesis in male F344 rats when compared with the same markers in control animals.^[38] In a separate trial, mice fed a rice-shochu vinegar-fortified feed (0.3% to 1.5% w/w) or control diet were inoculated with sarcoma 180 (group 1) or colon 38 (group 2) tumor cells (2×10^6

cells subcutaneously).^[39] At 40 days post-inoculation, vinegar-fed mice in both experimental groups had significantly smaller tumor volumes when compared with their control counterparts. A prolonged life span due to tumor regression was also noted in the mice ingesting rice-shochu vinegar as compared with controls, and in vitro, the rice-shochu vinegar stimulated natural killer cell cytotoxic activity.^[39]

The antitumor factors in vinegar have not been identified. In the human colonic adenocarcinoma cell line Caco-2, acetate treatment, as well as treatment with the other short-chain fatty acids (SCFA) n-butyrate and propionate, significantly prolonged cell doubling time, promoted cell differentiation, and inhibited cell motility.^[40] Because bacterial fermentation of dietary fiber in the colon yields the SCFA, the investigators concluded that the antineoplastic effects of dietary fiber may relate in part to the formation of SCFA. Others have also documented the antineoplastic effects of the SCFA in the colon, particularly n-butyrate.^[41] Thus, because acetic acid in vinegar deprotonates in the stomach to form acetate ions, it may possess antitumor effects.

Vinegars are also a dietary source of polyphenols,^[6] compounds synthesized by plants to defend against oxidative stress. Ingestion of polyphenols in humans enhances in vivo antioxidant protection and reduces cancer risk.^[42] Kurosu vinegar is particularly rich in phenolic compounds, and the in-vitro antioxidant activity of an ethyl acetate extract of Kurosu vinegar was similar to the antioxidant activity of alpha-tocopherol (vitamin E) and significantly greater than the antioxidant activities of other vinegar extracts, including wine and apple vinegars.^[43] Kurosu vinegar extracts also suppressed lipid peroxidation in mice treated topically with H₂O₂-generating chemicals.^[43] Currently, much interest surrounds the role of dietary polyphenols, particularly from fruits, vegetables, wine, coffee, and chocolate, in the prevention of cancers as well as other conditions including cardiovascular disease^[44]; perhaps vinegar can be added to this list of foods and its consumption evaluated for disease risk.

Epidemiologic data, however, is scarce and unequivocal. A case-control study conducted in Linzhou, China, demonstrated that vinegar ingestion was associated with a decreased risk for esophageal cancer (OR: 0.37).^[45] However, vinegar ingestion was associated with a 4.4-fold greater risk for bladder cancer in a case-control investigation in Serbia.^[46]

Blood Glucose Control

The antiglycemic effect of vinegar was first reported by Ebihara and Nakajima^[47] in 1988. In rats, the blood glucose response to a 10% corn starch load was significantly reduced when coadministered with a 2% acetic acid solution.^[45] In healthy human subjects, although the glucose response curve was not significantly altered, the area under the insulin response curve following the ingestion of 50 g sucrose was reduced 20% when coadministered with 60 mL strawberry vinegar.^[47] Several years later, Brighenti and colleagues^[48] demonstrated in normoglycemic subjects that 20 mL white vinegar (5% acetic acid) as a salad dressing ingredient reduced the glycemic response to a mixed meal (lettuce salad and white bread containing 50 g carbohydrate) by over 30% ($P < .05$). Salad dressings made from neutralized vinegar, formulated by adding 1.5 g sodium bicarbonate to 20 mL white vinegar, or a salt solution (1.5 g sodium chloride in 20 mL water) did not significantly affect the glycemic response to the mixed meal.^[48] Separate placebo-controlled trials have corroborated the meal-time, antiglycemic effects of 20 g vinegar in healthy adults.^[49-51]

While compiling a glycemic index (GI) table for 32 common Japanese foods, Sugiyama and colleagues^[52] documented that the addition of vinegar or pickled foods to rice (eg, sushi) decreased the GI of rice by 20% to 35%. In these trials, healthy fasted subjects ingested the reference and test foods, each containing 50 g carbohydrate, on random days, and the food GI was calculated using the areas under the 2-hour blood glucose response curves. In the vinegar-containing foods, the amount of acetic acid was estimated to be 0.3-2.3 g, an amount similar to that found in 20 g vinegar (approximately 1 g). Ostman and colleagues^[53] reported that

substitution of a pickled cucumber (1.6 g acetic acid) for a fresh cucumber (0 g acetic acid) in a test meal (bread, butter, and yogurt) reduced meal GI by over 30%^[53] in healthy subjects.

Recently, the antiglycemic property of vinegar was demonstrated to extend to individuals with marked insulin resistance or type 2 diabetes.^[54] In this crossover trial, individuals with insulin resistance ($n = 11$, fasting insulin concentrations greater than 20 mU/mL) or with diagnosed type 2 diabetes ($n = 10$) consumed a vinegar test drink (20 g vinegar, 40 g water, 1 tsp saccharine) or placebo immediately before the consumption of a mixed meal (87 g total carbohydrate). In the insulin-resistant subjects, vinegar ingestion reduced postprandial glycemia 64% as compared with placebo values ($P = .014$) and improved postprandial insulin sensitivity by 34% ($P = .01$). In individuals with type 2 diabetes, vinegar ingestion was less effective at reducing mealtime glycemia (-17%, $P = .149$); however, vinegar ingestion was associated with a slight improvement in postprandial insulin sensitivity in these subjects (+19%, $P = .07$).^[54] The lack of a significant effect of vinegar on mealtime glycemia in the type 2 diabetics may be related to the use of venous blood sampling in this trial. Greater within-subject variation in glucose concentrations are noted for venous blood as compared with capillary blood; moreover, the concentration of glucose in venous blood is lower than that in capillary blood. Thus, capillary blood sampling is preferred for determining the glycemic response to food.^[55]

The marked antiglycemic effect of vinegar in insulin-resistant subjects is noteworthy and may have important implications. Multicenter trials have demonstrated that treatment with antiglycemic pharmaceuticals (metformin or acarbose) slowed the progression to diabetes in high-risk individuals^[56,57]; moreover, because these drugs improved insulin sensitivity, the probability that individuals with impaired glucose tolerance would revert to a normal, glucose-tolerant state over time was increased.^[57]

In healthy subjects, Ostman and colleagues^[58] demonstrated that acetic acid had a dose-response effect on postprandial glycemia and insulinemia. Subjects consumed white bread (50 g carbohydrate) alone or with 3 portions of vinegar containing 1.1, 1.4, or 1.7 g acetic acid. At 30 minutes post-meal, blood glucose concentrations were significantly reduced by all concentrations of acetic acid as compared with the control value, and a negative linear relationship was calculated between blood glucose concentrations and the acetic acid content of the meal ($r = -0.47$, $P = .001$). Subjects were also asked to rate feelings of hunger/satiety on a scale ranging from extreme hunger (-10) to extreme satiety (+10) before meal consumption and at 15-minute intervals after the meal. Bread consumption alone scored the lowest rating of satiety (calculated as area under the curve from time 0-120 minutes). Feelings of satiety increased when vinegar was ingested with the bread, and a linear relationship was observed between satiety and the acetic acid content of the test meals ($r = 0.41$, $P = .004$).^[58]

In a separate trial, healthy adult women consumed fewer total calories on days that vinegar was ingested at the morning meal.^[50] In this trial, which used a blinded, randomized, placebo-controlled, crossover design, fasting participants consumed a test drink (placebo or vinegar) followed by the test meal composed of a buttered bagel and orange juice (87 g carbohydrate). Blood samples were collected for 1 hour after the meal. At the end of testing, participants were allowed to follow their normal activities and eating patterns the remainder of the day, but they were instructed to record food and beverage consumption until bedtime. Vinegar ingestion, as compared with placebo, reduced the 60-minute glucose response to the test meal (-54%, $P < .05$) and weakly affected later energy consumption (-200 kilocalories, $P = .111$). Regression analyses indicated that 60-minute glucose responses to test meals explained 11% to 16% of the variance in later energy consumption ($P < .05$).^[50] Thus, vinegar may affect satiety by reducing the mealtime glycemic load. Of 20 studies published between 1977 and 1999, 16 demonstrated that low-glycemic index foods promoted postmeal satiety and/or reduced subsequent hunger.^[59]

It is not known how vinegar alters meal-induced glycemia, but several mechanisms have been proposed. Ogawa and colleagues examined the effects of acetic acid and other organic acids on

disaccharidase activity in Caco-2 cells.^[60] Acetic acid (5 mmol/L) suppressed sucrase, lactase, and maltase activities in concentration- and time-dependent manners as compared with control values, but the other organic acids (eg, citric, succinic, L-malic, and L-lactic acids) did not suppress enzyme activities. Because acetic acid treatment did not affect the de-novo synthesis of the sucrase-isomaltase complex at either the transcriptional or translational levels, the investigators concluded that the suppressive effect of acetic acid likely occurs during the posttranslational processing of the enzyme complex.^[60] Of note, the lay literature has long proclaimed that vinegar interferes with starch digestion and should be avoided at meal times.^[61]

Several investigations examined whether delayed gastric emptying contributed to the antiglycemic effect of vinegar. Using noninvasive ultrasonography, Brighenti and colleagues^[50] did not observe a difference in gastric emptying rates in healthy subjects consuming bread (50 g carbohydrate) in association with acetic acid (ie, vinegar) vs sodium acetate (ie, vinegar neutralized by the addition of sodium bicarbonate); however, a significant difference in post-meal glycemia was noted between treatments with the acetic acid treatment lowering glycemia by 31.4%. In a later study, Liljeberg and Bjorck^[62] added paracetamol to the bread test meal to permit indirect measurement of the gastric emptying rate. Compared with reference values, postmeal serum glucose and paracetamol concentrations were reduced significantly when the test meal was consumed with vinegar. The results of this study should be carefully considered, however, because paracetamol levels in blood may be affected by food factors and other gastrointestinal events. In rats fed experimental diets containing the indigestible marker polyethyleneglycol and varying concentrations of acetic acid (0, 4, 8, 16 g acetic acid /100 g diet), dietary acetic acid did not alter gastric emptying, the rate of food intake, or glucose absorption.^[63]

Safety of Vinegar

Vinegar's use as a condiment and food ingredient spans thousands of years, and perhaps its use can be labeled safe by default. Yet there are rare reports in the literature regarding adverse reactions to vinegar ingestion. Inflammation of the oropharynx and second-degree caustic injury of the esophagus and cardia were observed in a 39-year-old woman who drank 1 tablespoon of rice vinegar in the belief it would dislodge a piece of crab shell from her throat.^[64] (The use of vinegar in these situations is a popular Chinese folk remedy.) Her symptoms resolved spontaneously after several days. Esophageal injury by vinegar is likely very rare but deserves notice. Chronic inflammation of the esophagus is a cancer risk; but, as reported previously,^[45] vinegar use was inversely related to risk for cancer of the esophagus.

The unintentional aspiration of vinegar has been associated with laryngospasm and subsequent vasovagal syncope that resolved spontaneously.^[65] Hypokalemia was observed in a 28-year-old woman who had reportedly consumed approximately 250 mL apple cider vinegar daily for 6 years.^[66] Although speculative, the hypokalemia was attributed to elevated potassium excretion related to the bicarbonate load from acetate metabolism.

These complications attributed to vinegar ingestion are isolated occurrences, but with the increased interest in vinegar as adjunct therapy in diabetes, carefully controlled trials to examine potential adverse effects of regular vinegar ingestion are warranted.

Summary

For more than 2000 years, vinegar has been used to flavor and preserve foods, heal wounds, fight infections, clean surfaces, and manage diabetes. Although vinegar is highly valued as a culinary agent, some varieties costing \$100 per bottle, much scrutiny surrounds its medicinal use. Scientific investigations do not support the use of vinegar as an anti-infective agent, either topically or orally. Evidence linking vinegar use to reduced risk for hypertension and cancer is equivocal. However, many recent scientific investigations have documented that vinegar

ingestion reduces the glucose response to a carbohydrate load in healthy adults and in individuals with diabetes. There is also some evidence that vinegar ingestion increases short-term satiety. Future investigations are needed to delineate the mechanism by which vinegar alters postprandial glycemia and to determine whether regular vinegar ingestion favorably influences glycemic control as indicated by reductions in hemoglobin A1c. Vinegar is widely available; it is affordable; and, as a remedy, it is appealing. But whether vinegar is a useful adjunct therapy for individuals with diabetes or prediabetes has yet to be determined.

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