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REPORT

Natural Solutions to Chronic Stomach Problems

By Julius G. Goepf, MD



In their quest to promote a long and healthy life, many Americans forget one of the first links in the chain—their stomachs. The consequences of stomach neglect range from simple heartburn all the way to ulcers and even cancer.

The pathological effects of alcohol, smoking, and stress, coupled with an epidemic rate of infection with the *Helicobacter pylori* 1-6 bacterium mean that all the ingredients are present for the “perfect storm” of stomach distress and disease.

Fortunately, a “dynamic trio” of nutrients—**zinc-carnosine, licorice extract, and cranberry**—work in concert to protect stomach function from the rough players in the environment. These nutrients both relieve distress and also support the body’s natural defense mechanisms in preventing inflammation and the changes that can lead to cancer.

A fourth stomach-protecting agent called **picrorhiza** protects the mucosa via additional mechanisms, and can now be included as part of a natural gastric health brigade.

THE STOMACH

The human stomach, even in the prime of health, is a tough neighborhood. Let’s take a quick tour of some of its most astonishing features, so that we can see why it’s so vulnerable to attack. The stomach’s extreme acidity provides a primary defense against infection and also assists in the first stages of digestion. Containing extreme levels of acidity, however, poses an intense biological challenge.

Indeed, the fact that the stomach doesn’t self-destruct is one of life’s major miracles! A thick coating of protective mucus is steadily secreted by the specialized surface mucous cells in the organ’s lining, and a rapid turnover of cells in the lining itself keeps “fresh troops” always at hand. Nonetheless, it’s a delicately balanced system, and with that amount of firepower around, any breach in the defenses rapidly grows into a major problem.

Virtually everyone has experienced at least mild gastritis or “upset stomach” we associate with overindulgence and stress. While these are usually thought of as annoyances, each episode causes a bit more lasting damage, eventually resulting in cellular injury which in turn causes inflammation.⁷ The inflammation then produces free radicals that go on to create still more tissue destruction,^{8,9} eventually damaging DNA and potentially leading to cancers of the stomach, which are among the most lethal malignancies known.⁶



Infection with the *H. pylori* bacterium produces all these effects and more. In fact, it is now recognized as a major cause of stomach and upper intestinal disorders, including ulcers of the stomach and duodenum (beginning of the small intestine), gastric cancers, and gastritis.^{10,11} After the organism sets up shop in the stomach lining (it has elaborate defense mechanisms that allow it to survive the acid), *H. pylori* produces an influx of inflammatory cells by secreting powerful “virulence factors.”¹⁰ In a microscopic “one-two punch,”¹² these bacterial proteins block normal function of certain immune cells, while boosting the free radical production from others,^{13,14} and stimulating still another group of immune cells to produce inflammatory cytokines, the messengers that call new inflammatory cells into the region.¹⁰

The discovery that *H. pylori* infection and inflammation lead to gastritis and ulcers was one of the major breakthroughs in modern medical science^{15,16} (two scientists won the Nobel prize for this discovery). The finding that eradication of the organism can relieve symptoms and prevent cancer is perhaps even more meaningful.¹⁷ While antibiotic treatment can be effective against *H. pylori*, there’s powerful evidence for the role of specific nutrients in alleviating the misery caused by this bacterial nemesis.^{18,19}

NUTRITIONAL APPROACHES TO MAINTAINING STOMACH HEALTH

Natural substances have been used around the world for millennia to promote stomach health.²⁰ Modern science is catching up, however, as scientists are finding that certain of these “folk remedies” have potent effects on boosting immunity, reducing inflammation, or simply providing improved physical protection to the delicate stomach lining.

ZINC

Zinc is a micronutrient that has multiple functions in human biology, chiefly functioning as a coenzyme in many enzyme systems that defend against free radical damage.^{13,14,21,22} Recognizing that *H. pylori* infection causes increased oxidative stress, a group of Ecuadorian scientists wondered if zinc deficiency might cause increased inflammation in the stomachs of people infected with the organism.²³ They studied 352 patients with dyspepsia (stomach pain and dysfunction) who had biopsy samples taken during endoscopy. Patients with *H. pylori* infections had significantly lower zinc concentrations in their tissue samples than uninfected patients. Indeed, the more severe the inflammation, the lower the zinc levels in the infected subjects.²³ These results and others have led some researchers to consider zinc to be a “gastric cytoprotective” (cell-saving) nutrient.²⁴

Zinc also has direct anti-inflammatory effects, helping to stabilize the membranes of cells called mast cells, which release bursts of inflammatory cytokines when stimulated by injury or allergy.^{25,26} Further, the mineral is well known as an immune modulator that can reduce the recurrence rate of certain inflammation-sensitive cancers.²⁷

Unfortunately, there’s some evidence that even with normal intakes, zinc may be less well absorbed in older people.²⁸ Furthermore, researchers at the University of Minnesota discovered that certain cholesterol-lowering diets, which are themselves healthy, can result in inadequate intake of certain micronutrients, including zinc, calcium, and vitamins A, D, and E.²⁹ For this reason, the researchers urged people concerned about their cholesterol to remember to obtain adequate zinc and other vital minerals while on otherwise healthful diets.



Fortunately, zinc supplementation has been shown to have powerful gastroprotective effects. In 1991, Spanish researchers conducted a multicenter trial of zinc versus two other anti-ulcer drugs in their effects on protecting the stomach lining.³⁰ In this study, 146 patients with stomach and duodenal ulcers that had recently been healed with prescription anti-acid medications, were randomly assigned to take either zinc acexamate (48 mg elemental zinc) once daily, or one of the other mucosal-protecting anti-ulcer drugs known as aceglutamide aluminum salt and magaldrate, each taken twice daily.

The researchers performed endoscopic examinations at the beginning of the study and at the end of 12 months, and the patients also had regular clinical examinations at three, six, and nine months. The zinc preparation was found to be superior to both of the other drugs in preventing relapses of ulcers, and the authors noted that patients tolerated the treatment extremely well.³⁰



Another Spanish study showed the powerful effects of zinc on prevention of gastritis and ulcers in patients who were taking nonsteroidal anti-inflammatory drugs (NSAIDs) such as naproxen.³¹ These drugs, commonly used to treat all sorts of inflammatory conditions, are notorious for their tendency to cause gastric injury by suppressing production of natural stomach-protective substances.⁹ This study enrolled 276 patients with known ulcers or intolerance to the NSAID medications, but who still needed them. All had normal endoscopy at the beginning of the study. Patients were then treated with an NSAID and either a zinc compound (48 mg elemental zinc) or placebo once daily at bedtime. Four weeks later, all patients had a clinical and endoscopic examination, and damage to the stomach and intestinal lining was graded using a standard scale. No patients taking zinc had gastric ulcers, while 6% of the placebo recipients did! Similarly, only one zinc-supplemented patient, compared with 12 placebo patients, had duodenal ulcers. Even mild duodenal and gastric damage was lower in the zinc group (just 5-8%) compared with the placebo group (19-25%). At the end of the study, 88% of the zinc-supplemented patients had completely normal endoscopy, compared with only 66% of the placebo patients. The authors concluded that zinc was effective and well tolerated for prevention of NSAID-induced gastro-duodenal damage.³¹

Perhaps the most dramatic demonstration of zinc’s gastroprotective effects comes from yet another large Spanish study,³² in which zinc was compared head-to-head with famotidine (Pepcid®), a commonly used commercial anti-acid drug. The researchers treated 199 patients with endoscopically verified acute duodenal ulcers, randomly assigning them to zinc (96 mg elemental zinc/day) or famotidine (Pepcid®, an anti-acid drug)(40 mg/day) for four weeks. Clinical exams at two and four weeks and repeat endoscopy at four weeks were used to gauge the results. Astonishingly, complete healing of the ulcers was seen in just over half the patients in both groups, and a reduction in ulcer size of more than 50% was seen in about 80% of both groups. Symptom relief was identical in the elemental zinc and famotidine-treated patients, and side effects were also infrequent in both. The researchers reached the obvious conclusion: the 96 mg daily dose of elemental zinc was as effective as the 40 mg daily dose of the pharmaceutical famotidine!³²

ZINC-CARNOSINE

There's simply no doubt that zinc is a potent antioxidant, anti-inflammatory, and gastroprotective nutrient. Another essential nutrient called carnosine can boost those effects even further. Japanese scientists have led the way in developing this zinc-carnosine compound. That's not surprising, because until quite recently gastric cancer (the result of gastritis and ulcer disease) was the top killer cancer in Japan—and the dramatic decline in this killer condition has been attributed in large part to dietary education of the Japanese people.³³ In fact, the zinc-carnosine compound, sold as polaprezinc, is a regulated prescription anti-ulcer drug in Japan.³⁴ Fortunately, this simple nutrient compound—comprising zinc and carnosine linked by a chemical bond—is available in the US as a non-prescription supplement that is safe for long-term use.

Exciting studies of the zinc-carnosine compound began to emerge from Japanese laboratories in the early 1990s, when animal trials showed how the combination stabilized the membranes of inflammatory cells and prevented them from releasing potent cytokines and the enzymes that can cause the stomach to actually digest itself.^{25,35} In study after study, ulcers caused by stress, ischemia (poor blood flow), alcohol, and other toxins were either prevented or rapidly healed when animals were given even single oral doses of zinc-carnosine.^{26,36-40}

By 1995, the mechanism by which this combination exerts its powerful effect was becoming clear. Using radioactive tracer compounds to “follow” the course of the preparation in animal stomachs, researchers were able to watch as the combination “stuck” to the stomach wall much more tightly than either zinc or carnosine alone, allowing the beneficial effects of both components to be delivered directly to the site where protection is most badly needed.⁴¹

In a dramatic, direct head-to-head comparison with a prescription drug, scientists in Japan showed that the zinc-carnosine combination was equally effective as sucralfate (which also promotes healing by sticking to stomach walls) at preventing ulcers in rats.⁴² An important distinction between the two ulcer-healing agents is that NSAID drugs inhibit the activity of the drug sucralfate, but do not interfere with the action of zinc-carnosine.

By the end of the last millennium it had become clear that the zinc-carnosine combination could not only prevent but actually speed the healing of existing ulcers, both through its antioxidant effects^{43,44} and also by increasing production of the vital insulin-like growth factor-1 (IGF-1), which is crucial to gastric wound repair.^{45,46} And in 1999, the first hard evidence emerged linking zinc-carnosine to cancer prevention, when a team at Keio University in Tokyo found that the combination prevented the fragmentation of DNA in stomach lining cells that can cause the cells to become cancerous.⁴⁷ The same group brought the research full circle in 2001, when they showed that zinc-carnosine also potently inhibited the stomach inflammation and cytokine release caused by infection with *H. pylori*,⁴⁸ thus demonstrating a powerful new means of breaking the infection-inflammation-cancer chain with nutritional management alone.

Zinc-carnosine also speeds the eradication of infection with *H. pylori* itself, as shown by another Japanese team in 1999.⁴⁹ The group enrolled 66 patients with known *H. pylori* infections and symptoms, randomly assigning them to zinc-carnosine or placebo. All patients were also given a cocktail of two potent antibiotics aimed at curbing the infections plus a proton pump inhibitor aimed at promoting gastric healing. Only 86% of the antibiotic-proton pump inhibitor group achieved complete cure (eradication of detectable organisms), while the full 100% of those supplemented with zinc-carnosine were cured.

Finally, in early 2007, Western scientists began to take zinc-carnosine seriously and to examine its mode of action and effectiveness. A British team used a laboratory model of gut injury and repair, and also conducted a clinical trial.⁵⁰ In the first study, they examined the effects of zinc-carnosine on cells lining animal digestive tracts after exposure to indomethacin (a potent NSAID notorious for its gastritis-producing tendencies) or to stress. The nutrient combination reduced stomach injury by 75% and small intestinal injury by 50%. It also stimulated migration and growth of cells in and near the sites of injury, hastening the healing process nearly threefold. In the clinical trial, 10 healthy volunteers took indomethacin 50 mg three times daily with either placebo or zinc-carnosine. Indomethacin increased gut permeability (impaired barrier function of the gut's lining that allows inflammation to get its start) by a factor of three in the placebo group, whereas in the supplemented group there was no increase at all in permeability. The researchers concluded that zinc-carnosine stabilized the mucosal lining cells of the stomach and small intestine—a conclusion that only hints at the potent gastroprotective effects found by dozens of their colleagues in Japan!

CRANBERRY

Certain fruits, especially cranberries, are rich in molecules called anthocyanins, which have intense antioxidant capabilities.^{51,52} Other polyphenol compounds found specifically in cranberries prevent bacteria from setting up shop in the urinary tract (and thereby preventing bladder infections). These compounds also inhibit *H. pylori* by preventing the organism from attaching itself to the gastrointestinal lining.^{18,53,54}

There's mounting clinical evidence of just how effective cranberries and their extracts can be in mitigating *H. pylori* and other stomach ailments. Chinese researchers gave cranberry juice or a placebo drink (about two cups per day) to 189 adults with *H. pylori* infection.⁵⁵ They checked for chemical evidence of continued infection at 35 and 90 days of treatment. More than 14% of the juice-supplemented group, and just 5% of the placebo group, showed complete eradication of the organism. The researchers concluded that "Regular consumption of cranberry juice can suppress *H. pylori* infection in endemically afflicted populations."



Israeli researchers found similar results in a very recent trial. They randomly assigned 177 patients with *H. pylori* infection to drink cranberry juice or a placebo drink, 250 mL twice daily, while also taking a triple-therapy drug treatment for *H. pylori* consisting of two antibiotics and a proton pump inhibitor (omeprazole).⁵⁶ *H. pylori* was eradicated in more than 95% of the female subjects who took the juice supplements, compared with only 80-86% of the non-supplemented patients. The *H. pylori* eradication rates were also lower in men who supplemented with the juice, but the sample size was not large enough to be statistically significant.

A large systematic review by nutritional experts has now concluded that regular intake of cranberry juice and other dietary products "might constitute a low-cost, large-scale alternative solution applicable for populations at risk for *H. pylori* colonization."⁵⁷ It thus seems clear that cranberries and their extracts can take their place alongside zinc-carnosine as important components of an effective stomach health regimen.

WHAT YOU NEED TO KNOW

Natural Solutions to Chronic Stomach Problems

- Gastritis (stomach irritation) and ulcer disease are among the most common ailments worldwide.
- More than half of all cases of gastritis and ulcers are actually caused by chronic infection with a bacterium called *Helicobacter pylori*.
- *H. pylori* infection produces increased oxidant stress leading to inflammation, breakdown of the stomach's protective mechanisms, and ultimately damage to DNA.
- Virtually all stomach cancers are the result of chronic damage caused by gastritis and/or ulcers, making gastric cancer a highly preventable, infection-related malignancy.
- Specific nutrient supplements fight each of the injuries found in stomach diseases, including *H. pylori* infection itself, oxidative injury, inflammation, and genetic damage.
- Laboratory and clinical evidence overwhelmingly supports a role for four specific nutrients: zinc-carnosine, cranberry extracts, licorice extracts, and extracts of a Himalayan herb called picrorhiza in not only preventing, but in many cases actually healing gastritis and ulcers of the stomach and small intestine.
- Dramatic declines in stomach illness, including gastric cancer, have been observed in populations who are well educated about nutrients and use them as part of an eradication program targeting *H. pylori*.

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LICORICE

Long recognized for their multiple health benefits,^{20,58} licorice extracts (with the potentially blood pressure-elevating glycyrrhizin molecule removed⁵⁹) provide yet another nutritional weapon in fighting *H. pylori* infection. Various laboratory studies have shown that these extracts have potent anti-inflammatory activities, reducing cytokine production while increasing production of protective stomach mucus.^{60,61} Licorice extracts can also actually kill *H. pylori* in stomach tissue,¹⁹ even antibiotic-resistant strains of the organism.^{62,63} Indeed, in one laboratory head-to-head comparison, licorice extracts were as effective as famotidine in preventing ulcers,⁶⁴ and animal studies have shown a potent effect on speeding the healing of existing ulcers.⁶⁵ These characteristics of licorice neatly complement those of zinc-carnosine and cranberry extracts, and, in the words of Dr. Rea Krausse, a German microbiologist, provide “hope that it can form the basis for an alternative therapeutic agent against *H. pylori*.”⁶³

Human studies conducted since the 1970s bear this out, showing that deglycyrrhizinated licorice could reduce aspirin-induced gastritis,⁶⁶ and also promote healing of duodenal ulcers.⁶⁷ The prestigious *British Medical Journal* published a report in 1978 showing that among patients 60 years and older, a deglycyrrhizinated licorice extract medication called “Caved-(S)” was as effective as cimetidine (Tagamet®), the first of the pharmaceutical anti-acid medications.⁶⁸ The same researchers extended their findings in a 1982 study, enrolling 100 patients with endoscopically proven gastric ulcers and giving them either cimetidine or Caved-(S).⁶⁹ At six weeks, 63% of patients were healed by endoscopic examination, and 91% at 12 weeks, with no difference between the drug and the licorice compound! And when the researchers examined the long-term effects of either treatment at preventing recurrence of ulcers, they again found that both the drug and the supplement had virtually identical effectiveness (and that ulcers rapidly recurred when either treatment was stopped).⁷⁰

PICRORHIZA

As we've seen, the “cocktail” of zinc-carnosine, cranberry, and deglycyrrhizinated licorice already provides a multi-armed approach to gastric protection and improved stomach health. News about another natural remedy called picrorhiza (*Picrorhiza kurroa*) is now generating intense excitement in the medical community.^{71,72} Well known to practitioners of Ayurvedic medicine, picrorhiza is a perennial herb found high in the Himalayas. Its extracts are now being found to have potent antioxidant,⁷³⁻⁷⁵ immune-stimulating,⁷⁶⁻⁸⁰ and anti-inflammatory⁸¹⁻⁸⁴ properties—activities that clearly have a role in gastric protection. Since picrorhiza so dramatically combats the very changes caused by *H. pylori* (infection, inflammation, oxidant stress, and tissue injury), it's no wonder that this ancient herb is now at the forefront of research on stomach health.



Already used to speed healing in other infectious gastrointestinal conditions such as hepatitis A,^{76,85} picrorhiza extracts also demonstrate unique wound-healing properties, stimulating tissue growth, nerve cell recovery, and blood vessel formation that may promote recovery from tissue damage.⁸⁶⁻⁸⁸ In a dramatic illustration of the extract's ability to combat stomach ulcers, Indian scientists administered it to rats with ulcers induced by the potent NSAID indomethacin.⁸⁹ Compared with an untreated group of animals, the supplemented group had much faster rates of ulcer healing, accompanied by a profound drop in levels of oxidized tissue components. And while antioxidant enzyme activity was decreased in the untreated animals, those treated with picrorhiza actually had elevated antioxidant activity.

SUMMARY

The health of the stomach has, ironically, been one of the most neglected areas for which excellent nutritional support is known. As modern scientists begin to recognize the genuine value of ancient practices, using ultra-modern techniques to understand them, the situation is changing for the better. We now understand that *H. pylori* causes the majority of serious stomach ailments through a complex series of infectious, inflammatory, oxidative, and tissue-destructive processes. The nutrient combination of zinc-carnosine with cranberry extract, licorice extract, and now picrorhiza extract brings together for the first time the infection-fighting, anti-inflammatory, antioxidant, and tissue-healing capabilities of multiple compounds with complementary actions. It seems likely that widespread use of these supplements may help the rest of the world follow in the footsteps of the Japanese, who have reduced the rates of stomach disorders such as cancer by careful attention to nutritional education.³³

References

1. Mallampalli A, Untupalli KK. Smoking and systemic disease. *Clin Occup Environ Med.* 2006;5(1):173-92.
2. Modena JL, Acrani GO, Micas AF, et al. Correlation between *Helicobacter pylori* infection, gastric diseases and life habits among patients treated at a university hospital in Southeast Brazil. *Braz J Infect Dis.* 2007 Feb;11(1):89-95.
3. Salih BA, Abasiyanik MF, Bayyurt N, Sander E. H pylori infection and other risk factors associated with peptic ulcers in Turkish patients: a retrospective study. *World J Gastroenterol.* 2007 Jun 21;13(23):3245-8.
4. Satyanarayana MN. Capsaicin and gastric ulcers. *Crit Rev Food Sci Nutr.* 2006;46(4):275-328.
5. Szabo S, Deng X, Khomenko T, et al. New Molecular Mechanisms of Duodenal Ulceration. *Ann NY Acad Sci.* 2007 Jul 26.
6. Fox JG, Wang TC. Inflammation, atrophy, and gastric cancer. *J Clin Invest.* 2007 Jan;117(1):60-9.
7. Davidson G, Kritas S, Butler R. Stressed mucosa. *Nestle Nutr Workshop Ser Pediatr Program.* 2007;59:133-42.
8. Boeckxstaens GE. Neuroimmune interaction in the gut: from bench to bedside. *Verh K Acad Geneeskdg Belg.* 2006;68(5-6):329-55.
9. Iezzi A, Ferri C, Mezzetti A, Cipollone F. COX-2: friend or foe? *Curr Pharm Des.* 2007;13(16):1715-21.
10. D'Elia MM, Montecucco C, de BM. VacA and HP-NAP, Ying and Yang of *Helicobacter pylori*-associated gastric inflammation. *Clin Chim Acta.* 2007 May;381(1):32-8.
11. Lai LH, Sung JJ. *Helicobacter pylori* and benign upper digestive disease. *Best Pract Res Clin Gastroenterol.* 2007;21(2):261-79.
12. Robinson K, Argent RH, Atherton JC. The inflammatory and immune response to *Helicobacter pylori* infection. *Best Pract Res Clin Gastroenterol.* 2007;21(2):237-59.
13. Gotz JM, van Kan CI, Verspaget HW, et al. Gastric mucosal superoxide dismutases in *Helicobacter pylori* infection. *Gut.* 1996 Apr;38(4):502-6.
14. Gotz JM, Thio JL, Verspaget HW, et al. Treatment of *Helicobacter pylori* infection favourably affects gastric mucosal superoxide dismutases. *Gut.* 1997 May;40(5):591-6.
15. Lochhead P, El-Omar EM. *Helicobacter pylori* infection and gastric cancer. *Best Pract Res Clin Gastroenterol.* 2007;21(2):281-97.
16. Wilson KT, Crabtree JE. Immunology of *Helicobacter pylori*: insights into the failure of the immune response and perspectives on vaccine studies. *Gastroenterology.* 2007 Jul;133(1):288-308.
17. Lesbros-Pantoflickova D, Corthesy-Theulaz I, Blum AL. *Helicobacter pylori* and probiotics. *J Nutr.* 2007 Mar;137(3 Suppl 2):812S-8S.
18. Lin YT, Kwon YI, Labbe RG, Shetty K. Inhibition of *Helicobacter pylori* and associated urease by oregano and cranberry phytochemical synergies. *Appl Environ Microbiol.* 2005 Dec;71(12):8558-64.
19. O'Mahony R, Al-Khtheeri H, Weerasekera D, et al. Bactericidal and anti-adhesive properties of culinary and medicinal plants against *Helicobacter pylori*. *World J Gastroenterol.* 2005 Dec 21;11(47):7499-507.
20. Langmead L, Rampton DS. Review article: herbal treatment in gastrointestinal and liver disease—benefits and dangers. *Aliment Pharmacol Ther.* 2001 Sep;15(9):1239-52.
21. Noguchi K, Kato K, Moriya T, et al. Analysis of cell damage in *Helicobacter pylori*-associated gastritis. *Pathol Int.* 2002

22. Tran CD, Campbell MA, Kolev Y, et al. Short-term zinc supplementation attenuates *Helicobacter felis*-induced gastritis in the mouse. *J Infect.* 2005 Jun;50(5):417-24.
23. Sempertegui F, Diaz M, Mejia R, et al. Low concentrations of zinc in gastric mucosa are associated with increased severity of *Helicobacter pylori*-induced inflammation. *Helicobacter.* 2007 Feb;12(1):43-8.
24. D'Souza RS, Dhume VG. Gastric cytoprotection. *Indian J Physiol Pharmacol.* 1991 Apr;35(2):88-98.
25. Cho CH, Luk CT, Ogle CW. The membrane-stabilizing action of zinc carnosine (Z-103) in stress-induced gastric ulceration in rats. *Life Sci.* 1991;49(23):L189-94.
26. Cho CH, Ogle CW. The pharmacological differences and similarities between stress- and ethanol-induced gastric mucosal damage. *Life Sci.* 1992;51(24):1833-42.
27. Barrera JL, Verastegui E, Meneses A, et al. Combination immunotherapy of squamous cell carcinoma of the head and neck: a phase 2 trial. *Arch Otolaryngol Head Neck Surg.* 2000 Mar;126(3):345-51.
28. Russell RM. Changes in gastrointestinal function attributed to aging. *Am J Clin Nutr.* 1992 Jun;55(6 Suppl):1203S-7S.
29. Bae CY, Keenan JM, Fontaine P, et al. Plasma lipid response and nutritional adequacy in hypercholesterolemic subjects on the American Heart Association Step-One Diet. *Arch Fam Med.* 1993 Jul;2(7):765-72.
30. Varas Lorenzo MJ, Lopez MA, Gordillo BJ, Mundet SJ. Comparative study of 3 drugs (aceglutamide aluminum, zinc acexamate, and magaldrate) in the long-term maintenance treatment (1 year) of peptic ulcer. *Rev Esp Enferm Dig.* 1991 Aug;80(2):91-4.
31. Rodriguez de la SA, az-Rubio M. Multicenter clinical trial of zinc acexamate in the prevention of nonsteroidal antiinflammatory drug induced gastroenteropathy. Spanish Study Group on NSAID Induced Gastroenteropathy Prevention. *J Rheumatol.* 1994 May;21(5):927-33.
32. García-Plaza A, Arenas JI, Belda O, et al. A multicenter clinical trial. Zinc acexamate versus famotidine in the treatment of acute duodenal ulcer. Study Group of Zinc acexamate (new UP doses). *Rev Esp Enferm Dig.* 1996 Nov;88(11):757-62.
33. Matsuzaka M, Fukuda S, Takahashi I, et al. The decreasing burden of gastric cancer in Japan. *Tohoku J Exp Med.* 2007 Jul;212(3):207-19.
34. Matsukura T, Tanaka H. Applicability of zinc complex of L-carnosine for medical use. *Biochemistry (Mosc.).* 2000 Jul;65(7):817-23.
35. Shimada T, Watanabe N, Ohtsuka Y, et al. Polaprezinc down-regulates proinflammatory cytokine-induced nuclear factor-kappaB activation and interleukin-8 expression in gastric epithelial cells. *J Pharmacol Exp Ther.* 1999 Oct;291(1):345-52.
36. Arakawa T, Satoh H, Nakamura A, et al. Effects of zinc L-carnosine on gastric mucosal and cell damage caused by ethanol in rats. Correlation with endogenous prostaglandin E2. *Dig Dis Sci.* 1990 May;35(5):559-66.
37. Cho CH, Hui WM, Chen BW, Luk CT, Lam SK. The cytoprotective effect of zinc L-carnosine on ethanol-induced gastric gland damage in rabbits. *J Pharm Pharmacol.* 1992 Apr;44(4):364-5.
38. Ito M, Tanaka T, Suzuki Y. Effect of N-(3-aminopropionyl)-L-histidinato zinc (Z-103) on healing and hydrocortisone-induced relapse of acetic acid ulcers in rats with limited food-intake-time. *Jpn J Pharmacol.* 1990 Apr;52(4):513-21.
39. Seiki M, Ueki S, Tanaka Y, et al. Studies on anti-ulcer effects of a new compound, zinc L-carnosine (Z-103). *Nippon Yakurigaku Zasshi.* 1990 May;95(5):257-69.
40. Yoshikawa T, Naito Y, Tanigawa T, et al. Effect of zinc-carnosine chelate compound (Z-103), a novel antioxidant, on acute gastric mucosal injury induced by ischemia-reperfusion in rats. *Free Radic Res Commun.* 1991;14(4):289-96.
41. Furuta S, Toyama S, Miwa M, et al. Residence time of polaprezinc (zinc L-carnosine complex) in the rat stomach and

adhesiveness to ulcerous sites. *Jpn J Pharmacol.* 1995 Apr;67(4):271-8.

42. Kato S, Nishiwaki H, Konaka A, Takeuchi K. Mucosal ulcerogenic action of monochloramine in rat stomachs: effects of polaprezinc and sucralfate. *Dig Dis Sci.* 1997 Oct;42(10):2156-63.
43. Hiraishi H, Sasai T, Oinuma T, et al. Polaprezinc protects gastric mucosal cells from noxious agents through antioxidant properties in vitro. *Aliment Pharmacol Ther.* 1999 Feb;13(2):261-9.
44. Nishiwaki H, Kato S, Sugamoto S, et al. Ulcerogenic and healing impairing actions of monochloramine in rat stomachs: effects of zinc L-carnosine, polaprezinc. *J Physiol Pharmacol.* 1999 Jun;50(2):183-95.
45. Watanabe S, Wang XE, Hirose M, et al. Insulin-like growth factor I plays a role in gastric wound healing: evidence using a zinc derivative, polaprezinc, and an in vitro rabbit wound repair model. *Aliment Pharmacol Ther.* 1998 Nov;12(11):1131-8.
46. Kato S, Tanaka A, Ogawa Y, et al. Effect of polaprezinc on impaired healing of chronic gastric ulcers in adjuvant-induced arthritic rats—role of insulin-like growth factors (IGF)-1. *Med Sci Monit.* 2001 Jan;7(1):20-5.
47. Suzuki H, Mori M, Seto K, et al. Polaprezinc, a gastroprotective agent: attenuation of monochloramine-evoked gastric DNA fragmentation. *J Gastroenterol.* 1999;34 Suppl 1143-46.
48. Suzuki H, Mori M, Seto K, et al. Polaprezinc attenuates the *Helicobacter pylori*-induced gastric mucosal leucocyte activation in Mongolian gerbils—a study using intravital videomicroscopy. *Aliment Pharmacol Ther.* 2001 May;15(5):715-25.
49. Kashimura H, Suzuki K, Hassan M, et al. Polaprezinc, a mucosal protective agent, in combination with lansoprazole, amoxicillin and clarithromycin increases the cure rate of *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 1999 Apr;13(4):483-7.
50. Mahmood A, FitzGerald AJ, Marchbank T, et al. Zinc carnosine, a health food supplement that stabilises small bowel integrity and stimulates gut repair processes. *Gut.* 2007 Feb;56(2):168-175.
51. Zafra-Stone S, Yasmin T, Bagchi M, et al. Berry anthocyanins as novel antioxidants in human health and disease prevention. *Mol Nutr Food Res.* 2007 Jun;51(6):675-83.
52. Ariga T. The antioxidative function, preventive action on disease and utilization of proanthocyanidins. *Biofactors.* 2004;21(1-4):197-201.
53. Vatterm DA, Ghaedian R, Shetty K. Enhancing health benefits of berries through phenolic antioxidant enrichment: focus on cranberry. *Asia Pac J Clin Nutr.* 2005;14(2):120-30.
54. Burger O, Weiss E, Sharon N, et al. Inhibition of *Helicobacter pylori* adhesion to human gastric mucus by a high-molecular-weight constituent of cranberry juice. *Crit Rev Food Sci Nutr.* 2002;42(3 Suppl):279-84.
55. Zhang L, Ma J, Pan K, et al. Efficacy of cranberry juice on *Helicobacter pylori* infection: a double-blind, randomized placebo-controlled trial. *Helicobacter.* 2005 Apr;10(2):139-45.
56. Shmueli H, Yahav J, Samra Z, et al. Effect of cranberry juice on eradication of *Helicobacter pylori* in patients treated with antibiotics and a proton pump inhibitor. *Mol Nutr Food Res.* 2007 Jun;51(6):746-51.
57. Gotteland M, Brunser O, Cruchet S. Systematic review: are probiotics useful in controlling gastric colonization by *Helicobacter pylori*? *Aliment Pharmacol Ther.* 2006 Apr 15;23(8):1077-86.
58. Olukoga A, Donaldson D. Licorice and its health implications. *J R Soc Health.* 2000 Jun;120(2):83-9.
59. Petry JJ, Hadley SK. Medicinal herbs: answers and advice, Part 2. *Hosp Pract (Minneap.).* 2001 Aug 15;36(8):55-9.
60. Khayyal MT, Seif-EI-Nasr M, EI-Ghazaly MA, et al. Mechanisms involved in the gastro-protective effect of STW 5 (Iberogast) and its components against ulcers and rebound acidity. *Phytomedicine.* 2006;13 Suppl 5:56-66.
61. Kim JK, Oh SM, Kwon HS, et al. Anti-inflammatory effect of roasted licorice extracts on lipopolysaccharide-induced inflammatory responses in murine macrophages. *Biochem Biophys Res Commun.* 2006 Jul 7;345(3):1215-23.

62. Fukai T, Marumo A, Kaitou K, et al. Anti-Helicobacter pylori flavonoids from licorice extract. *Life Sci.* 2002 Aug 9;71(12):1449-63.
63. Krausse R, Bielenberg J, Blaschek W, Ullmann U. In vitro anti-Helicobacter pylori activity of Extractum liquiritiae, glycyrrhizin and its metabolites. *J Antimicrob Chemother.* 2004 Jul;54(1):243-6.
64. Aly AM, Al-Alousi L, Salem HA. Licorice: a possible anti-inflammatory and anti-ulcer drug. *AAPS PharmSciTech.* 2005;6(1):E74-E82.
65. Baker ME. Licorice and enzymes other than 11 beta-hydroxysteroid dehydrogenase: an evolutionary perspective. *Steroids.* 1994 Feb;59(2):136-41.
66. Rees WD, Rhodes J, Wright JE, Stamford LF, Bennett A. Effect of deglycyrrhizinated liquorice on gastric mucosal damage by aspirin. *Scand J Gastroenterol.* 1979;14(5):605-7.
67. Larkworthy W, Holgate PF. Deglycyrrhizinated liquorice in the treatment of chronic duodenal ulcer. A retrospective endoscopic survey of 32 patients. *Practitioner.* 1975 Dec;215(1290):787-92.
68. Morgan AG, McAdam WA, Pacsoo C, Walker BE, Simmons AV. Cimetidine: an advance in gastric ulcer treatment? *Br Med J.* 1978 Nov 11;2(6148):1323-6.
69. Morgan AG, McAdam WA, Pacsoo C, Darnborough A. Comparison between cimetidine and Caved-S in the treatment of gastric ulceration, and subsequent maintenance therapy. *Gut.* 1982 Jun;23(6):545-51.
70. Morgan AG, Pacsoo C, McAdam WA. Maintenance therapy: a two year comparison between Caved-S and cimetidine treatment in the prevention of symptomatic gastric ulcer recurrence. *Gut.* 1985 Jun;26(6):599-602.
71. Anon. *Picrorhiza kurroa*. Monograph. *Altern Med Rev.* 2001 Jun;6(3):319-21.
72. Govindarajan R, Vijayakumar M, Rawat AK, Mehrotra S. Free radical scavenging potential of *Picrorhiza kurroa* Royle ex Benth. *Indian J Exp Biol.* 2003 Aug;41(8):875-9.
73. Chander R, Kapoor NK, Dhawan BN. Effect of picroliv on glutathione metabolism in liver and brain of *Mastomys natalensis* infected with *Plasmodium berghei*. *Indian J Exp Biol.* 1992 Aug;30(8):711-4.
74. Chander R, Singh K, Visen PK, Kapoor NK, Dhawan BN. Picroliv prevents oxidation in serum lipoprotein lipids of *Mastomys coucha* infected with *Plasmodium berghei*. *Indian J Exp Biol.* 1998 Apr;36(4):371-4.
75. Sun M, Fan HW, Ma HY, Zhu Q. Protective effect of total glucosides of *Picrorhiza scrophulariiflora* against oxidative stress in glomerular mesangial cells induced by high glucose. *Yao Xue Xue Bao.* 2007 Apr;42(4):381-5.
76. Vaidya AB, Antarkar DS, Doshi JC, et al. *Picrorhiza kurroa* (Kutaki) Royle ex Benth as a hepatoprotective agent—experimental & clinical studies. *J Postgrad Med.* 1996 Oct;42(4):105-8.
77. Gupta A, Khajuria A, Singh J, et al. Immunomodulatory activity of biopolymeric fraction RLJ-NE-205 from *Picrorhiza kurroa*. *Int Immunopharmacol.* 2006 Oct;6(10):1543-9.
78. Puri A, Saxena RP, Guru PY, et al. Immunostimulant Activity of Picroliv, the Iridoid Glycoside Fraction of *Picrorhiza kurroa*, and its Protective Action against *Leishmania donovani* Infection in Hamsters¹. *Planta Med.* 1992 Dec;58(6):528-32.
79. Sharma ML, Rao CS, Duda PL. Immunostimulatory activity of *Picrorhiza kurroa* leaf extract. *J Ethnopharmacol.* 1994 Feb;41(3):185-92.
80. Smit HF, Kroes BH, van den Berg AJ, et al. Immunomodulatory and anti-inflammatory activity of *Picrorhiza scrophulariiflora*. *J Ethnopharmacol.* 2000 Nov;73(1-2):101-9.
81. Barbieri SS, Cavalca V, Eligini S, et al. Apocynin prevents cyclooxygenase 2 expression in human monocytes through NADPH oxidase and glutathione redox-dependent mechanisms. *Free Radic Biol Med.* 2004 Jul 15;37(2):156-65.

82. Thomas M, Sheran J, Smith N, Fonseca S, Lee AJ. AKL1, a botanical mixture for the treatment of asthma: a randomised, double-blind, placebo-controlled, cross-over study. *BMC Pulm Med.* 2007;74.
83. Zhang Y, DeWitt DL, Murugesan S, Nair MG. Novel lipid-peroxidation- and cyclooxygenase-inhibitory tannins from *Picrorhiza kurroa* seeds. *Chem Biodivers.* 2004 Mar;1(3):426-41.
84. Zhang Y, DeWitt DL, Murugesan S, Nair MG. Cyclooxygenase-2 enzyme inhibitory triterpenoids from *Picrorhiza kurroa* seeds. *Life Sci.* 2005 Nov 4;77(25):3222-30.
85. Luper S. A review of plants used in the treatment of liver disease: part 1. *Altern Med Rev.* 1998 Dec;3(6):410-21.
86. Gaddipati JP, Mani H, Banaudha KK, et al. Picroliv modulates the expression of insulin-like growth factor (IGF)-I, IGF-II and IGF-I receptor during hypoxia in rats. *Cell Mol Life Sci.* 1999 Oct 15;56(3-4):348-55.
87. Li P, Matsunaga K, Ohizumi Y. Nerve growth factor-potentiating compounds from *Picrorhizae Rhizoma*. *Biol Pharm Bull.* 2000 Jul;23(7):890-2.
88. Singh AK, Sharma A, Warren J, et al. Picroliv accelerates epithelialization and angiogenesis in rat wounds. *Planta Med.* 2007 Mar;73(3):251-6.
89. Available at: <http://medind.nic.in/iaf/t02/i2/iaft02i2p44.pdf>. Accessed September 25,2007.

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