Bio-HPF®

Helicobacter pylori formula

The mammalian intestinal tract contains a complex, dynamic, and diverse society of nonpathologic bacteria. Undeniably, the number of bacteria that colonize the human body is so large that researchers have estimated that of the total number of cells in the human body, estimated at 10^{14} (100 trillion) cells, only 10% are not bacteria and belong to the human body proper.[1] Indeed the human large intestine is portrayed as a complex microbial ecosystem.

Many of these bacteria serve beneficial purposes in the intestinal tract, such as assisting with digestion, and in the making and processing of both short-chain fatty acids (SCFA)[2, 3, 4] and amino acids, in addition to their vital association with the intestinal epithelial cells, which affords immune homeostasis.[5] Additionally, recent evidence has singled out the epithelial cell-bacterial interaction, and its function in inhibiting the inflammatory signaling cascade via its action on blocking the activation of NF-κB.[5] In spite of these beneficial functions, the intestinal tract may become populated with noncomensal flora, one of these species being *Helicobacter pylori* (*H. pylori*) (formerly *Campylobacter pylori*), resulting in gastric distress and suboptimal gastric function. Bacterial imbalance in the colon has been described in IBD,[6] as well as in association with the development of a colitogenic flora.[5] Colonization of the gastric mucosa by noncommensal flora, including *H. pylori*, has been associated with diminished gastric health and associated illnesses.[7] An added compounding factor associated with *H. pylori* infection is iron deficiency anemia, established as an independent risk factor in both adolescent children[8] and adults.[9]

The bacterium *H. pylori* is characterized as a flagellated, curved or S-shaped gram-negative rod[10] that is able to penetrate the gastric mucosa and colonizes the gastric epithelium of humans, resulting in persistent infection with possible complications.[11] The parietal cells of the stomach secrete profuse amounts of hydrochloric acid, which serves to maintain the acidic environment stomach, characteristically at a pH of less than two (<2).[12] Despite this highly acidic environment, *H. pylori* is able to persist, thought to be due primarily to its characteristic spiral morphology, and its high motility.[13] Acute *H. pylori* induced gastritis is associated with hypochlorhydria, and colonization is speculated to have the ability to modify the net gastric acidity, but virtue of the substances the bacterium secretes.[15, 16] *H. pylori* infestation is associated with a dysregulation in the function of the gastric epithelial barrier,[17] as well as with increased epithelial permeability.[18] Once acquired, *H. pylori* can inhabit the human stomach for years, decades, or possibly for life.

Reports have also associated the colonization of *H. pylori* with the use of both acid suppressing drugs and nonsteroidal antiinflammatory drugs (NSAID). In regards to NSAID use, *H. pylori* infection is indicated as an independent risk factor for the development of peptic or bleeding ulcers, with additive implications indicated when these factors are correlated.[19] Added to the use of acid suppressing drugs, *H. pylori* infection is associated with lower acid secretion, attributed to the induction of an immune response, resulting in the synthesis and production of interleukin-1 (IL-1), which is a potent inhibitor of gastric acid secretion.[20] The overuse of acid suppressants, which in reality may offer little to no benefit for the patient, further compounds this scenario. In fact it has been documented that patients on proton pump inhibitors demonstrated benefits from the approved indications of these drugs in only 37% of the cases.[21]

The fact that *H. pylori* can live and survive in the hostile acidic environment of the gastric mucosa is proposed to result as a consequence of a pH gradient across its cell envelope.[22] It also possesses the ability to produce unusually high levels of urease, which is presumed to be critical for its colonization. High levels of urease result by virtue of its capability to hydrolyze urea, resulting in the production of ammonia. As a result of its ammonia producing ability, a thin acid-neutralizing layer, or "cloud" is formed around the bacterium, which in turn protects it from destruction by the acidic environment of the gut.[23] The production of urease, therefore, has been associated with a protective effect on the bacterium.[24]

There has been a growing interest in a phytochemical approach to the eradication this bacterium, primarily due to the decline in efficacy of the currently used drugs for treatment. Specific botanical preparations have documented benefits in supporting gastrointestinal health, as well as in mitigating *H. pylori*.

Phytochemical Support

Berberine HCl

Berberine is isolated as the main alkaloid derived from the roots and bark of *Berberis vulgaris*, a deciduous shrub, native to Central and Southern Europe, Northwest Africa and Western Asia. Significant antimicrobial activity against a variety of organisms, including bacteria, viruses, fungi,

parasites, including *Giardia lamblia,* and *Entamoeba histolytica, protozoans,* including *Trichomonas vaginalis,*[25] helminths, and chlamydia has been documented with Berberine extracts and decoctions.[26, 27]

The inhibitory effect of berberine on the growth of *H. pylori* is well recognized,[28] and its antiproliferative action, in a dosedependent manner, has been confirmed. The later attribute has been correlated to its action via the mitochondrial/caspase-dependent pathway.[29] *In vitro* studies have demonstrated berberine's ability to interact with nucleic acids, in particular DNA.[30] Berberine has also been demonstrated to induce G0/G1 cell cycle arrest in an animal model[31] to selectively inhibit the cell cycle at G2/M in a cell line model, (Balb/c 3T3),[32, 33] and to decrease experimentally induced apoptosis in a concentration- and time-dependent manner.[34, 35]

Wild Indigo *(Baptisia tinctoria)* (root). *Baptisia tinctoria*, commonly known as Wild Indigo, is an herbaceous perennial herb. The herb is noted for both its astringent[36] and immune stimulating properties.[37, 38] Traditionally used by North Americans Indians for its antiseptic properties, it is also a noted antibacterial cleansing agent.[39, 40] It has been associated with the promotion of normal cellular metabolism and in the support of healthy tissues.[41]

The chemical constituents of the root consists of glycoproteins, quinolizidine alkaloids, including cytisine and anagyrine, isoflavanoids, hydroxycumarins, and polysaccharides, including arabinogalactans.[42] Use has been associated with supporting the body's natural resistance to microorganisms and toxins via its activation of macrophages, and due to an increased production of interleukin-1. In animal studies the polysaccharide and glycoprotein fraction was demonstrated to produce an immune-stimulating effect.[42] Other research supports the use of arabinogalactan components for their antiinflammatory and immunostimulating properties.[43]

Licorice *(Glycyrrhiza glabra)* (root). Licorice is a perennial herb or sub-shrub containing numerous active compounds, including flavonoids, triterpene saponins, isoflavonoids and hydroxycoumarins. Of these, the component possessing the greatest activity is the triterpenoid saponin glycyrrhizin (GL), having demonstrated antiviral[44, 45, 46, 47] antimicrobial[48] and antifungal[49, 50] properties.

In animal studies GL was demonstrated to stimulate interferon gamma production by T-cells,[51] resulting in an antiviral effect,[52] and to augment the activity of natural killer cells.[53] In the human intestinal tract GL is converted primarily to its biologically active metabolite glycyrrhetinic acid (GA), and to a lesser extent to glycyrrhetinic acid-3-O-betaDglucuronide (GAMG) by the intestinal microflora.[54, 55] Both GL and GA have demonstrated antiinflammatory properties.[54, 56] GL has also been demonstrated to impair the growth of *H. pylori in vivo*, via the inhibition of the activity of arylamine N-acetyltransferase (NAT family of enzymes).[57] This family of enzymes functions to catalyze the transfer of acetyl groups from acetyl-coenzyme A to an aromatic amine, heterocyclic amine or hydrazine compound.[58] In a separate *in vitro* study GA, at a concentration of ≤50mg/L, was demonstrated to inhibit 79% (23/29) of the *H. pylori* stains tested, including two clarithromycin-resistant strains, noting both concentration- and strain-dependent bactericidal effects of GA.[56] A more recent *in vitro* study utilizing PC12 cells demonstrated that treatment with GA resulted in a neuroprotective effect, by virtue of a decrease in ROS, via the elevation of glutathione peroxidase and catalase, with a corresponding decrease in mitochondrial membrane potential. The authors concluded that GA treatment may play a role in modulating both the intracellular antioxidant system and mitochondria-induced apoptosis, resulting in cellular protection from ischemic injury.[59]

Clove *(Syzygium aromaticum)* (flower bud). Clove is a plant indigenous to the Moluccan Islands of Indonesia. It is cultivated on these islands, as well as in other tropical regions, including Tanzania, Madagascar and Brazil. Its active compounds include its volatile oils, flavonoids, tannins, triterpines and steroids, including beta-sitosterol.[60] The main component eugenol, comprising 85-95%, has been associated with the prevention of lipid peroxidation[61] and is recognized as a strong scavenger of active oxygen radicals.[62] It is considered an effective antimicrobial agent and has use as an antiseptic.[63]

A number of studies have demonstrated clove's activity against various bacterial species,[64] including *Bacillus subtilis,*[65] *Campylobacter jejuni, Salmonella enterides, Staphylococcus aureus* and *E. coli.*[66] An aqueous infusion of cloves was demonstrated to restrict cellular invasion, resulting in a notable reduction in the incidence of skin papilloma in animals, as well as in the multiplicity of the growth, in a dose dependent manner. At the most effective oral dose (100 µl/day), no adverse or toxic effects were noted.[67] It has also been specifically demonstrated to inhibit the growth of *H pylori.*[68] Clove is approved by the German Commission E for use as a topical antiseptic and as an anesthetic for inflammation.[69]

Slippery Elm *(Ulmus fulva)* (bark). Slippery Elm has been used for centuries by North American Indians for skin irritations including, wounds, boils, ulcers, burns, and skin inflammation, as well as orally for the relieve of coughs, sore throats, diarrhea, and stomach problems.[70] The powdered inner bark has mucilaginous qualities, which is indicated for relief of irritation of the mucus membranes, and may be useful for treating irritation or ulceration of the stomach lining and duodenum.[71] Its mucilaginous characteristics also contribute to its noted action, that of acting as a coating. In this regard it acts to soothe the mouth, throat, stomach, and intestines.[70]

Barberry *(Berberis vulgaris)* (bark). *B. vulgaris* is native to most of Europe. Its root bark contains several isoquinoline alkaloids including berberine, berbamine, and oxyacanthin. The root bark is also a source of vitamin C (citric acid), and contains chelidonic, malic and tartaric acids.[72] It possesses mild diuretic qualities[73] and also has confirmed antiinflammatory properties.[74] Furthermore, studies have validated the antiinflammatory action of berberine, demonstrating a significant downregulation in the expression of proinflammatory genes including TNF, IL1, IL6, MCP-1, iNOS and COX2 with treatment.[75, 76]

Berberine, a major alkaloid of Barberry possesses anti-inflammatory properties, having demonstrated to effectively inhibit, in a dose- and time-dependent manner, COX-2 transcriptional activity in a malignancy cell model,[77] as well as to reduce prostaglandin E2 (PGE2) production. The latter effect was noted to also result in a reduction of COX-2 protein production.[78] In a separate study berberine was demonstrated to decrease both the expression and protein binding on the hypoxia-response element of the vascular endothelial growth factor (VEGF) (VEGF is a critical growth factor in tumor angiogenesis).[79] Based on *in vitro* studies, it was proposed that berberine's action *in vivo* may be 'in abolishing the angiogenic function of vascular endothelial cells, preventing them from responding to the call for angiogenesis, and may also prevent hypoxic tumor cells from inducing angiogenesis,' thus retarding cellular proliferation. In fact hypoxia induced VEGF expression was demonstrated to be completely inhibited by berberine.[80]

Myrrh *(Commiphora molmol)* (gum resin). *C. molmol* is a highly valued botanical medicine in Ayurveda, the Indian system of medicine, as represented by the wide variety of Ayurvedic formulas containing Myrrh. In Arab medicine, *C. molmol* is used as part of a polyherbal formulation to improve digestion and to treat gastrointestinal maladies.[81, 82, 83] Its action is attributed to its positive effect on inflammation.[84]

In studies utilizing myrrh, a wide range of inhibitory action against both Gram (+) and Gram (-) bacteria has been demonstrated.[85] Myrrh, in a dose-dependent manner, was also demonstrated to protect the gastric mucosa against the necrotizing effects of various agents. This protective action was attributed to its positive effect on mucus production, as well as to its ability to increase both nucleic acid production, and the concentration of non-protien sulfhydryl compounds, noted for both their involvement in maintaining gastroduodenal integrity, as well as in the protection they offer against chemically-induced lesions in cells, tissues and organs.[86, 87, 88] These actions were associated to Myrrh's ability to scavenge free radicals, as well to its thyroid-stimulating and prostaglandin-inducing properties.[89] Endogenously produced prostaglandins have been attributed to functioning as activators of potassium ATP channels, which was demonstrated in part to mediate gastroprotection.[90]

Oregon Grape *(Berberis aquifolium)* (root). The major components of Berberis are berberine, a yellow colored isoquineoline alkaloid, beramine and oxyacanthine, which are both white alkaloids, along with phytosterin, gum and sugar. As noted above the medicinal value of Berberis is thought to be due to its high content of isoquineoline alkaloids, especially berberine, which is postulated to have antibiotic activity.[91] Its actions are noted in promoting excretion and secretion, improving digestion and assimilation, and in stimulating the lymphatic system. It is documented as having an 'invigorating power over the gastric functions.'[92]

Minerals

Bismuth citrate. Bismuth is a naturally occurring mineral that has documented activity against *H. pylori*.[93, 94] Bismuth salts have been used extensively for the alleviation of gastrointestinal irritation, as well as for irritation of the stomach and bowels.[95] Standard preparations of bismuth are used to decrease the flow of fluids and electrolytes into the bowel, to reduce inflammation within the intestine, and may serve to alleviate diarrhea causing organism.[96] Preparations are recognized as safe when taken as directed.[97]

Bentonite clay: Bentonite is an absorptive and colloidal clay, demonstrated to be a very effective absorber of toxins.[98] In one study a hepato-nephro (liver-kidney) protective effect against aflatoxins was demonstrated with bentonite use, indicating that it 'diminished most of the deleterious effects of the aflatoxin.' This effect was attributed the suppressive effect it exerted against chromosomal aberrations.[99]

The inflammatory response to *H. pylori* is well documented, implicated to result in cellular proliferation and gastric mucosal damage. *H. pylori* components have been demonstrated to act directly on gastric epithelium and to induce an increased release of cytokines.[100] These actions have been primarily attributed to the upregulation of inflammatory markers, including COX-2 and IL-1β.[101] To curtail this deleterious effect on the gastric mucosa, a comprehensive blend of phytochemical nutrients, known to have a positive impact on the gastrointestinal tissues, may aide in healing and repairing these tissues. Select herbs are recognized as possessing anti-*pylori* activity, noted to downregulate inflammatory markers associated with *H. pylori* infestation and correlated to gastric inflammation. Additionally, the use of select herbal components has demonstrated a positive effect in reducing the antigens associated with *H. pylori.*

References

1. Savage DC. 1977. Microbial ecology of the human gastrointestinal tract. *Annu.Rev. Microbiol. 31:107–33.*
2. Cummings JH. Short chain fatty acids in the human colon. *Gut. 1981 22:763-779.*
3. Cummings JH, Macfarlane. A review: the control and consequences of bacterial fermentation in the human colon. *J. Appl. Bacteriol. 1991 70:443-459.*
4. Rerat A, Fiszlewick M, Giusi A, Vaugeland P. Influence of meal frequency on postprandial variation in the production and absorption of volatile fatty acids in the digestive tract of conscious pigs. *J. Anim. Sci. 1986 64:448-456.*
5. Rescigno M. Gut commensal flora: tolerance and homeostasis. *F1000 Biology Reports. 2009. 1:9.*
6. Kennedy RJ, Kirk SJ, Gardiner KR. Mucosal barrier function and the commensal flora. *Gut. 2002 March; 50(3): 441–442.*
7. Deslandres C. 13C urea breath testing to diagnose *Helicobacter pylori* infection in children. *Gan J Gastroenterol. 1999 Sept; 13 (7): 567-70.*
8. Baggett HC, Parkinson AJ, Muth PT, Gold BD, Gessner BD. Endemic iron deficiency associated with Helicobacter pylori infection among schoolaged children in Alaska. *Pediatrics. 2006 117:e396–404.*
9. Cardenas VM, Mulla ZD, Ortiz M, Graham DY. Iron deficiency and *Helicobacter pylori* infection in the United States. *Am J Epidemiol. 2006 163:127–34.*
10. Brown LM. *Helicobacter pylori:* Epidemiology and Routes of Transmission. *Epidemiol Rev. 22(2):283–97.*
11. Di Leo A *et al. Helicobacter pylori* infection and host cell responses. *Immunopharmacol Immunotoxicol 1999 Nov; 21(4):803-46.*
12. Fox, S. I. 1991. *Perspectives on Human Biology. Wm. C. Brown Publishers, Dubuque, IA. p. 380.*
13. Blaser, MJ. *Helicobacter pylori*: microbiology of a "slow" bacterial infection. *Trends Microbiol. 1993 1:255-260.*
14. Morris A, Nicholson G. Ingestion of *Campylobacter pylori* causes gastritis and raised fasting gastric pH. *Am J Gastroenterol. 1987 82:192-9.*
15. Cave DR, Vargas M. Effect of *Campylobacter pylori* protein on acid secretion by parietal cells. *Lancet 1989; ii: 187-9.*
16. Beil W, Birkholz C, Wagner S, Sewing K-F. Interaction of *Helicobacter pylori* and its fatty acids with parietal cells and gastric H+/K+-ATPase. *Gut 1994 35:1176-80.*
17. Wroblewski LE, Shen L, Ogden S, Romero-Gallo J, Lapierre LA, Israel DA, Turner JR, Peek RM Jr. *Helicobacter pylori* dysregulation of gastric epithelial tight junctions by urease-mediated myosin II activation. *Gastroenterology. 2009 Jan;136(1):236-46. Epub 2008 Oct 9.*
18. Fedwick JP, Lapointe TK, Meddings JB, Sherman PM, Buret AG. *Helicobacter pylori* activates myosin light-chain kinase to disrupt claudin-4 and claudin-5 and increase epithelial permeability. *Infect Immun. 2005 Dec;73(12):7844-52.*
19. Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and nonsteroidal antiinflammatory drugs in pepticulcer disease: A metaanalysis. *Lancet 2002;359:14–22.*
20. Taché Y. Saperas E. Potent Inhibition of Gastric Acid Secretion and Ulcer Formation by Centrally and Peripherally Administered Interleukin-1a. *Ann. NY Acad. Sci. 2006 664:353-368.*
21. Naunton M, Peterson GM, Bleasel MD. *J Clin Pharm & Therap. 2000 25(5):333-340.*
22. Marshall BJ, Barrett LJ, C. Prakash C, McCallum RW, Guerrant RL. Urea protects *Helicobacter (Campylobacter) pylori* from the bactericidal effect of acid. *Gastroenterology. 1990 99:697-702.*
23. Lee A, and Mitchell H. Basic bacteriology of *H. pylori: H. pylori* colonization factors. In *Helicobacter pylori*: Basic Mechanisms to Clinical Cure. *Hunt, RH and Tytgat GNJ, editors. Kluwer Academic Publishers, Boston. 1994 59-72.*
24. Chen G, Fournier RL, Varanasi S, Mahama-Relue PA. *Helicobacter pylori* survival in gastric mucosa by generation of a pH gradient. *Biophysical Journal. 1997 73(2):1081-1088.*
25. Kaneda Y, Torii M, Tanaka T, Aikawa M. *In vitro* effects of berberine sulfate on the growth and structure of Entamoeba histolytica, Giardia lamblia, and *Trichomonas vaginalis. Ann Trop Med Parasitol 1991;85:417-425.*
26. Schmeller T *et al.* Biochemical activities of berberine, palmatine and sanguinarine mediating chemical deference against microorganisms and herbivors. *Phytochemistry 1997 Jan; 44 (2): 257-66.*
27. Murray MT, Pizzorno Jr. JE. *Textbook of Natural Medicine Vol 1, pp 776.*
28. Bae EA, Han MJ, Kim NJ, Kim DH. Anti-*Helicobacter pylori* activity of herbal medicines. *Biol Pharm Bull. 1998 Sep;21(9):990-2.*
29. Jantova S, Cipak L, Letasiova S. Berberine induces apoptosis through a mitochondrial/caspase pathway in human promonocytic U937 cells. Toxicol *In Vitro. 2007 Feb;21(1):25-31. Epub 2006 Aug 25.*
30. Yamagish H. Interaction between nuclei acid and berberine sulfate. *J Cell Biol 1962; 15: 589-592.*
31. Jantova S, Cipak L, Cermakova, Kost'alova D. Effect of berberine on proliferation, cell cycle and apoptosis in HeLa and L1210 cells. *J Pharm Pharmacol 2003; 55: 1143-1149.*
32. Hoshi A, Ikekawa T, Ikeda Y, Shirakawa S, Ligo M, Karetani K, Fukoka F. Antitumor activity of berberrubine derivatives. *Gann 1976; 67: 321-325.*
33. Dai X, Yamasaki K, Yang L, Sayama K, Shirakata Y, Tokumara S, Yahata Y, Tohyama M, Hashimoto K. Keratinocyte G2/M growth arrest by 1,25-dihydroxyvitamin D3 is caused by Cdc2 phosphorylation through Wee1 and Myt1 regulation. *J Invest Dermatol. 2004; 122: 1356-1364.*
34. Donaldson KL, Goolsby G.L, Kiene PA, Wahl AF. Activation of p34cdc2 coincident with taxol-induced apoptosis. *Cell Growth Diff 1994; 5: 1041-1050.*
35. Wartenberg M, Budde P, De Marees M, Grunheck F, Tsang SY, Huang Y, Chen ZY, Hescheler J, Sauer H. Inhibition of tumor-induced angiogenesis and matrix-metalloproteinase expression in confrontation cultures of embryoid bodies and tumor spheroids by plant ingredients used in traditional Chinese medicine. *Lab Invest 2003; 83: 87-98.*
36. Grieve M. Indigo (Wild) A Modern Herbal Botanical.com.
37. Foster. S. & Duke. J. A. A Field Guide to Medicinal Plants. Eastern and Central N. America. Houghton Mifflin Co. 1990 ISBN 0395467225.
38. Bown. D. Encyclopaedia of Herbs and their Uses. Dorling Kindersley, London. 1995 ISBN 0-7513-020-31.
39. Weiner. M. A. Earth Medicine, Earth Food. Ballantine Books 1980 ISBN 0-449-90589-6.
40. Bown. D. Encyclopaedia of Herbs and their Uses. Dorling Kindersley, London. 1995 ISBN 0-7513-020-31.
41. http://www.herbaltransitions.com/materiamedica/Baptisia.htm
42. PDR for Herbal Medicines. 2000. Medical Economica Company, Inc. Gruenwald J, Brendler T, Jaenicke C, eds. Wild Indigo (*Baptisia tinctoria*). pp 812-813.
43. Greenfield J, Davis JM. Medicinal Herb Production Guide. North Carolina Consortium on Natural Medicines and Public Health. www.naturalmedicinesofnc.org.
44. Pompei R, Flore O, Marccialis MA, Pani A, Loddo B. Glycyrrhizic acid inhibits virus growth and inactivates virus particles. *Nature. 1979 Oct 25;281(5733):689-90.*
45. Pompei R, Pani A, Flore O, Marcialis MA, Loddo B. Antiviral activity of glycyrrhizic acid. *Experientia. 1980 Mar 15;36(3):304.*
46. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr H. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. *The Lancet. 2003 361(9374):2045-2046.*
47. Fiore C, Eisenhut M, Krausse R, Ragazzi E, Pellati D, Armanini D, Bielenberg J. Antiviral effects of Glycyrrhiza species. Phytother Res. *2008Feb;22(2):141-8.*
48 Li W, *et al.* Antimicorbial flavonoids from *Glycyrrhiza glabra* hairy root cultures. *Planta Med 1998 Dec; 64 (8): 746-7.*
49. Utsunomiya T, Kobayashi M, Pollard RB, Ito M, Suzuki F. International Conference on AIDS. 1998 12:29 (abstract no. 11234).
50. Guo N. [Protective effect of glycyrrhizine in mice with systemic *Candida albicans* infection and its mechanism.] [Article in Chinese] Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 1991 Oct;13(5):380-3.
51. Abe N, Ebina T, Ishida N. Interferon induction by glycyrrhizin and glycyrrhetinic acid in mice. *Microbiol. Immunol. 1982 26:535–539.*
52. Utsunomiya T, Kobayashi M, Pollard RB, Suzuki F. Glycyrrhizin, an active component of licorice roots, reduces morbidity and mortality of mice infected with lethal doses of influenza virus. *Antimicrob Agents Chemother. 1997 Mar;41(3):551-6.*
53. Itoh K, Kumagai K. Augmentation of NK activity by several antiinflammatory agents. *Excerpta Med. 1983 641:460–464.*
54. Finney RSH, Somers GH. The antiinflammatory activity of glycyrrhetinic acid and derivatives. *J. Pharmacol. 1959 10:613–620.*
55. Kim DH, Hong SW, Kim BT, Bae EA, Park HY, Han MJ. Biotransformation of glycyrrhizin by human intestinal bacteria and its relation to biological activities. *Arch-Pharm-Res. 2000 Apr; 23(2):172-7.*
56. Krausse R, Bielenberg J, Blaschek W, Ullmann U. I*n vitro* anti-*Helicobacter pylori* activity of Extractum liquiritiae, glycyrrhizin and its metabolites. *J Antimicrob Chemother. 2004 Jul;54(1):243-6. Epub 2004 Jun 9.*
57. Chung, JG.Inhibitory actions of glycyrrhizic acid on arylamine N-acetyltransferase activity in strains of *Helicobacter pylori* from peptic ulcer patients. *Drug and Chemical Toxicology. 1998 21;355–70.*
58. Butcher NJ, Boukouvala S, Sim E, Minchin RF. Pharmacogenetics of the arylamine N-acetyltransferases. *J. Pharmacogenetics. 2002 2(1):30-42.*
59. Kao T-C, Shyu M-H, Yen G-C. Neuroprotective Effects of Glycyrrhizic Acid and 18β-Glycyrrhetinic Acid in PC12 Cells via Modulation of the PI3K/Akt Pathway. *J. Agric. Food Chem. 2009 57(2):754–761.*
60. PDR for Herbal Medicines. 2000. Medical Economica Company, Inc. Gruewald J, Brendler T, Jaenicke C, eds. *Clove, Syzygium aromaticum. pp 195-196.*
61. Hussein G, Miyashiro H, Nakamura N, Hattori M, Kakiuchi N, Shimotohno K. Inhibitory effect of Sudanese medicinal plant extracts on hepatitis C virus (HCV) protease. *Phytother Res. 2000 14:510-6.*
62. Oya T, Osawa T, Kawakishi S. Spice constituents scavenging free radicals and inhibiting pentosidine formation in a model system. *Biosci Biotechnol*

Biochem. 1997 61:263-6.
63. Banerjee S, Das S. Anticarcinogenic Effects of an Aqueous Infusion of Cloves on Skin Carcinogenesis. *Asian Pacific J Cancer Prev, 2005 6:304308.*
64. Fu Y, Zu Y, Chen L, Shi X, Wang Z, Sun S, Efferth T. Antimicrobial activity of clove and rosemary essential oils alone and in combination. *Phytother Res. 2007 Oct;21(10):989-94.*
65. El Hag EA, El Nadi AH, Zaitoon AA. Toxic and growth retarding effects of three plant extracts on *Culex pipiens* larvae (Diptera : Culicidae). *Phytother Res. 1999 13:388-92.*
66. Al-Khayant MA, Blank G. Phenolic spice components sporostatic to *Bascillus subtillis. J Food Sc, 1985 50:971-4.*
67. Banerjee S, Das S. Anticarcinogenic effects of an aqueous infusion of cloves on skin carcinogenesis. *Asian Pac J Cancer Prev. 2005 Jul-Sep;6(3):304-8.*
68. Bhamarapravati S, Pendland SL, Mahady GB. Extracts of spice and food plants from thai traditional medicine inhibit the growth of the human carcinogen *Helicobacter pylori. In Vivo. 2003 17:541-4.*
69. http://www.naturalstandard.com. Clove (*Eugenia aromatica*) and clove oil (eugenol).
70. http://www.umm.edu/altmed/articles/slippery-elm-000274.htm
71. PDR for Herbal Medicines. 2000. Medical Economica Company, Inc. Gruenwald J, Brendler T, Jaenicke C, eds. *Slippery Elm, Ulmus ruba (fluva). pp 697.*
72. Murray MT, Pizzorno Jr. JE. Textbook of Natural Medicine. *Chemical Composition of Berberis vulgaris. pp 776.*
73. PDR for Herbal Medicines. 2000. Medical Economica Company, Inc. Gruenwald J, Brendler T, Jaenicke C, eds. *Barberry, Berberis vulgaris. pp 61-62.*
74. Ivanovska N. Philipov S. Study on the antiinflammatory action of *Berberis vulgaris* root extract, alkaloid fractions and pure alkaloids. *Int J Immunopharmacol 1996 Oct; 18 (10): 553-61.*
75. Jeong HW, Hsu KC, Lee JW, Ham M, Huh JY, Shin HJ, Kim WS, Kim JB. Berberine Suppresses Proinflammatory Responses through AMPK Activation in Macrophages. *Am J Physiol Endocrinol Metab. 2009 Feb 10. [Epub ahead of print].*
76. Chen FL, Yang ZH, Liu Y, Li LX, Liang WC, Wang XC, Zhou WB, Yang YH, Hu RM. Berberine inhibits the expression of TNF , MCP-1, and IL-6 in AcLDL-stimulated macrophages through PPAR pathway. *Endocrine. 2008 Nov 26. [Epub ahead of print]*
77. Fukuda K, Hibiya Y, Mutoh M, Koshiji M, Akao S, Fujiwara H. Inhibition by berberine of cyclooxygenase-2 transcriptional activity in human colon cancer cells. *Journal of Ethnopharmacology. August 1999 66(2):227-233.*
78. Kuoa CL, Chia CW, Liu TY. The antiinflammatory potential of berberine *in vitro* and *in vivo. Cancer Letters. 2004 203(2): 127-137.*
79. Papetti M and Herman IM. Mechanisms of normal and tumor-derived angiogenesis. *Am J Physiol. 2002 282:C947–C970.*
80. Lin S, Tsai SC, Lee CC, Wang BW, Liou JY, Shyu KG. Berberine inhibits HIF-1 expression via enhanced proteolysis. *Mol Pharmacol. 2004 Sep;66(3):612-9.*
81. Dymock, W., Warden, C.J.H., Hopper, D., 1890. Pharmacographia indica. In: Kegan, P. (Ed.), A History of the Principal Drugs of Vegetable Origin. Trench, Trubner and Co. Ltd, London, p. 330.
82. Anonymous, 1967. Unani Pharmacopoeia, vol. II. Indian Medicine Department, Government of Andha Pradesh, Hyderabad, India, p. 21 (in Urdu).
83. Chopra, R.N., Nayer, S.L., Chopra, K., 1956. Glossary of Indian Medicinal Plants. CSIR, New Delhi, India, p. 75.
84. Murray MT, Pizzorno Jr. JE. *Textbook of Natural Medicine. Commiphora Mukul. pp. 681.*
85. Saeed MA, Sabir AW. Antibacterial activities of some constituents from oleo-gum-resin of *Commiphora mukul. Fitoterapia. 2004 Mar;75(2):204-8.*
86. Szabo S, Trier JS, Frankel PW. Sulfhydryl compounds may mediate gastric cytoprotection. *Science. 1981 214: 200-202.*
87. Boyd SC, Sasame HA, Boyd MR. Gastric glutathione depletion and acute ulcerogenesis by diethylmaleate given subcutaneously to rats. *Life Sci. 1981 28:2987-2992.*
88. Hoppenkamps R, Thies E, Younes M, Siegers CP. Glutathione and GSH-dependent enzymes in the human gastric mucosa. *Klin Wochenschr 1984 62:183-186.*
89. Al-Harbi MM, Qureshi S, Raza M, Ahmed MM, Afzal M, Shah AH. Gastric antiulcer and cytoprotective effect of *Commiphora molmol* in rats. *J Ethnopharmacol. 1997 Jan;55(2):141-50.*
90. Peskar BM, Ehrlich K, Peskar BA. Role of ATP-sensitive potassium channels in prostaglandin-mediated gastroprotection in the rat. *J Pharmacol Exp Ther. 2002 Jun;301(3):969-74.*
91. Murray MT, Pizzorno Jr. JE. Pharmacology of Natural Medicine-Hydrastis Canadensis. *Textbook of Natural Medicine. pp 776.*
92. Felter HW, Lloyd JU. King's American Distensatory. *Eclectic Medical Publications. 18th Edition Vol. 1. 1983. p. 384.*
93. Colin-Jones DG. *Helicobacter pylori* - our knowledge is growing. *Postgrad Med J. 1990 66:801–802.*
94. Bland MV, Ismail S, Heinemann JA, Keenan JI. The action of bismuth against *Helicobacter pylori* mimics but is not caused by intracellular iron deprivation. *Antimicrobial Agents and Chemotherapy. 2004 48(6):1983-1988.*
95. Felter HW, Lloyd JU. King's American Dispensatory. Vol. II 1983. pp. 1156.
96. http://www.nlm.nih.gov/Bismuth Subsalicylate
97. Murray MT, Pizzorno Jr. JE. Maldigestion. *Textbook of Natural Medicine. pp 497.*
98. Gitipour S *et al.* The use of modified Bentonite for removal of aromatic organ ics from contaminated soil. *J Colloid Interface Sci 1997 Dec; 196 (2): 191-198.*
99. Adbel-Wahhab MA, Nada SA, Farag IM, Abbas NF, Amra HA. Potential protective effect of HSCAS and bentonite against dietary aflatoxicosis in rat: with special reference to chromosomal aberrations. *Natural Toxins. 1999 6(5):211-218.*
100. Rieder G, Hatz RA, Moran AP, Walz A, Stolte M, Enders G. Role of adherence in interleukin-8 induction in *Helicobacter pylori* - associated gastritis. *Infect Immun 1997; 65:3622±30.*
101. Bartchewsky W Jr, Martini MR, Masiero M, Squassoni AC, Alvarez MC, Ladeira MS, Salvatore D, Trevisan M, Pedrazzoli J Jr, Ribeiro ML. Effect of *Helicobacter pylori* infection on IL-8, IL-1beta and COX-2 expression in patients with chronic gastritis and gastric cancer. *Scand J Gastroenterol. 2009;44(2):153-61.*

Supplement Facts

Serving Size: 2 Capsules — **Servings Per Container: 90**

	Amount Per Serving	% Daily Value
Proprietary Blend	1,200 mg	*
Deglycyrrhized Licorice (Glycyrrhiza glabra) (root)		*
Bentonite Clay		*
Slippery Elm (Ulmus rubra) (bark)		*
Myrrh (Commiphora mol·mol) (gum resin)		*
Bismuth Citrate		*
Clove (Syzygium aromaticum) (flower bud)		*
Berberine HCl		*
Anise (Pimpinella anisum) (seed)		*
Barberry (Berberis vulgaris) (bark)		*
Oregon Grape (Mahonia aquifolium) (root)		*
Wild Indigo (Baptisia tinctoria) (root)		*

***Daily Value not established**

Other ingredients: Gelatin, water and glycerin.

RECOMMENDATION: Two (2) capsules taken two (2) or three (3) times each day as a dietary supplement or as otherwise directed by a healthcare professional.

Caution: Not recommended for pregnant or lactating women.

NDC# 55146-07705 Rev. 1/08

Product Adjuncts

Garlic Plus™. Sivam GP. Protection against *Helicobacter pylori* and other bacterial infections by garlic. *J Nutr. 2001 Mar;131(3s):1106S-8S.*

Gastrazyme™

Neutrophil Plus®. Nielsen H, Andersen LP. Chemotactic activity of *Helicobacter pylori* sonicate for human polymorphonuclear leucocytes and monocytes. *Gut 1992; 33:738-42.*

BIOTICS® RESEARCH CORPORATION
"The Best of Science and Nature"
www.bioticsresearch.com