Intestinal Support Nutrients

Monograph prepared by Rebecca Provorse ND, LAc

L-Glutamine
N-Acetyl Glucosamine
Larch arabinogalactan
Quercetin
Deglycyrrhized licorice (DGL)
Lactobacillus sporogenes
Ginkgo biloba Extract 50:1

INDICATIONS

- Repair of Increased Intestinal Permeability
- Maintenance of Normal Intestinal Permeability
- Inflammatory Bowel Disease
- Prevention and Treatment of Chemotherapy-associated gastritis and diarrhea
- Gastric or duodenal ulcers

L-Glutamine

Glutamine is one of the 20 amino acids that serve as building blocks for proteins. Once labeled "non-essential" (because the body is capable of making it), glutamine is now considered "conditionally essential" because under certain conditions the body is unable to make adequate amounts and thus needs to obtain it from outside sources.

Pharmacology

Glutamine is well known as the major fuel source for rapidly dividing cells such as enterocytes, macrophages and lymphocytes. Glutamine stimulates water and electrolyte absorption in the jejunum.[1]

Oral supplementation with glutamine reduces Interleukin – 6 (IL-6) & Interleukin – 8 (IL-8) in the intestinal mucosa. The mechanism for this decrease in pro-inflammatory cytokine production is proposed as a post-transcriptional pathway.[2] Glutamine ingestion also appears to induce heme oxygenase-1, a heat-shock protein associated with gut protection.[3] When given orally, l-glutamine can prevent the disruption of tight-junctions in colonic mucosa and the destruction of cellular DNA.[4,5]

Research Trials

- In a 2005 double blind, placebo-controlled, randomized clinical trial, burn victims receiving enteral nutrition were assessed as to the affects of glutamine supplementation on protein metabolism. Burn victims took glutamine granules (0.5 g/kg) orally for 14 days. Compared to controls, patients supplemented with glutamine were found to have increased protein synthesis, inhibited protein decomposition, improved wound healing and reduced hospital stays.[6]
- In a randomized, clinical trial on 35 HIV-positive men receiving antiretroviral chemotherapy, L-glutamine significantly reduced diarrhea when the subjects concurrently were taking probiotics and soluble fiber. In this study, the men receiving the co-therapy, were given probiotics (1.2g/d) and soluble fiber (11g/d) for four weeks. If diarrhea persisted at week 4, 30g/d L-Glutamine was added. 54% of the subjects required L-Glutamine and, once taken, the number of stools per day decreased significantly. In control subjects (those on anti-retroviral therapy alone), the incidence of diarrhea remained unchanged.[7]
- A 2005 clinical trial on malnourished children showed supplementation with glutamine (at isosmolar concentration for 10 days) improved intestinal barrier function, as measured by the lactulose/mannitol excretion ratio.[8]
- In a clinical trial on infants of very low birth weight (VLBW), parenteral glutamine supplementation (3.0 g/kg/d for at least 3 days) was associated with lower whole-body proteolysis.[9]
- In two 2005, randomized-clinical trials on infants of VLBW and infants after major digestive tract surgery, glutamine-enriched enteral nutrition did not appear to improve short-term outcomes at the doses given.

However, infectious morbidity was significantly lowered in infants of VLBW, who received glutamine-enriched enteral nutrition.[10,11]

- In a randomized-clinical trial on adults with gastric carcinoma who had undergone major surgery, participants were given enteral nutrition supplemented with glutamine, arginine and omega fatty acids. After a week of the nutritional support, patients in the supplemented group had higher levels of immunoglobulin, CD4 cell counts, CD4/CD8 ratio and Interleukin –2 (IL-2) than those in the control group, whereas markers of inflammation (Interleukin –6 and Tumor Necrosis Factor-alpha) were significantly lower in the supplemented group.[12]

Toxicology
There is no known side-effect profile. Insufficient data is available at this time to determine safety during pregnancy or lactation.

Interactions
There are no known interactions with L-glutamine.

N-Acetyl Glucosamine
Glucosamine and its derivatives, such as glucosamine sulfate and N-acetyl-D-glucosamine (NAG) have been recognized for years as useful in the treatment of osteoarthritis.[13,14,15,16] Glucosamine and NAG are the primary building blocks of connective tissue matrix (glycosaminoglycans, chondroitin and hyaluronic acid). Recently research has revealed that glucosamine is effective as an antioxidant and hemostatic agent.[17, 18]

Pharmacology
The half-life of glucosamine is relatively short (estimated at 15 hours)[19] and therefore a polymeric form (Poly-NAG) can be used with sustained presence in the blood. NAG & Poly-NAG are absorbed by way of first-pass metabolism and levels of glucosamine rise in the blood about 48 hours after oral ingestion of NAG or Poly-NAG. Due to this rise, it is believed that conversion to glucosamine occurs in vivo. Poly-NAG forms appear to be as effective as the NAG form.[20] Bioavailability of oral NAG appears to be approximately 26%.[21] In addition to serving a structural function, NAG acts as an antioxidant, by scavenging reactive oxygen species.[22]

Research Trials

- An FDA-approved glucosamine patch has been used in clinical trials for hemostasis in cardiac catheterization. The patch has proven to be extremely safe and effective.[17,18]
- In a randomized, double-blind animal study N-acetyl-glucosamine was found to be as effective as glue or other hemostatic agents in repairing bleeding canine esophageal or gastric varices.[23]
- In one animal study, N-acetyl-glucosamine was shown to reduce (and even prevent) colonization of Candida albicans in the duodenum. Efficacy of treatment was improved with earlier treatment (i.e. pre-inoculation). Amount of NAG given was not available.[24]

Toxicology
Reported short-term adverse effects include mild gastrointestinal problems, drowsiness, skin reactions, and headache.[21] One case of asthma exacerbation has been documented.[25] There is currently insufficient safety data available on the use of this ingredient during pregnancy and/or lactation.

Interactions
There are no known interactions with N-acetyl glucosamine.

Larch arabinogalactan
Larch arabinogalactan is extracted from Larix occidentalis (Western Larch). The larch is a fast growing, long-lived, deciduous conifer native to alpine and subalpine forests of the northwestern United States and adjacent Canada. Trees over 900 years old have been reported.[26]

Part(s) used traditionally
The bark, branches, gum and pitch (or sap) have all been used traditionally.

Pharmacology
Arabinogalactan is a highly branched polysaccharide consisting of a galactan backbone with side-chains of galactose and arabinose sugars. This polysaccharide functions as a stimulator of growth and development in plants and is used by humans as emulsifiers in the food industry.[27] It is a soluble dietary fiber, said to resist hydrolytic enzyme action thereby arriving, intact, in the large intestine where it is fermented by at least three strains of human Bacteroides.[28,29]

Research Trials
- A randomized, clinical trial was performed to test several gastrointestinal parameters in response to larch arabinogalactan. Subjects consumed 15 or 30 g in addition to their usual diet. Significant increases in total fecal anaerobes and in Lactobacillus spp. was observed when subjects consumed either dose for a total of six weeks. Fecal ammonia levels also decreased.[29]
- In one animal study, mice were injected with larch arabinogalactan daily for 7 or 14 days and then assessed for immune response. Immediately following the 7- or 14-day course, a decrease in bone marrow lymphoid and natural killer cells was observed relative to controls. However, after 14 days of exposure to the polysaccharide, NK cells in the bone marrow had returned to normal levels, but were increased in the spleen to levels greater than 2-fold that of control. The cause of these results may be due to the immunopoiesis- and hemopoiesis-inhibiting cytokines that are prevalent in the presence of these polysaccharides.[30]

Toxicology
There is no known side-effect profile. There is currently insufficient safety data available on the use of this ingredient during pregnancy and/or lactation.

Interactions
The constituents of larch arabinogalactan may increase immune function[31], which may alter the effects of certain medications whose mechanism of action is to suppress or alter the immune system. These drugs include: azathioprine, basiliximab, cyclosporine, daclizumab, glatiramer, muromonab-cd3, mycophenolate mofetil, tacrolimus (FK506), sirolimus, methotrexate, prednisone, hydrocortisone, methylprednisolone, prednisolone, betamethasone, budesonide, triamcinolone, dexamethasone and cortisone. No specific interactions are reported at this time.

Quercetin
Quercetin is a flavonoid present in plant foods. Flavonoids are responsible for the pigment in many vegetables and fruits. It is one of the most highly studied flavonoid compounds.

Pharmacology
Uptake of the five naturally occurring quercetin glycosides appears to occur by the small intestine, though rate is dependent on the sugar moiety. [32] Quercetin, itself, may be absorbed from the colon after deglycosylation.[33] Excretion of quercetin is primarily by way of the biliary system and is digested by the anaerobic bacterium Clostridium orbiscindens.[32,34]

Quercetin (and its glycosides) have demonstrated anti-bacterial activity against Bacillus cereus and Salmonella enteritidis.[35] It appears to decrease inflammation by strongly inhibiting both tyrosine phosphorylation (a proinflammatory cytokine message) and cell adhesion.[36]

Research Trials
Several in vitro and animal studies have shown quercetin to reduce inflammation and edema through the stabilization of histamine-containing mast cells.[37,38,39] The following studies are specific to gastrointestinal conditions:
- In several animal studies, mice and rats with experimental-induced colitis were given quercetrin, the glycone of quercetin. Beneficial effects included potentiation of water absorption (reduced diarrhea), reduced hyperplasia and decreased inflammatory markers for both acute and chronic conditions.[40,41,42.]
- In a clinical trial measuring the oxidative DNA damage when pretreated with bioflavonoids, quercetin was third most effective (after luteolin and myricetin) at reducing oxidative damage in human lymphocytes.

Quercetrin and other derivatives also demonstrated benefits. Given together, quercetin and vitamin C had additive effects.[43]

Toxicology
There is no known side-effect profile. There is currently insufficient safety data available on the use of this ingredient during pregnancy and/or lactation.

Interactions
At least one in-vitro study asserts that quercetin bears the ability to interfere with secretory intestinal transport (and therefore absorption of other drugs and nutrients), as it modulates transport proteins.[44] A synergistic affect has been shown between quercetin and the following: vitamin C, kaempferol, cisplatin, and genistein.[43,45,46,47,48]

Deglycyrrhized licorice
Deglycyrrhized licorice (DGL) is from the plant *glycyrrhiza glabra*. Glycerrhiza glabra (licorice) is indigenous to Greece, Turkey, Spain, Iraq, Russia and China. It has been used traditionally as an emmolient, demulcent, attenuant, expectorant and diuretic. As deglycyrrhized licorice (DGL), glycyrrhizin has been removed.

Part(s) used traditionally - The root of licorice is the primary part used medicinally.

Pharmacology
Glycyrrhizin, one of the active constituents of licorice, is a triterpenoid saponin. The standardization of licorice is based on glycyrrhizin content. Glycyrrhizin (also known as glycyrrhetic acid) is converted into glycyrrhetinic acid by an enzyme, glycaronidase. Glycyrrhizin and glycyrrhetinic acid have been shown to inhibit the enzyme 11 beta-hydroxysteroid dehydrogenase (11 beta-HSD), which interconverts cortisol to cortisone.[49] This allows cortisol to stimulate mineralocorticoid receptors, which can result in hypernatremia and hypokalemia.[50] People who have essential hypertension appear to be more sensitive to this inhibition than those who do not.[51]

The effectiveness of DGL in prevention and treatment of ulcers is apparently via a non-prostaglandin mediated mechanism.[52,53]

Research Trials
A number of studies have been performed analyzing the effects of licorice and/or its constituents on gastric and duodenal ulcers, but most are not available in English.

- In a randomized, controlled, double-blinded multicenter trial, patients with functional dyspepsia were treated with an herbal preparation containing extracts from bitter candy tuft, matricaria flower, peppermint leaves, caraway, licorice root and lemon balm. Those given the herbal preparation had significant improvement of their symptoms compared to those who were given placebo.[54]
- A retrospective study was done on 32 patients with chronic duodenal ulcer treated with DGL. Endoscopic examination revealed that the majority had normal gastric mucosa after treatment.[55]
- There is one study on the effects of DGL on healing of gastric ulcers, where no improvement was seen. However, the full study is not available for analysis.[56]
- Aspirin coated with licorice or its derivatives (including DGL) produces fewer gastric ulcers than aspirin alone when administered to rats in animal trials.[57]

Toxicology
Daily intake high doses (100 grams or more) of licorice--equivalent to 150mg of glycyrrhetinic acid--can cause a rise in blood pressure, more significantly in hypertensive than normotensive persons and more in women than men.[51] Hypokalemia, headache and peripheral edema have also been reported at higher doses.[58,59] Two cases of hypertension encephalopathy have also been described.[60] Consumption of high doses of glycyrrhizin (>500g/wk) was associated with an increased risk of pre-term (<34wks) births in multiple studies, but did not significantly affect maternal blood pressure.[61,62]

No studies have been performed showing DGL causing hypertension and, presumably, consumption of DGL will not cause these effects, as it is glycyrrhizin and its metabolite glycyrrhetenic acid, which have shown such effect in the research.

There is currently insufficient safety data available on the use of this ingredient during pregnancy and/or lactation.

Interactions No interactions have been described for DGL at this time.

Lactobacillus sporogenes

L. sporogenes is a gram-positive, spore-forming, lactic acid-producing bacillus.

Pharmacology

Nearly 100 species of lactic acid-producing bacteria have been isolated from dairy products and preserved meats. Some are found to inhibit other bacteria growth such as that of *Staphylococcus aureus, Escherichia coli, Pseudomonas fluorescens* and *Bacillus spp*.[63] Vaginally, the bacteria is found to have antagonistic activity against uropathogens.[64]

Part(s) used traditionally - The entire organism is the primary part used medicinally.

Research Trials

- A double-blind, randomized, multicenter trial was performed on 120 Italian children with active infections that required antibiotics. Subjects were treated for 10 days. The experimental group was given an unspecified amount of *Lactobacillus sporogenes* with fructo-oligosaccharides in addition to the antibiotic protocol. The control group was given a placebo with the antibiotic protocol. The results were compared. 71% of the evaluable experimental participants had no diarrhea. Of those that had diarrhea, the duration was significantly reduced.[65]

Toxicology

Rare Lactobacillemia has been reported, though it does not appear that these instances occurred with oral supplementation.[66] There is currently insufficient safety data available on the use of this ingredient during pregnancy and/or lactation.

Interactions

A synergistic effect in antimicrobial activity has been shown to exist between some antibiotics and some *Lactobacilli* species.[67] None are reported for *L. sporogenes*, specifically at this time.

Ginkgo biloba

The leaves and fruit of the *Ginkgo biloba* tree have been historically used by herbalists to treat a multitude of conditions. The herb has been widely studied in the treatment of mild inflammation, cardiovascular conditions and neuro-congitive disorders.

Pharmacology

Gingko contains flavone glycosides, mostly quercetin and kaempferol--the antioxidant properties of which have been well demonstrated. However, at high levels kaempferol may demonstrate pro-oxidant properties.[68] Ginkgolide terpenes naturally occur in the roots and leaves. The terpenes are specific and potent antagonists of platelet-activating factor (PAF), an inflammatory signal molecule.[69]

Protection of the gastric mucosa is hypothesized to be from one or more of the following mechanisms: 1)inhibition of lipid peroxidation; (2) preservation of gastrointestinal mucus and non-protein sulfhydryl groups; and (3) blockade of cell apoptosis.[70, 71] The latter mechanism has been studied, with respect to human gastric carcinoma—with very promising results.[72]

Parts used traditionally - Leaves, primarily. The fruit is also used in Traditional Chinese Medicine (TCM).

Research Trials

- A prospective clinical human trial in Thailand showed *Ginkgo biloba* to be effective in the treatment of acute hemorrhoid attacks, as bleeding, pain, tenesmus and discharge were improved. Information provided does not indicate if the treatments were oral or topical.[73]

- Animal studies show *Ginkgo* extract to have protective and regenerative effects against laboratory-induced gastric and duodenal ulcers in rats and mice.[70,71,74]
- *Ginkgo* biloba extract has also demonstrated anti-inflammatory and analgesic effects in rats. [75]

Toxicology - Transient mild headache, gastric upset and transient cyanosis of nails and lips have been reported in a few subjects.[76,77] Nausea, vomiting and seizures have been reported in children that have consumed the raw seeds of the *Ginkgo* fruit. Pyridoxal phosphate (2 mg/kg) is used to stop the seizures.[78] There is currently insufficient safety data available on the use of this ingredient during pregnancy and/or lactation.

Drug Interactions
In animal studies, *Ginkgo biloba* extract given with indomethacin, rofecoxib, celecoxib, dexamethasone, trimipramineor, haloperidol, cyclosporin A or melatonin resulted in an additive effect.[75,79,80,81] There is mixed evidence regarding the effects of ginkgo on bleeding time. Fifteen cases have been reported of bleeding events where the patients were also using ginkgo. However, a 2005 review of those cases cited thirteen of them to have other risk factors.[82] Some available research shows that *Ginkgo* does not appear to significantly affect clotting status and/or the pharmacokinetics or pharmacodynamics of Warfarin in healthy subjects.[83,84]

Recommended Daily Intake

L-Glutamine	**600-1200mg 3-4 x a day**
N-Acetyl Glucosamine	**400-800mg 3-4 x a day**
Larch arabinogalactan	**150-300mg 3-4 x a day**
Quercetin	**100-200mg 3-4 x a day**
Deglycyrrhized licorice (DGL)	**80-160mg 3-4 x a day**
Lactobacillus sporogenes	**50-100mg 3-4 x a day**
Ginkgo biloba Extract 50:1	**40-80mg 3-4 x a day**

[1] Coeffier M, Hecketsweiler B, Hecketsweiler P, et al. Effect of glutamine on water and sodium absorption in human jejunum at baseline and during PGE1-induced secretion. *J Appl Physiol*. 2005 Jun;98(6):2163-8.
[2] Williams R, Olivi S, Li CS, et al. Oral glutamine supplementation decreases resting energy expenditure in children and adolescents with sickle cell anemia. *J Pediatr Hematol Oncol*. 2004 Oct;26(10):619-25.
[3] Coeffier M, Le Pessot F, Leplingard A, et al. Acute enteral glutamine infusion enhances heme oxygenase-1 expression in human duodenal mucosa. *J Nutr*. 2002 Sep;132(9):2570-3.
[4] Basuroy S, Sheth P, Mansbach CM, et al. Acetaldehyde disrupts tight junctions and adherens junctions in human colonic mucosa: protection by EGF and L-glutamine. *Am J Physiol Gastrointest Liver Physiol.* 2005 Aug;289(2):G367-75.
[5] Sestili P, Giacomoni PU, Cattabeni F, et al. L-glutamine prevents the L-histidine-mediated enhancement of hydrogen peroxide-induced cytotoxicity. *Biochem Pharmacol.* 1992 Dec 15;44(12):2418-21.
[6] Peng X, Yan H, You Z, et al. Clinical and protein metabolic efficacy of glutamine granules-supplemented enteral nutrition in severely burned patients. *Burns*. 2005 May;31(3):342-6.
[7] Heiser CR, Ernst JA, Barrett JT, et al. Probiotics, soluble fiber, and L-Glutamine (GLN) reduce nelfinavir (NFV)- or lopinavir/ritonavir (LPV/r)-related diarrhea. *J Int Assoc Physicians AIDS Care*. 2004 Oct-Dec;3(4):121-9.
[8] Lima AA, Brito LF, Ribeiro HB, et al. Intestinal barrier function and weight gain in malnourished children taking glutamine supplemented enteral formula. *J Pediatr Gastroenterol Nutr*. 2005 Jan;40(1):28-35.
[9] Kalhan SC, Parimi PS, Gruca LL, et al. Glutamine supplement with parenteral nutrition decreases whole body proteolysis in low birth weight infants. *J Pediatr*. 2005 May;146(5):642-7.
[10] van den Berg A, van Elburg RM, Westerbeek EA, et al. Glutamine-enriched enteral nutrition in very-low-birth-weight infants and effects on feeding tolerance and infectious morbidity: a randomized controlled trial. *Am J Clin Nutr*. 2005 Jun;81(6):1397-404.
[11] Albers MJ, Steyerberg EW, Hazebroek FW, et al. Glutamine supplementation of parenteral nutrition does not improve intestinal permeability, nitrogen balance, or outcome in newborns and infants undergoing digestive-tract surgery: results from a double-blind, randomized, controlled trial. *Ann Surg*. 2005 Apr;241(4):599-606.
[12] Chen da W, Wei Fei Z, Zhang YC, et al. Role of enteral immunonutrition in patients with gastric carcinoma undergoing major surgery. *Asian J Surg*. 2005 Apr;28(2):121-4.
[13] Bruyere O, Pavelka K, Rovati LC et al. Glucosamine sulfate reduces osteoarthritis progression in postmenopausal women with knee osteoarthritis: evidence from two 3-year studies. *Menopause*. 2004 Mar-Apr;11(2):134-5
[14] Cohen M, Wolfe R, Mai T, et al. A randomized, double blind, placebo controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for osteoarthritis of the knee. *J Rheumatol.* 2003 Mar;30(3):523-8.
[15] Rubin BR, Talent JM, Kongtawelert P et al. Oral polymeric N-acetyl-D-glucosamine and osteoarthritis. *J Am Osteopath Assoc.* 2001 Jun;101(6):339-44.
[16] Muller-Fassbender H, Bach GL, Haase W, et al. Glucosamine sulfate compared to ibuprofen in osteoarthritis of the knee. *Osteoarthritis Cartilage.* 1994 Mar;2(1):61-9.

[17] Nader RG, Garcia JC, Drushal K, et al. Clinical evaluation of SyvekPatch in patients undergoing interventional, EPS and diagnostic cardiac catheterization procedures. *J Invasive Cardiol.* 2002 Jun;14(6):305-7.
[18] Najjar SF, Healey NA, Healey CM, et al. Evaluation of poly-N-acetyl glucosamine as a hemostatic agent in patients undergoing cardiac catheterization: a double-blind, randomized study. *J Trauma*. 2004 Jul;57(1 Suppl):S38-41.
[19] Persiani S, Roda E, Rovati LC, et al. Glucosamine oral bioavailability and plasma pharmacokinetics after increasing doses of crystalline glucosamine sulfate in man. *Osteoarthritis Cartilage.* 2005 Dec;13(12):1041-9.
[20] Talent JM, Gracy RW. Pilot study of oral polymeric N-acetyl-D-glucosamine as a potential treatment for patients with osteoarthritis. *Clin Ther.* 1996 Nov-Dec;18(6):1184-90.
[21] Barclay TS, Tsourounis C, McCart GM. Glucosamine. *Ann Pharmacother.* 1998 May; 32(5):602-3
[22] Sato H, Takahashi T, Ide H, et al. Antioxidant activity of synovial fluid, hyaluronic acid, and two subcomponents of hyaluronic acid. Synovial fluid scavenging effect is enhanced in rheumatoid arthritis patients. *Arthritis Rheum.* 1988 Jan;31(1):63-71.
[23] Jensen DM, Machicado GA, Hirabayashi K. Randomized double-blind studies of polysaccharide gel compared with glue and other agents for hemostasis of large veins and bleeding canine esophageal or gastric varices. *J Trauma.* 2004 Jul;57(1 Suppl):S33-7.
[24] Ghannoum MA, Abu-Elteen K, Ibrahim A, et al. Protection against Candida albicans gastrointestinal colonization and dissemination by saccharides in experimental animals. *Microbios.* 1991;67(271):95-105. [abstract]
[25] Tallia AF, Cardone DA. Asthma exacerbation associated with glucosamine-chondroitin supplement. J *Am Board Fam Pract.* 2002 Nov-Dec;15(6):481-4.
[26] Fiedler, CE.; Lloyd, DA. Autecology and synecology of western larch 1995. In: USDA Forest Service Website at: http://www.fs.fed.us/database/feis/plants/tree/larocc
[27] Showalter AM. Arabinogalactan-proteins: structure, expression and function. *Cell Mol Life Sci.* 2001 Sep;58(10):1399-417.
[28] Salyers AA, Vercellotti JR, West SE, et al. Fermentation of mucin and plant polysaccharides by strains of Bacteroides from the human colon. *Appl Environ Microbiol.* 1977 Feb;33(2):319-22.
[29] Robinson RR, Feirtag J, Slavin JL. Effects of dietary arabinogalactan on gastrointestinal and blood parameters in healthy human subjects. *J Am Coll Nutr.* 2001 Aug;20(4):279-85.
[30] Currier NL, Lejtenyi D, Miller SC. Effect over time of in-vivo administration of the polysaccharide arabinogalactan on immune and hemopoietic cell lineages in murine spleen and bone marrow. *Phytomedicine.* 2003 Mar;10(2-3):145-53.
[31] [1] Hauer J, et al. Mechanism of Stimulation of Human Natural Killer Cytotoxicity by Arabinogalactan from Larix occidentalis. *Cancer Immunol Immunother.* 1993;36(4):237-44.
[32] Arts IC, Sesink AL, Faassen-Peters M, et al. The type of sugar moiety is a major determinant of the small intestinal uptake and subsequent biliary excretion of dietary quercetin glycosides. *Br J Nutr.* 2004 Jun;91(6):841-7.
[33] Hollman PC, Bijsman MN, van Gameren Y, et al. The sugar moiety is a major determinant of the absorption of dietary flavonoid glycosides in man. *Free Radic Res.* 1999 Dec;31(6):569-73.
[34] Schoefer L, Mohan R, Schwiertz A, et al. Anaerobic degradation of flavonoids by Clostridium orbiscindens. *Appl Environ Microbiol.* 2003 Oct;69(10):5849-54.
[35] Arima H, Ashida H, Danno G. Rutin-enhanced antibacterial activities of flavonoids against Bacillus cereus and Salmonella enteritidis. *Biosci Biotechnol Biochem.* 2002 May;66(5):1009-14.
[36] Stefanescu M, Matache C, Onu A, et al. Modulation of cell adhesion by tyrosine kinases and phosphatases inhibitors. *Roum Arch Microbiol Immunol.* 1997 Jan-Jun;56(1-2):3-15.
[37] Guardia T, Rotelli AE, Juarez AO, et al. Anti-inflammatory properties of plant flavonoids. Effects of rutin, quercetin and hesperidin on adjuvant arthritis in rat. *Farmaco.* 2001 Sep;56(9):683-7.
[38] Rotelli AE, Guardia T, Juarez AO, et al. Comparative study of flavonoids in experimental models of inflammation. *Pharmacol Res.* 2003 Dec;48(6):601-6.
[39] Otsuka H, Inaba M, Fujikura T, et al. Histochemical and functional characteristics of metachromatic cells in the nasal epithelium in allergic rhinitis: studies of nasal scrapings and their dispersed cells. *J Allergy Clin Immunol.* 1995 Oct;96(4):528-36.
[40] Galvez J, Sanchez de Medina F, Jimenez J, et al. Effect of quercitrin on lactose-induced chronic diarrhoea in rats. *Planta Med.* 1995 Aug;61(4):302-6.
[41] Sanchez de Medina F, Galvez J, Romero JA et al. Effect of quercitrin on acute and chronic experimental colitis in the rat. *J Pharmacol Exp Ther.* 1996 Aug;278(2):771-9.
[42] Sanchez de Medina F, Vera B, Galvez J, et al. Effect of quercitrin on the early stages of hapten induced colonic inflammation in the rat. *Life Sci.* 2002 May 17;70(26):3097-108.
[43] Noroozi M, Angerson WJ, Lean ME. Effects of flavonoids and vitamin C on oxidative DNA damage to human lymphocytes. *Am J Clin Nutr.* 1998 Jun;67(6):1210-8.
[44] Ofer M, Wolffram S, Koggel A, et al. Modulation of drug transport by selected flavonoids: Involvement of P-gp and OCT? *Eur J Pharm Sci.* 2005 Jun;25(2-3):263-71.
[45] Ackland ML, van de Waarsenburg S, Jones R. Synergistic antiproliferative action of the flavonols quercetin and kaempferol in cultured human cancer cell lines. *In Vivo.* 2005 Jan-Feb;19(1):69-76.
[46] Kuhlmann MK, Horsch E, Burkhardt G, et al. Reduction of cisplatin toxicity in cultured renal tubular cells by the bioflavonoid quercetin. *Arch Toxicol* 1998 Jul-Aug;72(8):536-540.
[47] Scambia G, Ranelletti FO, Benedetti Panici P, Bonanno G, De Vincenzo R, Piantelli M, Mancuso S. Synergistic antiproliferative activity of quercetin and cisplatin on ovarian cancer cell growth. *Anticancer Drugs.* 1990 Oct;1(1):45-48.
[48] Shen F, Weber G. Synergistic action of quercetin and genistein in human ovarian carcinoma cells. *Oncol Res.* 1997;9(11-12):597-602.
[49] Edwards CR, Benediktsson R, Lindsay RS, et al. 11 beta-Hydroxysteroid dehydrogenases: key enzymes in determining tissue-specific glucocorticoid effects. *Steroids.* 1996 Apr;61(4):263-9.
[50] Serra A, Uehlinger DE, Ferrari P, et al. Glycyrrhetinic acid decreases plasma potassium concentrations in patients with anuria. *J Am Soc Nephrol.* 2002 Jan;13(1):191-6.
[51] Sigurjonsdottir HA, Manhem K, Axelson M, et al. Subjects with essential hypertension are more sensitive to the inhibition of 11 beta-HSD by liquorice. *J Hum Hypertens.* 2003 Feb;17(2):125-31.

[52] Bennett A, Melhuish PB, Stamford IF. Carbenoxolone and deglycyrrhized liquorice have little or no effect on prostanoid synthesis by rat gastric mucosa ex vivo. *Br J Pharmacol.* 1985 Nov;86(3):693-5.
[53] Bennett A. Gastric mucosal formation of prostanoids and the effects of drugs. *Acta Physiol Hung.* 1984;64(3-4):215-7.
[54] Madisch A, Holtmann G, Mayr G, et al. Treatment of functional dyspepsia with a herbal preparation. A double-blind, randomized, placebo-controlled, multicenter trial. *Digestion.* 2004;69(1):45-52.
[55] Larkworthy W, Holgate PF. Deglycyrrhizinized liquorice in the treatment of chronic duodenal ulcer. A retrospective endoscopic survey of 32 patients. *Practitioner.* 1975 Dec;215(1290):787-92.
[56] Bardhan KD, Cumberland DC, Dixon RA, et al. Clinical trial of deglycyrrhizinised liquorice in gastric ulcer. Gut. 1978 Sep;19(9):779-82.
[57] Dehpour AR, Zolfaghari ME, Samadian T, et al. The protective effect of liquorice components and their derivatives against gastric ulcer induced by aspirin in rats. *J Pharm Pharmacol.* 1994 Feb;46(2):148-9.
[58] Epstein MT, Espiner EA, Donald RA, et al. Effect of eating liquorice on the renin-angiotensin aldosterone axis in normal subjects. *Br Med J.* 1977 Feb 19;1(6059):488-90.
[59] Bernardi M, D'Intino PE, Trevisani F, et al. Effects of prolonged ingestion of graded doses of licorice by healthy volunteers. *Life Sci.* 1994;55(11):863-72.
[60] Russo S, Mastropasqua M, Mosetti MA, et al. Low doses of liquorice can induce hypertension encephalopathy. Am J Nephrol. 2000 Mar-Apr;20(2):145-8.
[61] Strandberg TE, Andersson S, Jarvenpaa AL, et al. Preterm birth and licorice consumption during pregnancy. *Am J Epidemiol.* 2002 Nov 1;156(9):803-5.
[62] Strandberg TE, Jarvenpaa AL, Vanhanen H, et al. Birth outcome in relation to licorice consumption during pregnancy. *Am J Epidemiol.* 2001 Jun 1;153(11):1085-8.
[63] Davila E, Zamora LM, Pla M, et al. Identification and antagonistic activity of lactic acid bacteria occurring in porcine blood from industrial slaughterhouses-a preliminary study. *Int J Food Microbiol.* 2005 Nov 5
[64] Kale VV, Trivedi RV, Wate SP, et al. Development and evaluation of a suppository formulation containing lactobacillus and its application in vaginal diseases. *Ann N Y Acad Sci.* 2005 Nov;1056:359-65.
[65] La Rosa M, Bottaro G, Gulino N, et al. Prevention of antibiotic-associated diarrhea with Lactobacillus sporogens and fructo-oligosaccharides in children. A multicentric double-blind vs placebo study. *Minerva Pediatr.* 2003 Oct;55(5):447-52. [Article in Italian. Abstract in English.]
[66] Bayer AS, Chow AW, Betts D, et al. Lactobacillemia--report of nine cases. Important clinical and therapeutic considerations. *Am J Med.* 1978 May;64(5):808-13.
[67] Bayer AS, Chow AW, Morrison JO, et al. Bactericidal synergy between penicillin or ampicillin and aminoglycosides against antibiotic-tolerant lactobacilli. *Antimicrob Agents Chemother.* 1980 Mar;17(3):359-63.
[68] Hibatallah J, Carduner C, Poelman MC. In-vivo and in-vitro assessment of the free-radical-scavenger activity of Ginkgo flavone glycosides at high concentration. *J Pharm Pharmacol.* 1999 Dec;51(12):1435-40.
[69] Braquet P, Hosford D. Ethnopharmacology and the development of natural PAF antagonists as therapeutic agents. *J Ethnopharmacol.* 1991 Apr;32(1-3):135-9.
[70] Chen SH, Liang YC, Chao JC, et al. Protective effects of Ginkgo biloba extract on the ethanol-induced gastric ulcer in rats. *World J Gastroenterol.* 2005 Jun 28;11(24):3746-50.
[71] Chao JC, Hung HC, Chen SH, et al. Effects of Ginkgo biloba extract on cytoprotective factors in rats with duodenal ulcer. *World J Gastroenterol.* 2004 Feb 15;10(4):560-6.
[72] Xu AH, Chen HS, Sun BC, et al. Therapeutic mechanism of ginkgo biloba exocarp polysaccharides on gastric cancer. *World J Gastroenterol.* 2003 Nov;9(11):2424-7.
[73] Sumboonnanonda K, Lertsithichai P. Clinical study of the Ginko biloba--Troxerutin-Heptaminol Hce in the treatment of acute hemorrhoidal attacks. *J Med Assoc Thai.* 2004 Feb;87(2):137-42.[abstract only]
[74] Wang Q, Zhao WZ, Ma CG. Protective effects of Ginkgo biloba extract on gastric mucosa. *Acta Pharmacol Sin.* 2000 Dec;21(12):1153-6.
[75] Abdel-Salam OM, Baiuomy AR, El-batran S, et al. Evaluation of the anti-inflammatory, anti-nociceptive and gastric effects of Ginkgo biloba in the rat. *Pharmacol Res.* 2004 Feb;49(2):133-42.
[76] Cesarani A, Meloni F, Alpini D, et al. Ginkgo biloba (EGb 761) in the treatment of equilibrium disorders. *Adv Ther.* 1998 Sep-Oct;15(5):291-304.
[77] Peters H, Kieser M, Holscher U. Demonstration of the efficacy of ginkgo biloba special extract EGb 761 on intermittent claudication--a placebo-controlled, double-blind multicenter trial. *Vasa.* 1998 May;27(2):106-10.
[78] Kajiyama Y, Fujii K, Takeuchi H, et al. Ginkgo seed poisoning. *Pediatrics.* 2002 Feb;109(2):325-7.
[79] Hemmeter U, Annen B, Bischof R, et al. Polysomnographic effects of adjuvant ginkgo biloba therapy in patients with major depression medicated with trimipramine. *Pharmacopsychiatry.* 2001 Mar;34(2):50-9.
[80] Zhou D, Zhang X, Su J, et al. The effects of classic antipsychotic haloperidol plus the extract of ginkgo biloba on superoxide dismutase in patients with chronic refractory schizophrenia. *Chin Med J (Engl).* 1999 Dec;112(12):1093-6.
[81] Mahmoud F, Abul H, Onadeko B, et al. In vitro effects of Ginkgolide B on lymphocyte activation in atopic asthma: comparison with cyclosporin A. *Jpn J Pharmacol.* 2000 Jul;83(3):241-5.
[82] Bent S, Goldberg H, Padula A, et al. Spontaneous bleeding associated with ginkgo biloba: a case report and systematic review of the literature: a case report and systematic review of the literature. *J Gen Intern Med.* 2005 Jul;20(7):657-61.
[83] Kim SH, Lee EK, Chang JW, et al. Effects of Ginkgo biloba on haemostatic factors and inflammation in chronic peritoneal dialysis patients. *Phytother Res.* 2005 Jun;19(6):546-8.
[84] Jiang X, Williams KM, Liauw WS, et al. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br J Clin Pharmacol.* 2005 Apr;59(4):425-32.