

# Protectagen™ (with AC-11®)

## Powerful Botanical Support for Inflammation, DNA Repair, Immune Function, and Gastrointestinal Healing

### DESCRIPTION

Protectagen™ is an advanced approach to boosting the body's natural defenses against environmental stress, inflammation, infection, and aging. Protectagen™ contains AC-11®, a patented hot-water extract of *Uncaria tomentosa*, commonly known as cat's claw, rich in phytochemical compounds called carboxyl alkyl esters. These patent process carboxyl alkyl esters (CAE™) are potent antioxidants and possess a unique capacity to attenuate inflammatory responses while promoting DNA repair and immunocompetence. AC-11® supports cellular resistance to a wide variety of environmental stressors and may be particularly beneficial for gastrointestinal healing. Each vegetarian Protectagen™ capsule provides 350 mg of AC-11® standardized to contain 8-10% carboxyl alkyl esters and ultra-filtered to remove all potentially harmful, high-molecular weight compounds such as conjugated tannins and alkaloids.

### OVERVIEW

Chronic stress, inadequate nutrition, gut dysbiosis, and environmental toxin exposure induce indiscriminate damage to cells and tissues by heightening free radical activity, activating inflammatory cytokines, and inhibiting the body's natural DNA repair mechanisms. Mounting evidence suggests these noxious influences give rise to accelerated aging, impaired immunity, and the onset of many degenerative diseases. Environmental stressors and pathogens can be particularly damaging to the delicate gastrointestinal lining, disrupting its protective barrier function and predisposing to infectious and/or inflammatory disorders. *Uncaria tomentosa* is rich in phytochemical compounds that operate at the molecular level to enhance cellular defense mechanisms, modulate inflammatory responses, repair DNA, boost immunocompetency, and promote gastrointestinal healing.

#### *Uncaria tomentosa* Background and Pharmacology

*Uncaria tomentosa* is a thorny, climbing vine indigenous to South and Central America. For millennia, hot-water extracts of the bark and roots of *Uncaria tomentosa* have been used in traditional medicine by cultures of the Amazonian River Basin for ailments including immunologic, inflammatory, and gastrointestinal disorders. Phytochemical assays have identified over 50 bioactive compounds in cat's claw and related *Uncaria* species including alkaloids, phytosterols, polyphenols, triterpenes, and carboxyl alkyl esters. For a number of years, research focused primarily on the pharmacological activity of pentacyclic oxindole alkaloids (POAs) and tetracyclic oxindole alkaloids (TOAs) in *Uncaria tomentosa* because solvent extractions of the herb produce relatively high concentrations of these compounds. Preliminary research suggested *Uncaria tomentosa* preparations with high levels of POAs were capable of exerting immunoregulatory and anti-inflammatory activity, but subsequent studies revealed the bioactivity of cat's claw is largely unrelated to its alkaloid content and more likely derives from the presence of other chemical components such as carboxyl alkyl esters. This finding is consistent with observations that indigenous cultures used water extractions of *Uncaria tomentosa* which naturally contain far higher concentrations of carboxyl alkyl esters than the poorly hydrosoluble oxindole alkaloids.

While the full range of carboxyl alkyl esters in *Uncaria tomentosa* has not been elucidated, quinic acid esters are believed to constitute the most important bioactive fraction of carboxyl alkyl esters. Quinic acid is a ubiquitous plant constituent essential to the formation of health-promoting phytonutrients such as chlorogenic acid and other polyphenolic compounds. Chlorogenic acid and polyphenols are well-established antioxidants that exert a range of health benefits including anti-inflammatory, antihyperglycemic, antihypertensive, antiobesity, vasoprotective, and chemopreventive effects. Quinic acid and quinic acid esters can also be metabolized by intestinal microflora to essential nutrients such as tryptophan and nicotinamide (vitamin B<sub>3</sub>) and a range of other health protective substances including caffeic and ferulic acids. Studies suggest that up to 90% of the bioactivity of cat's claw may be due to carboxyl alkyl esters, and that a significant portion of this activity is due to the presence of quinic acid and its patented esters.



## Physiological Benefits

### Antioxidant Effects

One of the principal benefits of the concentrated AC-11® aqueous extract of *Uncaria tomentosa* is its potent antioxidant activity. Studies indicate *Uncaria tomentosa* extracts offer protection from a number of different free radical species. *In vitro*, *Uncaria tomentosa* effectively scavenges peroxynitrite, an oxidant and nitrosating agent capable of damaging a variety of cellular structures including DNA. Aqueous *Uncaria tomentosa* extracts also efficiently scavenge superoxide and hydroxyl radicals and protect biological membranes from lipid peroxidation. In cytotoxicity assays, *Uncaria tomentosa* protects cells against both ultraviolet irradiation and chemical oxidation by the radical DPPH (1,1-diphenyl-2-picrylhydrazyl).

### Anti-inflammatory Effects

In addition to its antioxidant properties, *Uncaria tomentosa* attenuates inflammatory processes in the body by modulating the activity of nuclear factor-kappa beta (NF-κB). NF-κB is a pivotal mediator in the induction of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins-1, 2, 6, and 8. *In vitro* and *in vivo* studies indicate cat's claw effectively inhibits NF-κB activity and dampens inflammatory responses. *In vitro*, water extracts of *Uncaria tomentosa* have been shown to reduce activation of NF-κB by up to 50%. *Uncaria tomentosa* extract has also been shown to inhibit production of NF-κB's downstream inflammatory cytokine TNF-α by 65-85%. These biochemical restraints on inflammatory processes translate into measurable anti-inflammatory activity *in vivo*. In a mouse model of ozone-induced acute pulmonary inflammation, 8-day pre-treatment with a decoction (hot-water extract) of *Uncaria tomentosa* significantly reduced levels of neutrophilic infiltration, protein accumulation, and epithelial cell necrosis in bronchiolar tissue and lavage samples. In a rat model of indomethacin-induced enteritis, oral administration of aqueous *Uncaria tomentosa* extract significantly diminished the inflammatory response and prevented the pronounced disruption of intestinal mucosal architecture observed in rats treated with indomethacin alone.

### DNA Repair

One of the more intriguing characteristics of carboxyl alkyl esters found in AC-11® are their capacity to promote DNA repair. DNA damage is caused mainly by exposure to oxygen, nitrogen, and lipid radicals and is often a precursor to mutagenesis and/or cell death. Cells have a number of mechanisms for repairing DNA, but these processes can be downregulated by oxidative stress and inflammation. *Uncaria tomentosa* AC-11® preserves cellular DNA reparative processes through its dual antioxidative and anti-inflammatory activities. Living cells exposed to UVB radiation exhibit a variety of DNA lesions including thymine-thymine dimers (TT-dimers). *In vitro*, co-culturing of human keratinocytes with a water extract of *Uncaria tomentosa* previously called C-Med-100® (later renamed AC-11®) significantly reduced the percentage of cells exhibiting TT-dimers 24 hours post-UVB irradiation. In rats, AC-11® markedly increased the repair of single-strand and double-strand DNA breaks in the splenic cells of rats exposed to whole body gamma irradiation. And in humans, administration of either 250 or 350 mg/day of AC-11® for 6-8 weeks significantly enhanced the repair of peroxide-induced single-strand DNA breaks measured in peripheral blood lymphocytes.

### Immune Support

*Uncaria tomentosa* has traditionally been used for a variety of immune-related disorders and modern research confirms that carboxyl alkyl ester-rich botanical extracts exert important immunomodulatory activity. Preclinical and clinical data show *Uncaria tomentosa* aqueous extracts enhance the proliferation and survival of a broad range of immune cells. In mice, supplementation of AC-11® significantly and dose-dependently increases numbers of splenic T cells, B cells, and NK cells. In rats with chemically induced leukopenia, administration of AC-11® was shown to be as effective as the granulocyte colony-stimulating factor Neupogen® in promoting the recovery of leukocyte populations. Interestingly, while Neupogen® elevated only neutrophil levels, *Uncaria tomentosa* exerted much broader immunostimulatory activity by proportionally increasing all white blood cell fractions. In a study involving mice infected with the pathogen *Listeria monocytogenes*, pre-treatment with *Uncaria tomentosa* extract significantly prevented the depletion of bone marrow immunocyte progenitor cells. By enhancing the reserve of myeloid progenitors, *Uncaria tomentosa* increased the percentage of surviving animals from 0% in the control group to up to 35% in the *Uncaria tomentosa* pre-treated group. In humans, *Uncaria tomentosa* has been shown to boost both cell-mediated and humoral immunity. In one trial, supplementation of healthy adult males with 350 mg/day of AC-11® for 6 weeks significantly increased total white blood cell counts in a grouped analysis. In another trial, administration of 350 mg of AC-11® twice daily for 2 months significantly prolonged antibody responses to pneumococcal vaccine in 11 healthy subjects.

The stimulatory effect of cat's claw on immunocompetence can be attributed in part to its ability to scavenge free radicals and promote DNA repair. Oxidative damage to DNA, lipid membranes, and other cellular structures adversely impacts immune cell activity and contributes to premature



immunosenescence. Restoring intracellular antioxidant capacity and improving DNA repair mechanisms improves the functional capacity of immunocytes and most likely prolongs their survival. Cat's claw also exerts unique influences on immunomodulatory cytokines. As discussed in the previous section, cat's claw effectively inhibits the activity of pro-inflammatory mediators such as NF- $\kappa$ B and TNF- $\alpha$ , but it has also been shown to augment the activity of the immunostimulatory cytokine interleukin-1 beta (IL-1 $\beta$ ). Typically, NF- $\kappa$ B and IL-1 $\beta$  work in a synergistic fashion to heighten inflammatory responses, but their differential regulation by cat's claw may help rein in the damaging effects of NF- $\kappa$ B-induced inflammation while preserving IL-1 $\beta$ -mediated immune responsiveness.

#### *Gastrointestinal Support*

The antioxidative, anti-inflammatory, and DNA-reparative effects of *Uncaria tomentosa* AC-11<sup>®</sup> aqueous extracts suggest it can be highly beneficial for ameliorating gastrointestinal disorders. Gastrointestinal pathology often involves overproduction of free radicals which can lead not only to tissue injury, but maintenance of a hyperinflammatory state. Oxidative damage, for example, contributes to the pathogenesis of inflammatory bowel disorders and may facilitate their progression to colon cancer. Gastrointestinal disease is also frequently associated with impaired gut mucosal integrity which can reduce nutrient absorption and increase intestinal permeability. The documented ability of water soluble AC-11<sup>®</sup> to neutralize free radicals, downregulate the activity of pro-inflammatory mediators, and promote cellular repair mechanisms can minimize these damaging effects and help restore and maintain normal functioning of the gastrointestinal system. *Uncaria tomentosa*'s immunomodulatory activity may also support against gastrointestinal infection. As previously discussed, *Uncaria tomentosa* has been shown to significantly increase the murine immune response to the foodborne pathogen *L. monocytogenes*. *Uncaria tomentosa* aqueous extracts also demonstrate *in vitro* antimicrobial activity against potentially enteroinvasive organisms such as *Staphylococcus* and *Klebsiella* species.

Studies suggest the salutary effects of *Uncaria tomentosa* on gastrointestinal health may depend, at least in part, on the presence of a healthy intestinal microflora. The microbiota of the intestinal tract is an essential deterrent to colonization by enteric pathogens and undoubtedly augments *Uncaria tomentosa*'s anti-infective and antimicrobial activity. Perhaps more importantly, intestinal microorganisms have the capacity to hydrolyze the types of quinic acid esters found in hot water extracts of *Uncaria tomentosa* and release important hydroxycinnamic metabolites such as caffeic and ferulic acids. These compounds exert antioxidant and anti-inflammatory activity that can protect the delicate intestinal mucosa and possibly prevent or mitigate the severity of inflammatory gastrointestinal disorders. Preclinical data demonstrate, for example, that caffeic acid strongly inhibits TNF- $\alpha$ -induced secretion of interleukin-8, a cytokine implicated in the development of inflammatory bowel disease. Among the organisms shown capable of releasing metabolites from quinic acid esters are members of the health-promoting *Lactobacillus* and *Bifidobacteria* genera. Production of hydroxycinnamate metabolites by these beneficial intestinal microorganisms suggest concurrent administration of AC-11<sup>®</sup> and probiotic supplements may yield synergistic health benefits.

It has also recently been shown that quinic acid can be metabolized by intestinal microorganisms to the amino acid tryptophan. Tryptophan is a precursor to serotonin, a powerful monoamine regulator of motility, secretion, and sensorineural activity in the gastrointestinal tract. Up to 90% of the body's serotonin is stored within intestinal enterochromaffin cells, an indicator of the critical importance of serotonin to proper gastrointestinal function. Studies show intestinal serotonin content and/or metabolism may be deranged in gastrointestinal disorders such as inflammatory bowel disease and irritable bowel syndrome. Abnormally low serotonin levels, for example, have been found in the inflamed mucosae of persons with both Crohn's disease and ulcerative colitis. Increased shunting of tryptophan away from serotonin biosynthesis into catabolic pathways has also been reported in women with irritable bowel syndrome. It is possible, therefore, that provision of quinic acid from AC-11<sup>®</sup> may help normalize serotonin levels and activity in the gut by increasing the availability of tryptophan. Since the bioconversion from quinic acid to tryptophan is microflora-dependent, simultaneous use of AC-11<sup>®</sup> and a broad-spectrum probiotic supplement may once again prove to be a highly beneficial therapeutic combination.

## INDICATIONS

Protectagen™ with AC-11<sup>®</sup> is designed for individuals who wish to mitigate the impacts of oxidative and environmental stress, modulate inflammatory processes, and enhance immune function. Aging, elderly, or chronically ill individuals, persons with high exposure to environmental toxins, and those with gastrointestinal dysbiosis and dysfunction may benefit the most from Protectagen™.



## FORMULA

### Supplement Facts


Serving Size 1 Capsule • Servings Per Container 60

#### Amount Per Capsule

AC-11\*\*\* patented water-soluble extract of *Uncaria tomentosa*, min. 8% carboxy alkyl esters 350 mg\*

\*Daily Value not established.

Other ingredients: Vegetarian capsule (hydroxypropyl methylcellulose, water), cellulose, L-leucine, and silicon dioxide.

 \*\*AC-11<sup>®</sup> is a registered trademark of Optigenex Inc. Covered by U.S. Patents 6,039,949, 6,238,675 B1, 6,361,805 B2, 6,964,784 B2, 7,579,023 B2, and 7,595,064 B2.

## SUGGESTED USE

As a dietary supplement, take one to two (1-2) capsules daily with food, or as directed by a healthcare professional. For maximum benefit, Protectagen™ may be combined with probiotic and/or prebiotic supplements that support a healthy, balanced intestinal microflora.

## ADVERSE REACTIONS

No adverse reactions to Protectagen™ with AC-11<sup>®</sup> have been reported. The traditional use of cat's claw is recognized as safe and nontoxic. The AC-11<sup>®</sup> aqueous extract, by way of its patented extraction process replicates the traditional usage of *Uncaria tomentosa* root bark as a tea. AC-11<sup>®</sup> has no significant oxindole alkaloid content (<0.05%) and has an excellent safety profile. There are over 30 reports dealing with the efficacy and lack of toxicity of water-soluble *Uncaria tomentosa* products which includes cells, tissues, rodents and humans. In all these studies there was no reported toxicity from the hundreds of observations in animals and humans. In contrast, indole alkaloid extracts of cat's claw have often been associated with toxic side effects.

## DRUG INTERACTIONS

The immunostimulating activity of *Uncaria tomentosa* could theoretically reduce the efficacy of immunosuppressant drugs. *Uncaria tomentosa* has also been shown to inhibit cytochrome P450 3A4 (CYP3A4) activity *in vitro* and thus may theoretically alter blood levels of drugs metabolized by this enzyme. Currently, there are no published reports of interactions between *Uncaria tomentosa* and immunosuppressant or CYP3A4-metabolized drugs.

## CONTRA-INDICATIONS

Persons taking immunosuppressant medications or drugs known to be metabolized by the CYP3A4 enzyme may wish to consult with a doctor before using this product.

## HOW SUPPLIED

60 vegetarian capsules per bottle with full-bottle shrinkwrap. Packaged 12 bottles per case.

## STORAGE

Store in a cool, dry place (59°F-85°F) away from direct light. Keep out of reach of children.

## REFERENCES

- Akesson C, Lindgren H, Pero RW, Leanderson T, Ivars F. An extract of *Uncaria tomentosa* inhibiting cell division and NF-kappa B activity without inducing cell death. *Int Immunopharmacol* 2003;3:1889-900.
- Akesson C, Pero RW, Ivars F. C-Med 100, a hot water extract of *Uncaria tomentosa*, prolongs lymphocyte survival *in vivo*. *Phytomedicine* 2003;10:23-33.
- Alvarado C, Alvarez P, Puerto M, Gausseres N, Jimenez L, De la Fuente M. Dietary supplementation with antioxidants improves functions and decreases oxidative stress of leukocytes from prematurely aging mice. *Nutrition* 2006;22:767-77.
- Bartsch H, Nair J. Chronic inflammation and oxidative stress in the genesis and perpetuation of cancer: role of lipid peroxidation, DNA damage, and repair. *Langenbecks Arch Surg* 2006;391:499-510.
- Bors W, Michel C. Chemistry of the antioxidant effect of polyphenols. *Ann NY Acad Sci* 2002;957:57-69.
- Budzinski JW, Foster BC, Vandenhoeck S, Arnason JT. An *in vitro* evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. *Phytomedicine* 2000;7:273-82.
- Camilleri M. Serotonergic modulation of visceral sensation: lower gut. *Cut* 2002;51 Suppl 1:i81-6.
- Ccahuana-Vasquez RA, Santos SS, Koga-Ito CY, Jorge AO. Antimicrobial activity of *Uncaria tomentosa* against oral human pathogens. *Braz Oral Res* 2007;21:46-50.
- Cheng AC, Jian CB, Huang YT, Lai CS, Hsu PC, Pan MH. Induction of apoptosis by *Uncaria tomentosa* through reactive oxygen species production, cytochrome c release, and caspases activation in human leukemia cells. *Food Chem Toxicol* 2007;45:2206-18.



- Cisneros FJ, Jayo M, Niedziela L. An *Uncaria tomentosa* (cat's claw) extract protects mice against ozone-induced lung inflammation. *J Ethnopharmacol* 2005;96:355-64.
- Coates MD, Mahoney CR, Linden DR, et al. Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. *Gastroenterology* 2004;126:1657-64.
- Conner EM, Brand SJ, Davis JM, Kang DY, Grisham MB. Role of reactive metabolites of oxygen and nitrogen in inflammatory bowel disease: toxins, mediators, and modulators of gene expression. *Inflam Bowel Dis* 1996;2:133-47.
- Couteau D, McCartney AL, Gibson GR, Williamson G, Faulds CB. Isolation and characterization of human colonic bacteria able to hydrolyse chlorogenic acid. *J Appl Microbiol* 2001;90:873-81.
- Dincer Y, Erzin Y, Himmetoglu S, Gunes KN, Bal K, Akcay T. Oxidative DNA damage and antioxidant activity in patients with inflammatory bowel disease. *Dig Dis Sci* 2007;52:1636-41.
- Dragsted LO. Antioxidant actions of polyphenols in humans. *Int J Vitam Nutr Res* 2003;73:112-9.
- Eberlin S, dos Santos LM, Queiroz ML. *Uncaria tomentosa* extract increases the number of myeloid progenitor cells in the bone marrow of mice infected with *Listeria monocytogenes*. *Int Immunopharmacol* 2005;5:1235-46.
- Erowele GI, Kalejaiye AO. Pharmacology and therapeutic uses of cat's claw. *Am J Health Syst Pharm* 2009;66:992-5.
- Fitzgerald P, Cassidy Eugene M, Clarke G, et al. Tryptophan catabolism in females with irritable bowel syndrome: relationship to interferon-gamma, severity of symptoms and psychiatric co-morbidity. *Neurogastroenterol Motil* 2008;20:1291-7.
- Ghosh D, Scheepens A. Vascular action of polyphenols. *Mol Nutr Food Res* 2009;53:322-31.
- Goncalves C, Dinis T, Batista MT. Antioxidant properties of proanthocyanidins of *Uncaria tomentosa* bark decoction: a mechanism for anti-inflammatory activity. *Phytochemistry* 2005;66:89-98.
- Guo W, Kong E, Meydani M. Dietary polyphenols, inflammation, and cancer. *Nutr Cancer* 2009;61:807-10.
- Heitzman ME, Neto CC, Winiarz E, Vaisberg AJ, Hammond GB. Ethnobotany, phytochemistry and pharmacology of *Uncaria* (Rubiaceae). *Phytochemistry* 2005;66:5-29.
- Hosseinimehr SJ, Zakaryae V, Ahmadi A, Akhlaghpour S. Radioprotective effects of chlorogenic acid against mortality induced by gamma-irradiation in mice. *Methods Find Exp Clin Pharmacol* 2008;30:13-6.
- Ichijima T, Ueno Y, Isumi H, Niimi A, Matsubara T, Furukawa S. An immunoglobulin agent (IVIg) inhibits NF-kappaB activation in cultured endothelial cells of coronary arteries *in vitro*. *Inflam Res* 2004;53:253-6.
- Jaruga P, Jaruga B, Olczak A, Halota W, Olinski R. Oxidative DNA base damage in lymphocytes of HIV-infected drug users. *Free Radic Res* 1999;31:197-200.
- Keplinger K, Laus G, Wurm M, Dierich MP, Teppner H. *Uncaria tomentosa* (Willd.) DC. – ethnomedicinal use and new pharmacological, toxicological and botanical results. *J Ethnopharmacol* 1999;64:23-34.
- Keshavarzian A, Banan A, Farhadi A, et al. Increases in free radicals and cytoskeletal protein oxidation and nitration in the colon of patients with inflammatory bowel disease. *Gut* 2003;52:720-8.
- Lamm S, Sheng Y, Pero RW. Persistent response to pneumococcal vaccine in individuals supplemented with a novel water soluble extract of *Uncaria tomentosa*, C-Med-100. *Phytomedicine* 2001;8:267-74.
- Magro F, Vieira-Coelho MA, Fraga S, et al. Impaired synthesis or cellular storage of norepinephrine, dopamine, and 5-hydroxytryptamine in human inflammatory bowel disease. *Dig Dis Sci* 2002;47:216-24.
- Mammone T, Akesson C, Gan D, Giampapa V, Pero RW. A water soluble extract from *Uncaria tomentosa* (Cat's Claw) is a potent enhancer of DNA repair in primary organ cultures of human skin. *Phytother Res* 2006;20:178-83.
- Maynard S, Schurman SH, Harboe C, de Souza-Pinto NC, Bohr VA. Base excision repair of oxidative DNA damage and association with cancer and aging. *Carcinogenesis* 2009;30:2-10.
- Mazzucchelli L, Hauser C, Zraggen K, et al. Expression of interleukin-8 gene in inflammatory bowel disease is related to the histological grade of active inflammation. *Am J Pathol* 1994;144:997-1007.
- McKenzie SJ, Baker MS, Buffinton GD, Doe WF. Evidence of oxidant-induced injury to epithelial cells during inflammatory bowel disease. *J Clin Invest* 1996;98:136-41.
- Mur E, Hartig F, Eibl G, Schirmer M. Randomized double blind trial of an extract from the pentacyclic alkaloid-chemotype of *uncaria tomentosa* for the treatment of rheumatoid arthritis. *J Rheumatol* 2002;29:678-81.
- Pero RW. Historical development of *Uncaria* preparations and their related bioactive components. In: Thomas AE (ed). DNA Repair: Damage, Repair Mechanisms and Aging. Hauppauge, NY: Nova Science Publishers, Inc; 2010.
- Pero RW, Giampapa V, Vodjani A. Comparison of a broad spectrum and antiaging nutritional supplement with and without the addition of a DNA repair enhancing cat's claw extract. *J Antiaging Med* 2002;5:345-53.
- Pero RW, Lund H, Leanderson T. Antioxidant metabolism induced by quinic acid. Increased urinary excretion of tryptophan and nicotinamide. *Phytother Res* 2009;23:335-46.
- Pilarski R, Poczekaj-Kostrzewska M, Ciesiolka D, Szyfler K, Gulewicz K. Antiproliferative activity of various *Uncaria tomentosa* preparations on HL-60 promyelocytic leukemia cells. *Pharmacol Rep* 2007;59:565-72.
- Plumb, GW, Garcia-Conesa MT, Kroon PA, Rhodes M, Ridley S, Williamson G. Metabolism of chlorogenic acid by human plasma, liver, intestine and gut microflora. *J Sci Food Agric* 1999;79:390-2.
- Roessner A, Kuester D, Malfertheiner P, Schneider-Stock R. Oxidative stress in ulcerative colitis-associated carcinogenesis. *Pathol Res Pract* 2008;204:511-24.
- Sandoval M, Charbonnet RM, Okuhama NN, et al. Cat's claw inhibits TNFalpha production and scavenges free radicals: role in cytoprotection. *Free Radic Biol Med* 2000;29:71-8.
- Sandoval M, Okuhama NN, Zhang XJ, et al. Anti-inflammatory and antioxidant activities of cat's claw (*Uncaria tomentosa* and *Uncaria guianensis*) are independent of their alkaloid content. *Phytomedicine* 2002;9:325-37.
- Sandoval-Chacon M, Thompson JH, Zhang XJ, et al. Antiinflammatory actions of cat's claw: the role of NF-kappaB. *Aliment Pharmacol Ther* 1998;12:1279-89.
- Senatore A, Cataldo A, Iaccarino FP, Elberti MG. [Phytochemical and biological study of *Uncaria tomentosa*]. *Boll Soc Ital Biol Sper* 1989;65:517-20. [Article in Italian; abstract in English]
- Sheng Y, Bryngelsson C, Pero RW. Enhanced DNA repair, immune function and reduced toxicity of C-MED-100, a novel aqueous extract from *Uncaria tomentosa*. *J Ethnopharmacol* 2000;69:115-26.
- Sheng Y, Li L, Holmgren K, Pero RW. DNA repair enhancement of aqueous extracts of *Uncaria tomentosa* in a human volunteer study. *Phytomedicine* 2001;8:275-82.
- Sheng Y, Pero RW, Amiri A, Bryngelsson C. Induction of apoptosis and inhibition of proliferation in human tumor cells treated with extracts of *Uncaria tomentosa*. *Anticancer Res* 1998;18:3363-8.
- Sheng Y, Pero RW, Wagner H. Treatment of chemotherapy-induced leukopenia in a rat model with aqueous extract from *Uncaria tomentosa*. *Phytomedicine* 2000;7:137-43.
- Sikander A, Rana SV, Prasad KK. Role of serotonin in gastrointestinal motility and irritable bowel syndrome. *Clin Chim Acta* 2009;403:47-55.



- Steinberg PN. [Cat's Claw: an herb from the Peruvian Amazon]. *Sidhara* 1995;35-6. [Article in Spanish; abstract in English]
- Styczyński J, Wysocki M. Alternative medicine remedies might stimulate viability of leukemic cells. *Pediatr Blood Cancer* 2006;46:94-8.
- Thom E. The effect of chlorogenic acid enriched coffee on glucose absorption in healthy volunteers and its effect on body mass when used long-term in overweight and obese people. *J Int Med Res* 2007;35:900-8.
- University of Texas, MD Anderson Cancer Center website. Cat's claw detailed scientific review.  
<http://www.mdanderson.org/education-and-research/resources-for-professionals/clinical-tools-and-resources/cimer/therapies/herbal-plant-biologic-therapies/cats-claw-scientific.html>. Accessed 7/20/10.
- van Dijk AE, Olthof MR, Meeuse JC, Seebus E, Heine RJ, van Dam RM. Acute effects of decaffeinated coffee and the major coffee components chlorogenic acid and trigonelline on glucose tolerance. *Diabetes Care* 2009;32:1023-5.
- Wagner H, Kreutzkamp B, Jurcic K. [The alkaloids of *Uncaria tomentosa* and their phagocytosis-stimulating action]. *Planta Med* 1985;51:419-23. [Article in German; abstract in English]
- Watanabe T, Arai Y, Mitsui Y, et al. The blood pressure-lowering effect and safety of chlorogenic acid from green coffee bean extract in essential hypertension. *Clin Exp Hypertens* 2006;28:439-49.
- Zang LY, Cosma G, Gardner H, Castranova V, Vallyathan V. Effect of chlorogenic acid on hydroxyl radical. *Mol Cell Biochem* 2003;247:205-10.
- Zhao Z, Shin HS, Satsu H, Totsuka M, Shimizu M. 5-caffeoylquinic acid and caffeic acid down-regulate the oxidative stress and TNF-alpha-induced secretion of interleukin-8 from Caco-2 cells. *J Agric Food Chem* 2008;56:3863-8.

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These statements have not been evaluated by the Food and Drug Administration.  
This product is not intended to diagnose, treat, cure, or prevent any disease.

For ordering information, please contact:

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