

Clinical Reference Guide

InnerActin™

Milk Thistle extract (seed)

A. Liver protection, alcohol abuse, glutathione regeneration

1. Beckmann-Knopp S, Rietbrock S, Weyhenmeyer R, Bocker RH, Beckurts KT, Lang W, Hunz M, Fuhr U. Inhibitory effects of silibinin on cytochrome P-450 enzymes in human liver microsomes. *Pharmacol Toxicol.* 2000 Jun;86(6):250-6.
2. Campos R, et al. Silybin Dihemisuccinate Protects Against Glutathione Depletion and Lipid Peroxidation Induced by Acetaminophen on Rat Liver. *Planta Medica.* 1989;55:417-19.
3. *Cardui mariae fructus (Milk Thistle fruit).* Commission E Monograph. Mar1986;Bundesanzeiger:no. 50.
4. Carrescia O, et al. Silymarin in the Prevention of Hepatic Damage by Psychopharmacologic Drugs. *Experimental Premises and Clinical Evaluations.* *Clin Ter.* 1980;95(2):157-64.
5. De Martiis M, Fontana M, Assogna G, D'Ottavi R, D'Ottavi O. Milk thistle (*Silybum marianum*) derivatives in the therapy of chronic hepatopathies. *Clin Ter.* 1980 Aug 15;94(3):283-315.
6. Deak G, Muzes G, Lang I, Niederland V, Nekam K, Gonzalez-Cabello R, Gergely P, Feher J. Immunomodulator effect of silymarin therapy in chronic alcoholic liver diseases. *Orv Hetil.* 1990 Jun 17;131(24):1291-2, 1295.
7. Dehmlow C, Erhard J, de Groot H. Inhibition of Kupffer Cell Functions as an Explanation for the Hepatoprotective Properties of Silibinin. *Hepatology.* Apr1996;23(4):749-54.
8. Faulstich H, Jahn W, Wieland T. Silibinin inhibition of amatoxin uptake in the perfused rat liver. *Arzneim-Forsch Drug Res* 1980;30:452-4.
9. Feher J, Lang I, Deak G, et al. Free radicals in tissue damage in liver diseases and therapeutic approach. *Tokai J Exp Clin Med* 1986;11:121-34.
10. Ferenci P, Dragosics B, Dittrich H, et al. Randomized Controlled Trial of Silymarin Treatment in Patients with Cirrhosis of the Liver. *J Hepatol.* Jul1989;9(1):105-13.
11. Flora K, Hahn M, Rosen H, Benner K. Milk thistle (*Silybum marianum*) for the therapy of liver disease. *Am J Gastroenterol.* 1998 Feb;93(2):139-43.

12. Hikino H, Kiso Y, Wagner H, Fiebig M. Antihepatotoxic actions of flavonolignans from *Silybum marianum* fruits. *Planta Medica* 1984;50:248–50.
13. Kiesewetter E, Leodolter I, Thaler H. Results of two double-blind studies on the effect of silymarine in chronic hepatitis. *Leber Magen Darm*. 1977 Oct;7(5):318-23.
14. Leng-Peschlow E. Alcohol-related liver diseases-use of Legalon®. *Z Klin Med* 1994;2:22–7.
15. Margaroli P, Rossi M, Arcabasso GD, Cosini I, Malacrida C. Evaluation of the therapeutic effects of silymarin. *Clin Ter*. 1980 Dec 31;95(6):663-72.
16. Morelli I. Constituents of *Silybum marianum* and their therapeutic use. *Boll Chim Farm*. 1978 May;117(5):258-67.
17. Pares A, Plancs R, Torres M, et al. Effects of silymarin in alcoholic patients with cirrhosis of the liver: results of a controlled, double-blind, randomized and multicenter trial. *J Hepatol* 1998;28:615–21.
18. Realini S, Gonvers JJ, Hofstetter JR. Clinical investigation of silymarin in chronic liver diseases. *Schweiz Rundsch Med Prax*. 1975 May 13;64(19):595-8.
19. Reutter FW, Haase W. Clinical experience with silymarin in the treatment of chronic liver disease. *Schweiz Rundsch Med Prax*. 1975 Sep 9;64(36):1145-51.
20. Rue YC. Advances in Pharmacological Studies of Silymarin. *Mem Inst Oswaldo Cruz*. 1991;86(Suppl 2):79-85.
21. Saliou C, Rihn B, Cillard J, Okamoto T, Packer L. Selective inhibition of NF-kappaB activation by the flavonoid hepatoprotector silymarin in HepG2. Evidence for different activating pathways. *FEBS Lett*. 1998 Nov 27;440(1-2):8-12.
22. Salmi H, Sama S. Effect of Silymarin on Chemical, Functional, and Morphological Alterations of the Liver. A Double-blind Controlled Study. *Scand J Gastroent*. 1982;17:517-21.
23. Sawaryn T, Szymonski K, Machalska M. Silymarin in the treatment of chronic hepatitis. *Przegl Epidemiol*. 1977;31(4):445-50.
24. Schopen RD, et al. Therapy of Hepatoses. Therapeutic Use of Silymarin. *Med Welt*. 1969;21:691-98.
25. Tuchweber B, Sieck R, Trost W. Prevention by silibinin of phalloidin induced hepatotoxicity. *Toxicol Appl Pharmacol* 1979;51:265–75.

26. Valenzuela A, et al. Selectivity of Silymarin on the Increase of the Glutathione Content in Different Tissues of the Rat. *Planta Medica*. 1989;55:1550-52.
27. Varga M, et al. Ethanol Elimination in Man Under Influence of Hepatoprotective Silibinin. *Blutalkohol*. Nov1991;28(6):405-08.
28. Velussi M, Cernogoi AM, De Monte A, et al. Long-term (12 months) treatment with an antioxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients. *J Hepatology* 1997;26:871-9.
29. Wichtl M in Bissett NA, ed. *Herbal Drugs and Phytopharmaceuticals*. Stuttgart: Scientific Press; 1994:121-23.

B. Liver structure and function

1. Ferenci P, Dragosics B, Dittrich H, et al. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *J Hepatol* 1989;9:105-13.
2. Sonnenbichler J, Zetl I. Stimulating influence of a flavanolignan derivative on proliferation, RNA synthesis and protein synthesis in liver cells. In *Assessment and Management of Hepatobiliary Disease*, ed. L Okolicsanyi, G Csomos, G Crepaldi. Berlin: Springer-Verlag, 1987, 265-72.

C. Bile, cholesterol and fat metabolism

1. Edwards J, Grange LL, Wang M, et al. Fetoprotectivity of the Flavanolignan Compound Siliphos Against Ethanol-induced Toxicity. *Phytother Res*. Nov2000;14(7):517-21.
2. Krecman V, Skottova N, Walterova D, et al. Silymarin Inhibits the Development of Diet-induced Hypercholesterolemia in Rats. *Planta Med*. Mar1998;64(2):138-42.
3. Nassuato G, Iemmolo RM, Strazzabosco M, et al. Effect of silibinin on biliary lipid composition. Experimental and clinical study. *J Hepatol* 1991;12:290-5.
4. Skottova N, Krecman V, Walterova D, et al. Effect of Silymarin on Serum Cholesterol Levels in Rats. *Acta Univ Palacki Olomuc Fac Med*. 1998;141:87-9.
5. Skottova N, Krecman V. Silymarin as a Potential Hypocholesterolaemic Drug. *Physiol Res*. 1998;47(1):1-7.

D. Antioxidation/detoxification

1. Allain H, Schück S, Lebreton S, et al. Aminotransferase levels and silymarin in de novo tacrine-treated patients with Alzheimer's disease. *Dementia Geriatr Cogn Disorders* 1999;10:181-5.
2. Berkson BM. A conservative triple antioxidant approach to the treatment of hepatitis C. Combination of alpha lipoic acid (thioctic acid), silymarin, and selenium: three case histories. *Med Klin*. 1999 Oct 15;94 Suppl 3:84-9.
3. Desplaces A, et al. The Effects of Silymarin on Experimental Phalloidine Poisoning. *Arzneim-Forsch/Drug Res*. 1975;25:89-96.
4. Palasciano G, Portinascasa P, Palmieri V, et al. The effect of silymarin on plasma levels of malondialdehyde in patients receiving long-term treatment with psychotropic drugs. *Curr Ther Res* 1994;S5:S37-45.
5. Par A, Roth E, Rumi G Jr, Kovacs Z, Nemes J, Mozsik G. Oxidative stress and antioxidant defense in alcoholic liver disease and chronic hepatitis C. *Orv Hetil*. 2000 Jul 23;141(30):1655-9.
6. Stickel F, Egerer G, Seitz HK. Hepatotoxicity of botanicals. *Public Health Nutr*. 2000 Jun;3(2):113-24.
7. Valenzuela A, et al. Silymarin Protection Against Hepatic Lipid Peroxidation Induced by Acute Ethanol Intoxication in the Rat. *Biochem Pharm*. 1985;34:2209-12.
8. Vogel G, et al. Protection by Silibinin Against Amanita Phalloides Intoxication in Beagles. *Toxicol Appl Pharm*. 1984;73:355-62.

E. Oxygen depletion

1. Zhao J, Sharma Y, Agarwal R. Significant inhibition by the flavonoid antioxidant silymarin against 12-O-tetradecanoylphorbol 13-acetate-caused modulation of antioxidant and inflammatory enzymes, and cyclooxygenase 2 and interleukin-1alpha expression in SENCAR mouse epidermis: implications in the prevention of stage I tumor promotion. *Mol Carcinog*. 1999 Dec;26(4):321-33.

F. Fibrotic tissue

1. Schuppan D, Strösser W, Burkard G, Walosek G. Legalon® lessens fibrosing activity in patients with chronic liver diseases. *Zeits Allgemeinmed* 1998;74:577-84.

G. Acetaminophen poisoning

1. Shear NH, Malkiewicz IM, Klein D, et al. Acetaminophen-induced Toxicity to Human Epidermoid Cell Line A431 and Hepatoblastoma Cell Line Hep G2, In Vitro, is Diminished by Silymarin. *Skin Pharmacol*. 1995;8(6):279-91.

H. Inflammation

1. Fiebrich F, et al. Silymarin, an Inhibitor of Prostaglandin Synthetase. *Experimenta*. 1979;35:150-52.
2. Gupta OP, Sing S, Bani S, et al. Anti-inflammatory and Anti-arthritic Activities of Silymarin Acting Through Inhibition of 5-lipoxygenase. *Phytomedicine*. Mar2000;7(1):21-4.
3. Manna SK, Mukhopadhyay A, Van NT, et al. Silymarin Suppresses TNF-induced Activation of NF-kappa B, c-Jun N-terminal Kinase, and Apoptosis. *J Immunol*. Dec1999;163(12):6800-9.

N-acetyl l-cysteine

A. Mucolytic activity

1. Boman G, Bäcker U, Larsson S, et al. Oral acetylcysteine reduces exacerbation rate in chronic bronchitis: a report of a trial organized by the Swedish Society for Pulmonary Diseases. *Eur J Respir Dis* 1983;64:405–15.
2. Brumas V, et al. Can N-acetyl-L-cysteine affect zinc metabolism when used as a paracetamol antidote? *Agents Actions*. Jul1992;36(3-4):278-88.
3. Grandjean EM, Berthet P, Ruffmann R, Leuenberger P. Efficacy of oral long-term N-Acetylcysteine in chronic bronchopulmonary disease: A meta-analysis of published double-blind, placebo-controlled clinical trials. *Clin Ther* 2000;22:209–21.
4. Multicenter Study Group. Long-term oral acetylcysteine in chronic bronchitis. A double-blind controlled study. *Eur J Respir Dis* 1980;61:111:93–108.
5. Pela R, Calcagni AM, Subiaco S, Isidori P, Tubaldi A, Sanguinetti CM. N-acetylcysteine reduces the exacerbation rate in patients with moderate to severe COPD. *Respiration*. 1999 Nov-Dec;66(6):495-500.
6. Tattersall AB, Bridgman KM, Huitson A. Acetylcysteine (Fabrol) in chronic bronchitis—a study in general practice. *J Int Med Res* 1983;11(5):279–84.
7. van Herwaarden CL, et al. The Role of N-Acetylcysteine in the Treatment of Chronic Obstructive Pulmonary Disease. *The Netherlands Journal of Medicine*. 1995;47:45-48.

B. Glutathione synthesis

1. de Quay B, Malinverni R, Lauterburg BH. Glutathione depletion in HIV-infected patients: role of cysteine deficiency and effect of oral N-acetylcysteine. *AIDS* 1992;6:815-9.

C. Antioxidation and Detoxification

1. Ballatori N, et al. N-acetylcysteine as an antidote in methylmercury poisoning. *Environ Health Perspect*. May1998;106(5):267-71.
2. Banzet N, Francois D, Polla BS. Tobacco smoke induces mitochondrial depolarization along with cell death: effects of antioxidants. *Redox Rep*. 1999;4(5):229-36.
3. Cavallini L, Alexandre A. Oral N-acetyl-cysteine increases the production of anti HIV chemokines in peripheral blood mononuclear cells. *Life Sci*. 2000;67(2):147-54.
4. Cereser C, Boget S, Parvaz P, Revol A. Thiram-induced cytotoxicity is accompanied by a rapid and drastic oxidation of reduced glutathione with consecutive lipid peroxidation and cell death. *Toxicology*. Jun2001;163(2-3):153-62.
5. Faintuch J, Aguilar PB, Nadalin W. Relevance of N-acetylcysteine in clinical practice: fact, myth or consequence? *Nutrition*. 1999 Feb;15(2):177-9.
6. Floyd RA. Antioxidants, oxidative stress, and degenerative neurological disorders. *Proc Soc Exp Biol Med*. 1999 Dec;222(3):236-4.
7. Grootveld M, Silwood CJ, Lynch EJ, Patel IY, Blake DR. The role of N-acetylcysteine in protecting synovial fluid biomolecules against radiolytically-mediated oxidative damage: a high field proton NMR study. *Free Radic Res*. 1999 May;30(5):351-69.
8. Kawasaki S, Takizawa H, Takami K, et al. Benzene-extracted components are important for the major activity of diesel exhaust particles: effect on interleukin-8 gene expression in human bronchial epithelial cells. *Am J Respir Cell Mol Biol*. Apr2001;24(4):419-26.
9. Malorni W, Rivabene R, Lucia BM, Ferrara R, Mazzone AM, Cauda R, Paganelli R. The role of oxidative imbalance in progression to AIDS: effect of the thiol supplier N-acetylcysteine. *AIDS Res Hum Retroviruses*. 1998 Nov 20;14(17):1589-96.
10. Martinez M, Martinez N, Hernandez AI, Ferrandiz ML. Hypothesis: can N-acetylcysteine be beneficial in Parkinson's disease? *Life Sci*. 1999;64(15):1253-7.
11. Molnar Z, MacKinnon KL, Shearer E, Lowe D, Watson ID. The effect of N-acetylcysteine on total serum anti-oxidant potential and urinary albumin excretion in critically ill patients. *Intensive Care Med*. 1998 Mar;24(3):230-5.

12. Rahman Q, Abidi P, Afaq F, Schiffmann D, Mossman BT, Kamp DW, Athar M. Glutathione redox system in oxidative lung injury. *Crit Rev Toxicol.* 1999 Nov;29(6):543-68.
13. Ruffmann R. Reactive oxygen species in acute lung injury. *Eur Respir J.* 1998 Dec;12(6):1486.
14. Supinski G. Free radical induced respiratory muscle dysfunction. *Mol Cell Biochem.* 1998 Feb;179(1-2):99-110.
15. Van Schayck CP, Dekhuijzen PNR, Gorgels WJM, et al. Are anti-oxidant and anti-inflammatory treatments effective in different subgroups of COPD? A hypothesis. *Respir Med* 1998;92:1259–64.
16. Walsh TS, Lee A. N-acetylcysteine administration in the critically ill. *Intensive Care Med.* 1999 May;25(5):432-4.
17. Zed PJ, Krenzelok EP. Treatment of acetaminophen overdose. *Am J Health Syst Pharm.* Jun1999;56(11):1081-91.

D. Liver

1. Ben-Ari Z, Vaknin H, Tur-Kaspa R. N-acetylcysteine in acute hepatic failure (non-paracetamol-induced). *Hepatogastroenterology* 2000;47:786–9.

Colon

1. Estensen RD, Levy M, Klopp SJ, et al. N-acetylcysteine suppression of the proliferative index in the colon of patients with previous adenomatous colonic polyps. *Cancer Lett* 1999;147:109–14.

E. Immune system

1. De la Fuente M, Victor VM. Anti-oxidants as modulators of immune function. *Immunol Cell Biol.* 2000 Feb;78(1):49-54.
2. Droge W. Cysteine and glutathione in catabolic conditions and immunological dysfunction. *Curr Opin Clin Nutr Metab Care.* 1999 May;2(3):227-3.

F. Cardiovascular function

1. Gavish D, et al. Lipoprotein (a) Reduction by N-Acetylcysteine. *Lancet.* Jan1991;337:203-204.

2. Koivusalo AM, Yildirim Y, Vakkuri A, Lindgren L, Hockerstedt K, Isoniemi H. Experience with albumin dialysis in five patients with severe overdoses of paracetamol. *Acta Anaesthesiol Scand*. Oct2003;47(9):1145-50.
3. Marchetti G, Lodola E, Licciardello L, Colombo A. Use of N-acetylcysteine in the management of coronary artery diseases. *Cardiologia*. 1999 Jul;44(7):633-7.

G. Exercise and endurance

1. Sen CK, Packer L. Thiol homeostasis and supplements in physical exercise. *Am J Clin Nutr*. 2000 Aug;72(2 Suppl):653S-69S.

H. Renal Function

1. Tepel M, van der Giet M, Schwarzfeld C, et al. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med* 2000;343:180-4.
2. Vadoud-Seyedi J, de Dobbeleer G, Simonart T. Treatment of haemodialysis-associated pseudoporphyria with N-acetylcysteine: report of two cases. *Br J Dermatol* 2000;142:580-1.

Trimethylglycine (TMG) (sometimes referred to as Betaine)

A. Liver function, liver protection, fat metabolism, fat reduction, and detoxification

1. Babucke G, Sarre B. Clinical experience with betain citrate. *Med Klin* 1973;68:1109-13 [in German].
2. Barak AJ, Beckenhauer HC, Badakhsh S, Tuma DJ. The effect of betaine in reversing alcoholic steatosis. *Alcohol Clin Exp Res* 1997;21:1100-2.
3. Barak AJ, Beckenhauer HC, Matti J, Tuma DJ. Dietary betaine promotes generation of hepatic S-adenosylmethioine and protects the liver from ethanol-induced fatty infiltration. *Alcohol Clin Exp Res* 1993;17:552-5.
4. Barak AJ, Beckenhauer HC, Tuma DJ. Betaine, ethanol, and the liver: a review. *Alcohol* 1996;13:395-8 [review].
5. Barak AJ, Tuma DJ. Betaine, metabolic by-product or vital methylating agent? *Life Sci* 1983;32:771-4 [review].
6. Cachin M, Pergola F. Betaine aspartate in the hepato-digestive domain. *Sem Ther* 1966;42:423-4 [in French].

7. Cairella M, Volpari B. Betaine aspartate in the therapy of liver diseases. *Clin Ter* 1972;60:513–34 [in Italian].
8. Hilt G, Tuzin P. Clinical results using betaine citrate (Flacar) in fatty livers. *Med Monatsschr* 1973;27:322–5 [in German].
9. Junnila M, Barak AJ, Beckenhauer HC, Rahko T. Betaine reduces hepatic lipidosis induced by carbon tetrachloride in Sprague-Dawley rats. *Vet Hum Toxicol* 1998;40:263–6.
10. Kandziora J. Therapeutic experience with the lipotropic hepatic drug Flacar in the internal medicine practice. *ZFA* 1976;52:1561–3 [in German].
11. Murakami T, Nagamura Y, Hirano K. The recovering effect of betaine on carbon tetrachloride-induced liver injury. *J Nutr Sci Vitaminol* 1998;44:249–55.
12. Nicrosini F. Therapeutic activity of betaine aspartate. *Clin Ter* 1972;15;61:227–36 [in Italian].
13. Semmler F. Treatment of liver diseases, especially of fatty liver with betaine citrate. *Ther Ggw* 1977;116:2113–24 [in German].

B. Cellular function

1. Kim SK, Kim YC, Kim YC. Effects of singly administered betaine on hepatotoxicity of chloroform in mice. *Food Chem Toxicol* 1998;36:655–61.

C. Kidney function

1. Chambers ST. Betaines: their significance for bacteria and the renal tract. *Clin Sci* 1995;88:25–7 [review].

D. Cardiovascular, skeletal, homocysteine

1. Gahl WA, Bernardini I, Chen S, et al. The effect of oral betaine on vertebral body bone density in pyridoxine-non-responsive homocystinuria. *J Inherit Metab Dis* 1988;11:291–8 .
2. Selhub J. Homocysteine metabolism. *Annu Rev Nutr* 1999;19:217–46 [review].
3. van Guldener C, Janssen MJ, de Meer K, et al. Effect of folic acid and betaine on fasting and postmethionine-loading plasma homocysteine and methionine levels in chronic haemodialysis patients. *J Intern Med* 1999;245:175–83.

4. Wendel U, Bremer HJ. Betaine in the treatment of homocystinuria due to 5,10-methylenetetrahydrofolate reductase deficiency. *Eur J Pediatr* 1984;142:147–50.
5. Wilcken DE, Wilcken B, Dudman NP, Tyrrell PA. Homocystinuria—the effects of betaine in the treatment of patients not responsive to pyridoxine. *N Engl J Med* 1983;309:448–53.

Pomegranate extract (fruit)

A. Metabolic effects

1. Brown D. *Encyclopedia of Herbs and Their Uses*. London: Dorling Kindersley; 1995.

B. Antioxidant activity, liver and cell function

1. Afaq F, Saleem M, Krueger CG, Reed JD, Mukhtar H. Anthocyanin- and hydrolyzable tannin-rich pomegranate fruit extract modulates MAPK and NF-kappaB pathways and inhibits skin tumorigenesis in CD-1 mice. *Int J Cancer*. 2004 Sep 28.
2. Chidambara Murthy KN, Jayaprakasha GK, Singh RP. Studies on antioxidant activity of pomegranate (*Punica granatum*) peel extract using in vivo models. *J Agric Food Chem*. 2002 Aug 14;50(17):4791-5.
3. Gil MI, Tomas-Barberan FA, Hess-Pierce B, Holcroft DM, Kader AA. Antioxidant activity of pomegranate juice and its relationship with phenolic composition and processing. *J Agric Food Chem*. 2000 Oct;48(10):4581-9.
4. Harman D. Role of free radicals in aging and disease. *Ann NY Acad Sci*. 1992 Dec 26;673:126-41.
5. Hora JJ, Maydew ER, Lansky EP, Dwivedi C. Chemopreventive effects of pomegranate seed oil on skin tumor development in CD1 mice. *J Med Food*. 2003 Fall;6(3):157-61.
6. Kim ND, Mehta R, Yu W, et al. Chemopreventive and adjuvant therapeutic potential of pomegranate (*Punica granatum*) for human breast cancer. *Breast Cancer Res Treat*. 2002 Feb;71(3):203-17.
7. Kohno H, Suzuki R, Yasui Y, Hosokawa M, Miyashita K, Tanaka T. Pomegranate seed oil rich in conjugated linolenic acid suppresses chemically induced colon carcinogenesis in rats. *Cancer Sci*. 2004 Jun;95(6):481-6.
8. Seeram NP, Lee R, Heber D. Bioavailability of ellagic acid in human plasma after consumption of ellagitannins from pomegranate (*Punica granatum* L.) juice. *Clin Chim Acta*. 2004 Oct;348(1-2):63-8.

C. Cardiovascular health

1. Aviram M, Rosenblat M, Gaitini D, et al. Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation. *Clin Nutr.* 2004 Jun;23(3):423-33.
2. Aviram M, Dornfeld L. Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure. *Atherosclerosis.* 2001 Sep;158(1):195-8.
3. Esmailzadeh A, Tahbaz F, Gaieni I, Alavi-Majd H, Azadbakht L. Concentrated pomegranate juice improves lipid profiles in diabetic patients with hyperlipidemia. *J Med Food.* 2004 Fall;7(3):305-8.

Broccoli extract (aerial)

A. Antioxidant activity and detoxification

1. Barcelo S, Gardiner JM, Gescher A, Chipman JK. CYP2E1-mediated mechanism of anti-genotoxicity of the broccoli constituent sulforaphane. *Carcinogenesis* 1996;17:277–82.
2. Clapper ML, Szarka CE, Pfeiffer GR, et al. Preclinical and clinical evaluation of broccoli supplements as inducers of glutathione S-transferase activity. *Clin Cancer Res* 1997;3:25–30.
3. Fahey JW, Talalay P. Antioxidant functions of sulforaphane: a potent inducer of Phase II detoxication enzymes. *Food Chem Toxicol* 1999;37:973–9.
4. Fahey JW, Zhang Y, Talalay P. Broccoli sprouts: an exceptionally rich source of inducers of enzymes that protect against chemical carcinogens. *Proc Natl Acad Sci* 1997;94:10367–72.
5. Hecht SS. Chemoprevention of cancer by isothiocyanates, modifiers of carcinogen metabolism. *J Nutr* 1999;129:768S–74S [review].
6. Maheo K, Morel F, Langouet S, et al. Inhibition of cytochromes P-450 and induction of glutathione S-transferases by sulforaphane in primary human and rat hepatocytes. *Cancer Res* 1997;57:3649–52.
7. Nestle M. Broccoli sprouts as inducers of carcinogen-detoxifying enzyme systems: clinical, dietary, and policy implications. *Proc Natl Acad Sci* 1997;94:11149–51 [review].
8. Nestle M. Broccoli sprouts in cancer prevention. *Nutr Rev* 1998;56:127–30 [review].

9. Nijhoff WA, Mulder TP, Verhagen H, et al. Effects of consumption of Brussels sprouts on plasma and urinary glutathione S-transferase class-alpha and -pi in humans. *Carcinogenesis* 1995;16:955-7.
10. Talalay P, Zhang Y. Chemoprotection against cancer by isothiocyanates and glucosinolates. *Biochem Soc Trans* 1996;24:806-10.
11. Verhoeven DT, Goldbohm RA, van Poppel G, et al. A review of mechanisms underlying anticarcinogenicity by brassica vegetables. *Chem Biol Interact* 1997;103:79-129 [review].
12. Verhoeven DT, Goldbohm RA, van Poppel G, et al. Epidemiological studies on brassica vegetables and cancer risk. *Cancer Epidemiol Biomarkers Prev* 1996;5:733-48 [review].
13. Zhang Y, Talalay P, Cho CG, Posner GH. A major inducer of anticarcinogenic protective enzymes from broccoli: isolation and elucidation of structure. *Proc Natl Acad Sci* 1992;89:2399-403.

Artichoke extract (leaf)

A. Liver structure and function

1. Adzet T, et al. Hepatoprotective Activity of Polyphenolic Compounds From *Cynara scolymus* Against CCl₄ Toxicity in Isolated Rat Hepatocytes. *J Nat Prod*. Jul1987;50(4):612-17.
2. Gebhardt R. Antioxidative and Protective Properties of Extracts from Leaves of the Artichoke (*Cynara scolymus* L.) Against Hydroperoxide-induced Oxidative Stress in Cultured Rat Hepatocytes. *Toxicol Appl Pharmacol*. Jun1997;144(2):279-86.
3. Khadzhai I, et al. Effect of Artichoke Extracts on the Liver. *Farmakol Toksikol*. Nov1971;34(6):685-87.
4. Maros T, et al. Effects of *Cynara Scolymus* Extracts On The Regeneration of Rat Liver. *Arzneim-Forsch Drug/Res*. Feb1966;16(2):127-29.
5. Maros T, et al. Effect of *Cynara Scolymus*-Extracts on the Regeneration of Rat Liver. *Arzneim-Forsch/Drug Res*. Jul1968;18(7):884-86.

B. Antioxidant activity

1. Gebhardt R. Antioxidative and Protective Properties of Extracts from Leaves of the Artichoke (*Cynara scolymus* L.) Against Hydroperoxide-induced Oxidative Stress in Cultured Rat Hepatocytes. *Toxicol Appl Pharmacol*. Jun1997;144(2):279-86.

2. Perez-Garcia F, Adzet T, Canigueral S. Activity of artichoke leaf extract on reactive oxygen species in human leukocytes. *Free Radic Res.* Nov2000;33(5):661-5.

C. Colon function, digestive function

1. Marakis G, Walker AF, Middleton RW, Booth JC, Wright J, Pike DJ. Artichoke leaf extract reduces mild dyspepsia in an open study. *Phytomedicine.* Dec2002;9(8):694-9.
2. Walker AF, Middleton RW, Petrowicz O. Artichoke leaf extract reduces symptoms of irritable bowel syndrome in a post-marketing surveillance study. *Phytother Res.* Feb2001;15(1):58-61.

D. Cardiovascular function

1. Brown JE, Rice-Evans CA. Luteolin-rich Artichoke Extract Protects Low Density Lipoprotein from Oxidation In Vitro. *Free Radic Res.* Sep1998;29(3):247-55.
2. Englisch W, et al. Efficacy of Artichoke dry extract in patients with hyperlipoproteinemia. *Arzneimittelforschung.* Mar2000;50(3):260-5.
3. Heckers H, et al. Inefficiency of Cynarin as Therapeutic Regimen in Familial Type II Hyperlipoproteinaemia. *Atherosclerosis.* Feb1977;26(2):249-53.
4. Kirchhoff R, et al. Increase in Choleresis by Means of Artichoke Extract. *Phytomedicine.* 1994;1:107-15.
5. Wegener T, Fintelmann V. Pharmacological Properties and Therapeutic Profile of Artichoke. *Wien Med Wochenschr.* 1999;149(8-10):241-7.
6. Wojcicki J, et al. The Influence of Cynarine on Serum Lipids in Patients Affected With Diabetes Mellitus. *Pun Med.* 1974;16:127-29.

Alpha Lipoic Acid

A. Antioxidant activity, detoxification

1. Anuradha B, Varalakshmi P. Protective role of DL-alpha-lipoic acid against mercury-induced neural lipid peroxidation. *Pharmacol Res.* Jan1999;39(1):67-80.
2. Arivazhagan P, Panneerselvam C. Effect of DL - alpha -lipoic acid on neural antioxidants in aged rats. *Pharmacol Res.* 2000 Sep;42(3):219-22.
3. Berkson BM. Thiocctic acid in treatment of hepatotoxic mushroom (Phalloides) poisoning. *N Engl J Med.* Feb1979;300(7):371.

4. Biewenga GP, Haenen GR, Bast A. The pharmacology of the antioxidant lipoic acid. *Gen Pharmacol.* 1997 Sep;29(3):315-31.
5. Busse E, Zimmer G, Schorpohl B, et al. Influence of alpha-lipoic acid on intracellular glutathione in vitro and in vivo. *Arzneimittel-Forschung* 1992;42:829–31.
6. Dovinova I. alpha-Lipoic acid--a natural disulfide cofactor and antioxidant with anticarcinogenic effects. *Ceska Slov Farm.* 1996 Sep;45(5):237-41.
7. Gurer H, Ozgunes H, Oztezcan S, Ercal N. Antioxidant role of alpha-lipoic acid in lead toxicity. *Free Radic Biol Med.* Jul1999;27(1-2):75-81.
8. Hagen TM, Ingersoll RT, Lykkesfeldt J, Liu J, Wehr CM, Vinarsky V, Bartholomew JC, Ames AB. (R)-alpha-lipoic acid-supplemented old rats have improved mitochondrial function, decreased oxidative damage, and increased metabolic rate. *FASEB J.* 1999 Feb;13(2):411-8.
9. Kagan V, Khan S, Swanson C, et al. Antioxidant action of thiocetic acid and dihydrolipoic acid. *Free Radic Biol Med* 1990;9S:15.
10. Kagan V, Serbinova E, Packer L. Antioxidant effects of ubiquinones in microsomes and mitochondria are mediated by tocopherol recycling. *Biochem Biophys Res Commun* 1990;169:851–7.
11. Kagan VE, Shvedova A, Serbinova E, et al. Dihydrolipoic acid--a universal antioxidant both in the membrane and in the aqueous phase. Reduction of peroxy, ascorbyl and chromanoxyl radicals. *Biochem Pharmacol.* Oct1992;44(8):1637-49.
12. Lykkesfeldt J, Hagen TM, Vinarsky V, Ames BN. Age-associated decline in ascorbic acid concentration, recycling, and biosynthesis in rat hepatocytes—reversal with (R)-alpha-lipoic acid supplementation. *FASEB J* 1998;12:1183–9.
13. Monograph:Alpha-Lipoic Acid. *Altern Med Rev.* Aug1998;3(4):308-11.
14. Nichols TW Jr. Alpha-lipoic acid: biological effects and clinical implications. *Altern Med Rev* 1997;2:177–83 [review].
15. Nickander KK, McPhee BR, Low PA, Tritschler H. Alpha-lipoic acid: antioxidant potency against lipid peroxidation of neural tissues in vitro and implications for diabetic neuropathy. *Free Radic Biol Med.* 1996;21(5):631-9.
16. Packer L. alpha-Lipoic acid: a metabolic antioxidant which regulates NF-kappa B signal transduction and protects against oxidative injury. *Drug Metab Rev.* 1998 May;30(2):245-75.

17. Packer L, Tritschler HJ, Wessel K. Neuroprotection by the metabolic antioxidant alpha-lipoic acid. *Free Radic Biol Med.* 1997;22(1-2):359-78.
18. Packer L, Witt EH, Tritschler HJ. Alpha-lipoic acid as a biological antioxidant. *Free Radic Biol Med* 1995 Aug;19(2):227–50 [review].
19. Panigrahi M, Sadguna Y, Shivakumar BR, Kolluri SV, Roy S, Packer L, Ravindranath V. alpha-Lipoic acid protects against reperfusion injury following cerebral ischemia in rats. *Brain Res.* 1996 Apr 22;717(1-2):184-8.
20. Parish RC, Doering PL. Treatment of Amanita mushroom poisoning: a review. *Vet Hum Toxicol.* Aug 1986;28(4):318-22.
21. Podda M, Tritschler HJ, Ulrich H, Packer L. Alpha-lipoic acid supplementation prevents symptoms of vitamin E deficiency. *Biochem Biophys Res Commun.* 1994 Oct 14;204(1):98-104.
22. Scholich H, Murphy ME, Sies H. Antioxidant activity of dihydrolipoate against microsomal lipid peroxidation and its dependence on alpha-tocopherol. *Biochem Biophys Acta* 1989;1001:256–61.
23. Scholz RW, Reddy PV, Wynn MK, Graham KS, Liken AD, Gumprich E, Reddy CC. Glutathione-dependent factors and inhibition of rat liver microsomal lipid peroxidation. *Free Radic Biol Med.* 1997;23(5):815-28.
24. Serbinova E, Khwaja S, Reznick AZ, Packer L. Thiocctic acid protects against ischemia-reperfusion injury in the isolated perfused Langendorff heart. *Free Radic Res Commun.* 1992;17(1):49-58.
25. Sigel H, Prijs B, McCormick DB, Shih JCH. Stability and structure of binary and ternary complexes of a-lipoate and lipoate derivatives with Mn²⁺, Cu²⁺, and Zn²⁺ in solution. *Arch Biochem Biophys.* 1978;187:208-214.
26. Sumathi R, Baskaran G, Varalakshmi P. Relationship between glutathione and DL alpha-lipoic acid against cadmium-induced hepatotoxicity. *Jpn J Med Sci Biol.* Apr 1996;49(2):39-48.

B. Glucose uptake and metabolism

1. Estrada DE, Ewart HS, Tsakiridis T, et al. Stimulation of glucose uptake by the natural coenzyme alpha-lipoic acid/thioctic acid: participation of elements of the insulin signaling pathway. *Diabetes.* 1996;45:1798-1804.
2. Evans JL, Goldfine ID. Alpha-lipoic acid: a multifunctional antioxidant that improves insulin sensitivity in patients with type 2 diabetes. *Diabetes Technol Ther. Sep* 2000;2(3):401-13.

3. Konrad D. The antihyperglycemic drug alpha-lipoic acid stimulates glucose uptake via both GLUT4 translocation and GLUT4 activation: potential role of p38 mitogen-activated protein kinase in GLUT4 activation. *Diabetes*. Jun 2000;50(6):1464-71.
4. Konrad T, Vicini P, Kusterer K, Hoflich A, Assadkhani A, Bohles HJ, Sewell A, Tritschler HJ, Cobelli C, Usadel KH. alpha-Lipoic acid treatment decreases serum lactate and pyruvate concentrations and improves glucose effectiveness in lean and obese patients with type 2 diabetes. *Diabetes Care*. 1999 Feb;22(2):280.

C. Visual function

1. Filina AA, Davydova NG, Endrikhovskii SN, et al. Lipoic acid as a means of metabolic therapy of open-angle glaucoma. *Vestn Oftalmol* Dec 1995;111(4):6-8.
2. Kilic F, et al. Modelling Cortical Cataractogenesis XX. In Vitro Effect of Alpha-lipoic Acid on Glutathione Concentrations in Lens in Model Diabetic Cataractogenesis. *Biochem Mol Biol Int*. Oct1998;46(3):585-95.
3. Stoyanovsky DA, Goldman R, Darrow RM, et al. Endogenous ascorbate regenerates vitamin E in the retina directly and in combination with exogenous dihydrolipoic acid. *Curr Eye Res*. Mar1995;14(3):181-9.
4. Ziegler D, Gries FA. Alpha-lipoic acid in the treatment of diabetic peripheral and cardiac autonomic neuropathy. *Diabetes*. 1997 Sep;46 Suppl 2:S62-6.

D. Cellular energy production

1. Khanna S, Atalay M, Lodge JK, Laaksonen DE, Roy S, Hanninen O, Packer L, Sen CK. Skeletal muscle and liver lipoyllysine content in response to exercise, training and dietary alpha-lipoic acid supplementation. *Biochem Mol Biol Int*. 1998 Oct;46(2):297-30.

E. Cellular structure and function

1. Hagen TM, Ingersoll RT, Lykkesfeldt J, Liu J, Wehr CM, Vinarsky V, Bartholomew JC, Ames AB. (R)-alpha-lipoic acid-supplemented old rats have improved mitochondrial function, decreased oxidative damage, and increased metabolic rate. *FASEB J*. 1999 Feb;13(2):411-8.

F. Metabolic function

1. Baur A, Harrer T, Peukert M, et al. Alpha-lipoic acid is an effective inhibitor of human immuno-deficiency virus (HIV-1) replication. *Klin Wochenschr* 1991;69:722-4.

2. Hagen TM, Ingersoll RT, Lykkesfeldt J, Liu J, Wehr CM, Vinarsky V, Bartholomew JC, Ames AB. (R)-alpha-lipoic acid-supplemented old rats have improved mitochondrial function, decreased oxidative damage, and increased metabolic rate. *FASEB J.* 1999 Feb;13(2):411-8.
3. Khanna S, Atalay M, Lodge JK, Laaksonen DE, Roy S, Hanninen O, Packer L, Sen CK. Skeletal muscle and liver lipoyllysine content in response to exercise, training and dietary alpha-lipoic acid supplementation. *Biochem Mol Biol Int.* 1998 Oct;46(2):297-30.
4. Roy S, Sen CK, Tritschler HJ, Packer L. Modulation of cellular reducing equivalent homeostasis by alpha-lipoic acid. Mechanisms and implications for diabetes and ischemic injury. *Biochem Pharmacol.* 1997 Feb 7;53(3):393-9.
5. Vasdev S, Ford CA, Parai S, Longrich L, Gadag V. Dietary alpha-lipoic acid supplementation lowers blood pressure in spontaneously hypertensive rats. *J Hypertens.* 2000 May;18(5):567-73.

G. Liver function

1. Berkson BM. A conservative triple antioxidant approach to the treatment of hepatitis C. Combination of alpha lipoic acid (thioctic acid), silymarin, and selenium: three case histories. *Med Klin.* Oct1999;94(Suppl 3):84-9.
2. Berkson BM. Thioctic acid in treatment of hepatotoxic mushroom (Phalloides) poisoning. *N Engl J Med.* Feb1979;300(7):371.
3. Plotzker R, Jensen DM, Payne JA. Case report. Amanita virosa acute hepatic necrosis: treatment with thioctic acid. *Am J Med Sci.* Mar1982;283(2):79-82.
4. Scholz RW, Reddy PV, Wynn MK, Graham KS, Liken AD, Gumprich E, Reddy CC. Glutathione-dependent factors and inhibition of rat liver microsomal lipid peroxidation. *Free Radic Biol Med.* 1997;23(5):815-28.
5. Sumathi R, Baskaran G, Varalakshmi P. Relationship between glutathione and DL alpha-lipoic acid against cadmium-induced hepatotoxicity. *Jpn J Med Sci Biol.* Apr1996;49(2):39-48.

H. Nervous system

1. Low PA, et al. The Roles of Oxidative Stress and Antioxidant Treatment in Experimental Diabetic Neuropathy. *Diabetes.* Sep1997;46(Suppl 2):S38-42.
2. Nickander KK, McPhee BR, Low PA, Tritschler H. Alpha-lipoic acid: antioxidant potency against lipid peroxidation of neural tissues in vitro and implications for diabetic neuropathy. *Free Radic Biol Med.* 1996;21(5):631-9.

3. Packer L, Tritschler HJ, Wessel K. Neuroprotection by the metabolic antioxidant alpha-lipoic acid. *Free Radic Biol Med.* 1997;22(1-2):359-78.
4. Roy S, Sen CK, Tritschler HJ, Packer L. Modulation of cellular reducing equivalent homeostasis by alpha-lipoic acid. Mechanisms and implications for diabetes and ischemic injury. *Biochem Pharmacol.* 1997 Feb 7;53(3):393-9.
5. Ziegler D, Gries FA. Alpha-lipoic acid in the treatment of diabetic peripheral and cardiac autonomic neuropathy. *Diabetes.* 1997 Sep;46 Suppl 2:S62-6.
6. Ziegler D, Ulrich H, Schatz H, et al. Effects of treatment with the antioxidant alpha-lipoic acid on cardiac autonomic neuropathy in NIDDM patients. *Diabetes Care* 1997;20:369-73.