

Literaturservice I-GAP

Alpha Lipoic acid

1: Toxicol Ind Health 2008 Nov;24(10):635-42

Influence of alpha lipoic acid on antioxidant status in D-galactosamine-induced hepatic injury.

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D-Galactosamine (GalN)-induced liver injury is associated with reactive oxygen species and oxidative stress. In the present study, we evaluated the effect of alpha lipoic acid (ALA) supplementation on acute GalN-induced oxidative liver injury. Hepatotoxicity induced by single intraperitoneal injection of GalN (500 mg/kg body wt) was evident from increase in lipid peroxidation and serum marker enzymes (aspartate transaminase, alanine transaminase, alkaline phosphatase, and lactate dehydrogenase). The decreased activities of enzymic antioxidants (superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase) as well as glutathione levels were the salient features observed in GalN-induced hepatotoxicity. Pretreatment with ALA (50 mg/kg body weight for 7 days) significantly precluded these changes and prevents the hepatic injury. Hence, this study clearly exemplified that ALA might be a suitable candidate against GalN-induced cellular abnormalities.

2: Biol Reprod 2008 Dec;

Alpha-Lipoic Acid Inhibits Tumor Necrosis Factor-Induced Remodeling and Weakening of Human Fetal Membranes.

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Untimely rupture of the fetal membranes (FM) is a major precipitant of preterm birth. Although the mechanism of FM weakening leading to rupture is not completely understood, pro-inflammatory cytokines, including tumor necrosis factor (TNF) and interleukin 1 beta (IL1B), have been shown to weaken FM concomitant with the induction of reactive-oxygen species, collagen remodeling, and prostaglandin release. We hypothesized that alpha-lipoic acid, a dietary antioxidant, may block the effect of inflammatory mediators and thereby inhibit FM weakening. Full thickness FM fragments were incubated with control media or TNF, with or without alpha-lipoic acid pre-treatment. FM rupture strength, as well as release of matrix metalloproteinase 9 (MMP9) and Prostaglandin E2 (PGE2) from the full thickness FM fragments was determined. The two constituent cell populations in amnion, the mechanically strongest FM component, were similarly examined. Amnion epithelial and mesenchymal cells were treated with TNF or IL1B, with or without alpha-lipoic acid pre-treatment. MMP9 and PGE2 were analyzed by ELISA, Western Blot and Zymography. TNF decreased FM rupture strength 50% while increasing MMP9 and PGE2 release. Lipoic acid inhibited these TNF-induced effects. Lipoic acid pre-treatment also inhibited TNF and IL1B-induced increases in MMP9 protein, activity and release in amnion epithelial cells, and PGE2 increases in both amnion epithelial and mesenchymal cells. In summary, lipoic acid pre-treatment inhibited TNF-

induced weakening of FM and cytokine induced MMP9 and PGE2 in both intact FM and amnion cells. We speculate that dietary supplementation with alpha-lipoic acid might prove clinically useful in prevention of preterm premature rupture of fetal membranes.

3: Nutr Res 2008 Jun;28(6):399-405

The combination of alpha-lipoic acid supplementation and aerobic exercise inhibits lipid peroxidation in rat skeletal muscles.

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We investigated the effect of DL-alpha-lipoic acid (LA) supplementation and regular aerobic exercise on the concentrations of malondialdehyde (MDA) and vitamin E, the activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx), and the levels of glutathione (GSH) in rat skeletal muscles (soleus and red gastrocnemius). For 8 weeks, rats (n = 7 per group) were (1) exercised on a treadmill for 30 min d(-1), (2) treated with supplemental LA, or (3) exercised and treated with supplemental LA. Control rats (n = 7) did not receive LA and were not exercised. DL-alpha-lipoic acid (100 mg kg(-1)) was administered daily as an oral supplement. The rats were exercised in a graded manner for 5 d wk(-1). The concentration of MDA in the soleus and red gastrocnemius was significantly lower in rats that exercised and received LA than in the other groups. Compared with the other groups, rats that exercised and received LA had a significantly higher vitamin E concentration in the soleus. The SOD and GPx activities in the soleus and red gastrocnemius were significantly higher in rats that exercised and received LA. These results suggest that LA supplementation combined with aerobic treadmill exercise inhibits lipid peroxidation in skeletal muscles. This effect was especially remarkable in the soleus, which is particularly sensitive to oxidative stress, as revealed by the increased vitamin E level and SOD and GPx activities.

4: Ophthalmic Physiol Opt 2008 Nov;28(6):503-23

Nutritional supplementation for type 2 diabetes: a systematic review.

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The role of nutritional supplementation is of increasing interest with regard to ocular disease. Randomised controlled trials have demonstrated the effectiveness of supplementation for age-related macular degeneration, and formulations are now being developed for use by people with diabetes and diabetic retinopathy. The aim of this review was to synthesise the evidence for use of nutritional supplementation in type 2 diabetes. MEDLINE and EMBASE databases were searched using a systematic approach. Only double-masked randomised controlled trials were selected. A total of 50 trials were identified as suitable for inclusion. The potential role of alpha-lipoic acid, chromium, folic acid, isoflavones, magnesium, Pycnogenol, selenium, vitamin C, vitamin E, and zinc in the treatment of type 2 diabetes is discussed. The review of trials identifies positive effects of these nutrients on various outcome measures relating to insulin

resistance and cardiovascular factors. Chromium was the most studied supplement, accounting for 16 of the 50 trials. A majority of the trials found a positive effect of chromium on fasting plasma glucose. Isoflavones were found to have a positive effect on insulin resistance and cardiovascular outcome measures, but only when combined with soy proteins. Vitamin E is reported to reduce oxidative stress at levels of 200 mg day(-1) or more.

5: Nutr Rev 2008 Nov;66(11):646-57

Alpha-lipoic acid supplementation and diabetes.

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Diabetes is a common metabolic disorder that is usually accompanied by increased production of reactive oxygen species or by impaired antioxidant defenses. Importantly, oxidative stress is particularly relevant to the risk of cardiovascular disease. Alpha-lipoic acid (LA), a naturally occurring dithiol compound, has long been known as an essential cofactor for mitochondrial bioenergetic enzymes. LA is a very important micronutrient with diverse pharmacologic and antioxidant properties. Pharmacologically, LA improves glycemic control and polyneuropathies associated with diabetes mellitus; it also effectively mitigates toxicities associated with heavy metal poisoning. As an antioxidant, LA directly terminates free radicals, chelates transition metal ions, increases cytosolic glutathione and vitamin C levels, and prevents toxicities associated with their loss. These diverse actions suggest that LA acts by multiple mechanisms both physiologically and pharmacologically. Its biosynthesis decreases as people age and is reduced in people with compromised health, thus suggesting a possible therapeutic role for LA in such cases. Reviewed here is the known efficacy of LA with particular reference to types 1 and 2 diabetes. Particular attention is paid to the potential benefits of LA with respect to glycemic control, improved insulin sensitivity, oxidative stress, and neuropathy in diabetic patients. It appears that the major benefit of LA supplementation is in patients with diabetic neuropathy.

6: Methods Find Exp Clin Pharmacol 2008 Jun;30(5):367-74

Coenzyme Q(10) and alpha-lipoic acid supplementation in diabetic rats: conduction velocity distributions.

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Diabetic neuropathies are a family of nerve disorders caused by diabetes. Patients with diabetes can develop nerve problems at any time, but the longer a person has diabetes the greater the risk. This study aims to investigate diabetes- and coenzyme Q(10) (CoQ(10)) or alpha-lipoic acid (ALA) supplementation-induced changes in the conduction velocity (CV) distributions of rat sciatic nerve fibers. Sciatic nerve compound action

potentials (CAPs) were recorded by suction electrode and CV distributions by the collision technique. Diabetes resulted in a significant increase in time to peak, rheobase and chronaxie values of these CAP waveforms, whereas the maximum depolarization, area, kinetics and CVs of both fast and slow nerve fiber groups were found to be decreased. Coenzyme Q(10) (CoQ(10)) supplementation was found to have some positive effect on the diabetes-induced alterations. CoQ(10) supplementation induced positive changes mainly in the area and fall-down phase of the kinetics of CAP waveforms, as well as rheobase, chronaxie and speed of the intermediately conducting groups (approximately or equal to 40 m/s). alpha-Lipoic acid (ALA) supplementation did not produce statistically significant effects. This study has shown for the first time that diabetes induces a shift of actively contributing nerve fibers toward slower CVs, and supplementation with CoQ(10) not only stopped this shift but also tended to restore velocities toward those of the age-matched control group. In addition to its effects on mitochondrial alterations, these positive effects of CoQ10 on diabetic neuropathy can be attributed to its antioxidant activity.

7: J Urol 2008 Nov;180(5):2234-40

The beneficial effect of coenzyme Q10 and lipoic acid on obstructive bladder dysfunction in the rabbit.

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PURPOSE: Recent evidence indicates that ischemia and reperfusion are major etiological factors in the bladder dysfunction that occurs after partial bladder outlet obstruction. Coenzyme Q10 and alpha-lipoic acid are found naturally in mitochondria and act as potent antioxidants. We investigated the beneficial effects of coenzyme Q10 plus alpha-lipoic acid in a rabbit model of bladder outlet obstruction. **MATERIALS AND METHODS:** Twenty male rabbits were divided into 5 groups. Group 1 served as control and group 2 received three weeks of coenzyme Q10 plus alpha-lipoic acid supplementation. Rabbits in group 3 underwent surgical partial bladder outlet obstruction for duration of four weeks and groups 4 and 5 were obstructed for seven weeks. In group 5, coenzyme Q10 plus alpha-lipoic acid supplementation was given following 4 weeks obstruction and continued till the end of the seven weeks. The contractile responses to various agents were determined. The protein nitration and carbonylation levels were studied by immunoblotting. Nerve function was determined by choline acetyltransferase activity and nerve density. **RESULTS:** The contractile responses to different forms of stimulations, including field stimulation, ATP, carbachol and KCl all showed decreases following 4 and 7 weeks obstruction. Treatment with coenzyme Q10 plus alpha-lipoic acid significantly restored contractile responses to all forms of stimulation. Treatment also had mitochondrial and neuronal effects and reduced protein nitration and carbonylation. Histologically there was less detrusor muscle hypertrophy. **CONCLUSIONS:** The current study clearly demonstrates that coenzyme Q10 and alpha-lipoic acid supplementation can improve bladder function after outlet obstruction.

8: Clin Sci (Lond) 2008 Sep;

Oral antioxidants and cardiovascular health in the exercise trained and untrained elderly: a radically different outcome.

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Both antioxidant supplementation and exercise training have been identified as interventions which may reduce oxidative stress and thus improve cardiovascular health, but the interaction of these interventions on arterial blood pressure and vascular function has not been studied in older humans. Thus, in six older (71 +/- 2 yrs) mildly hypertensive men, arterial blood pressure was evaluated non-invasively at rest and during small muscle mass (knee-extensor) exercise with and without a pharmacologic dose of oral antioxidants (Vitamins C, E, and alpha-lipoic acid). The efficacy of the antioxidant intervention to decrease plasma free radical concentration was verified via electron paramagnetic resonance (EPR) spectroscopy, while changes in endothelial function in response to exercise training and antioxidant administration were evaluated via flow-mediated vasodilation (FMD). Subjects were re-evaluated after a six-week aerobic exercise training program. Prior to training, acute antioxidant administration did not change resting arterial blood pressure or FMD. Six weeks of knee-extensor exercise training reduced systolic (from 150 +/- 8 to 138 +/- 3 mmHg, pre- vs. post-training) and diastolic (from 91 +/- 5 to 79 +/- 3 mmHg, pre- vs. post-training) blood pressure, and improved FMD (1.5 +/- 1% to 4.9 +/- 1%, pre- vs. post-training). However, antioxidant administration after exercise training negated these improvements, returning subjects to a hypertensive state and blunting training-induced improvements in FMD. The paradoxical effects of these interventions suggest a need for caution when exercise and acute antioxidant supplementation are combined in elderly, mildly hypertensive individuals.

9: Biogerontology 2008 Dec;9(6):421-8

Dietary supplementation with N-acetylcysteine, alpha-tocopherol and alpha-lipoic acid prevents age related decline in Na(+),K(+)-ATPase activity and associated peroxidative damage in rat brain synaptosomes.

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This study has shown that in aged rat brain (22-24 months) crude synaptosomes in comparison to that in young animals (4-6 months), a striking decrease in the activity of Na(+),K(+)-ATPase occurs along with decreased K (m) and V (max) but without any change in enzyme content as seen by immunoblotting. This is associated with an accumulation of peroxidative damage products in aged brain. When rats are given antioxidant supplementation in the diet with a combination of N-acetylcysteine, alpha-tocopherol and alpha-lipoic acid daily from 18 months onwards and sacrificed at 22-24 months for experimentation, the age associated decrease of Na(+),K(+)-ATPase activity, alterations of its kinetic parameters and accumulation of peroxidative damage products in brain synaptosomes are prevented nearly completely. Because of the critical importance of Na(+),K(+)-ATPase in neuronal functions, the results of this study may be of potential implications in controlling age-related functional deficits of the brain.

10: *Neurol Res* 2008 Sep;30(7):710-9

Examining the evidence: complementary adjunctive therapies for multiple sclerosis.

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OBJECTIVE: The purpose of this article is to provide a comprehensive overview of the most frequently encountered non-conventional approaches trialed for use in multiple sclerosis (MS). The efficacy and safety of non-conventional approaches ranging from bee venom therapy (BVT) to an array of vitamins and herbal products were discussed and evaluated. **METHODS:** Relevant English-language articles were identified through searches of MEDLINE (1990-2006), PubMed (1999-2006), Cochrane (1995-2006) and Toxnet (2000-2006). Classification of available literature was conducted according to the evidence based guidelines established by the American Academy of Neurology (AAN). However, due to the non-conventional nature of these treatment approaches, most available literature was derived from anecdotal reports and suboptimal clinical studies, lacking the rigor of evidence-based practice. **RESULTS:** There is presently only marginal supportive evidence for BVT in MS treatment. The inability to identify and quantify the active component of BVT combined with the associated risk of anaphylaxis has deterred its widespread use. The most promising evidence comes from prophylactic daily supplementation with vitamin D. Despite beneficial reports regarding non-herbal supplements such as alpha-lipoic acid (ALA), luteolin, evening primrose oil and vitamins such as B12, the lack of evidence does not support their prophylactic use. **DISCUSSION:** Based on available evidence, the prophylactic use of vitamin D is a viable option as an adjunct to conventional medicine. Although there is a lack of conclusive evidence to support the use of other non-conventional treatments, patients are still opting to trial and bare the risks of these products which are accessible without the intervention of a healthcare professional. Controlled, evidence-based trials are essential for healthcare professionals to competently intervene and recommend these products.

11: *Free Radic Biol Med* 2008 Sep;45(5):636-44

Small molecular antioxidants effectively protect from PUVA-induced oxidative stress responses underlying fibroblast senescence and photoaging.

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Exposure of human fibroblasts to 8-methoxypsoralen plus ultraviolet-A irradiation (PUVA) results in stress-induced cellular senescence in fibroblasts. We here studied the role of the antioxidant defense system in the accumulation of reactive oxygen species (ROS) and the effect of the antioxidants alpha-tocopherol, N-acetylcysteine, and alpha-lipoic acid on

PUVA-induced cellular senescence. PUVA treatment induced an immediate and increasing generation of intracellular ROS. Supplementation of PUVA-treated fibroblasts with alpha-tocopherol (alpha-Toc), N-acetylcysteine (NAC), or alpha-lipoic acid (alpha-LA) abrogated the increased ROS generation and rescued fibroblasts from the ROS-dependent changes into the cellular senescence phenotype, such as cytoplasmic enlargement, enhanced expression of senescence-associated-beta-galactosidase and matrix-metalloproteinase-1, hallmarks of photoaging and intrinsic aging. PUVA treatment disrupted the integrity of cellular membranes and impaired homeostasis and function of the cellular antioxidant system with a significant decrease in glutathione and hydrogen peroxide-detoxifying enzymes activities. Supplementation with NAC, alpha-LA, and alpha-Toc counteracted these changes. Our data provide causal evidence that (i) oxidative stress due to an imbalance in the overall cellular antioxidant capacity contributes to the induction and maintenance of the PUVA-induced fibroblast senescence and that (ii) low molecular antioxidants protect effectively against these deleterious alterations.

12: Mech Ageing Dev 2008 Jun;129(6):341-8

Dietary lipoic acid supplementation can mimic or block the effect of dietary restriction on life span.

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Dietary restriction feeding extends survival in a range of species but a detailed understanding of the underlying mechanism is lacking. There is interest therefore in identifying a more targeted approach to replicate this effect on survival. We report that in rats dietary supplementation with alpha-lipoic acid, has markedly differing effects on lifetime survival depending upon the dietary history of the animal. When animals are switched from DR feeding to ad libitum feeding with a diet supplemented with alpha-lipoic acid, the extended survival characteristic of DR feeding is maintained, even though the animals show accelerated growth. Conversely, switching from ad libitum feeding a diet supplemented with alpha-lipoic acid to DR feeding of the non-supplemented diet, blocks the normal effect of DR to extend survival, even after cessation of lipoic acid supplementation. Unlike the dynamic effect of switching between DR and ad libitum feeding with a non-supplemented diet where the subsequent survival trajectory is determined by the new feeding regime, lipoic acid fixes the survival trajectory to that established by the initial feeding regime. Ad libitum feeding a diet supplemented with lipoic acid can therefore act as mimetic of DR to extend survival.

13: J Endocrinol 2008 May;197(2):287-96

Antioxidants preserve redox balance and inhibit c-Jun-N-terminal kinase pathway while improving insulin signaling in fat-fed rats: evidence for the role of oxidative stress on IRS-1 serine phosphorylation and insulin resistance.

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The oxidative stress-sensitive c-Jun-N-terminal kinase (JNK) pathway is known to be activated in diabetic condition and is involved in the progression of insulin resistance. However, the effect of antioxidants on JNK pathway and insulin resistance has not been investigated. The present study was aimed to investigate the effect of antioxidants on redox balance, insulin sensitivity, and JNK pathway in high-fat-fed rats. Male Wistar rats were divided into four groups: the control group - received a rodent chow; control+antioxidant group - fed with rodent chow supplemented with 0.2% (w/w) vitamin E, 0.3% (w/w) vitamin C, and 0.5% (w/w) alpha-lipoic acid; high-fat group - received high-fat diet; and high fat+antioxidant group - fed with high-fat diet supplemented with above antioxidants. Fat feeding to rats for 9 weeks significantly increased IRS-1 serine phosphorylation, reduced insulin-stimulated IRS-1 tyrosine phosphorylation and insulin sensitivity. High-fat diet also impaired redox balance and activated the redox-sensitive serine kinase - JNK pathway. Antioxidant supplementation along with high-fat diet preserved the free radical defense system, inhibited the activation of JNK pathway, and improved insulin signaling and insulin sensitivity. The present study shows for the first time that antioxidants inhibit JNK pathway and IRS-1 serine phosphorylation while improving insulin sensitivity in fat-fed rats. These findings implicate the beneficial effect of antioxidants in obesity-/dyslipidemia-induced insulin resistance in humans.

14: J Cell Mol Med 2008 Mar;

Neuronal mitochondrial amelioration by feeding acetyl-L-carnitine and lipoic acid to aged rats.

Aliev, G, Liu, J, Shen, J C, Fischbach, K, Pacheco, G J, Chen, S G, Obrenovich, M E, Ward, W F, Richardson, A G, Smith, M A, Gasimov, E, Perry, G, Ames, B N

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Brain function declines with age and is associated with diminishing mitochondrial integrity. The neuronal mitochondrial ultrastructural changes of young (4 mo) and old (21 mo) F344 rats supplemented with two mitochondrial metabolites, acetyl-L-carnitine (ALCAR, 0.2% [wt/vol] in the drinking water) and R-alpha-lipoic acid (LA, 0.1% (wt/wt) in the chow), were analyzed using qualitative and quantitative electron microscopy techniques. Two independent morphologists blinded to sample identity examined and scored all electron micrographs. Mitochondria were examined in each micrograph, and each structure was scored according to the degree of injury. Controls displayed an age-associated significant decrease in the number of intact mitochondria ($p = 0.026$) as well as increase in mitochondria with broken cristae ($p < 0.001$) in the hippocampus as demonstrated by electron microscopic observations. Neuronal mitochondrial damage was associated with damage in vessel wall cells, especially vascular endothelial cells. Dietary supplementation of young and aged animals increased the proliferation of intact mitochondria and reduced the density of mitochondria associated with vacuoles and lipofuscin. Feeding old rats ALCAR and LA significantly reduced the number of severely damaged mitochondria ($p = 0.02$) and increased the number of intact mitochondria ($p < 0.001$) in the hippocampus. These results suggest that feeding ALCAR with LA may ameliorate age-associated mitochondrial ultrastructural decay, and are consistent with previous studies showing improved brain function.

15: Nutrition 2008 Jun;24(6):582-8

Lipoic acid prevents high-fat diet-induced dyslipidemia and oxidative stress: a microarray analysis.

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OBJECTIVE: We previously found that lipoic acid (LA) improved high-fat diet (HFD)-induced dyslipidemia in rats. To elucidate the molecular mechanisms of that effect, we carried out experiments aimed at analyzing biochemical parameters and gene expression profiles. **METHODS:** C57BL/6 mice were randomly assigned to one of three groups (n = 8). The control group consumed an ordinary diet (4.89% fat, w/w). The other two experimental groups were fed with an HFD (21.45% fat, w/w) or an HFD plus 0.1% LA. After 6 wk, plasma lipid level and antioxidant status were examined. To investigate the molecular mechanisms underlying the effects of LA on lipid metabolism and oxidative stress, we examined gene expression profiles in liver using the GeneChip microarray system. The differential expression of genes of interest identified by microarray technique was validated by real-time reverse transcription-polymerase chain reaction. **RESULTS:** HFD resulted in significant alterations in lipid profiles and a depressed antioxidant defense system. LA supplementation induced decreases in lipid peroxidation, plasma cholesterol, triacylglycerols, and low-density lipoprotein cholesterol and an increase in high-density lipoprotein in HFD-fed mice. DNA microarray analysis of the liver showed that LA ingestion upregulated the expression of genes related to beta-oxidation and free radical scavenger enzymes, whereas those involved in cholesterol synthesis were downregulated. **CONCLUSION:** LA can prevent HFD-induced dyslipidemia by modulating lipid metabolism, especially by increasing beta-oxidation and decreasing cholesterol synthesis, and oxidative stress by increasing those of free radical scavenger enzyme gene expression.

16: Radiat Res 2008 Apr;169(4):384-96

Dietary antioxidants protect hematopoietic cells and improve animal survival after total-body irradiation.

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The purpose of this study was to determine whether a dietary supplement consisting of L-selenomethionine, vitamin C, vitamin E succinate, alpha-lipoic acid and N-acetyl cysteine could improve the survival of mice after total-body irradiation. Antioxidants significantly increased the 30-day survival of mice after exposure to a potentially lethal dose of X rays when given prior to or after animal irradiation. Pretreatment of animals with antioxidants resulted in significantly higher total white blood cell and neutrophil counts in peripheral blood at 4 and 24 h after 1 Gy and 8 Gy. Antioxidants were effective in preventing peripheral lymphopenia only after low-dose irradiation. Antioxidant supplementation was also associated with increased bone marrow cell counts after irradiation. Supplementation with antioxidants was associated with increased Bcl2 and decreased Bax, caspase

9 and TGF-beta1 mRNA expression in the bone marrow after irradiation. Maintenance of the antioxidant diet was associated with improved recovery of the bone marrow after sublethal or potentially lethal irradiation. Taken together, oral supplementation with antioxidants appears to be an effective approach for radioprotection of hematopoietic cells and improvement of animal survival, and modulation of apoptosis is implicated as a mechanism for the radioprotection of the hematopoietic system by antioxidants.

17: Br J Pharmacol 2008 Apr;153(8):1587-8

Lipoic acid supplementation and endothelial function.

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Endothelial dysfunction is caused by all the recognized cardiovascular risk factors and has been implicated in the complex processes leading to the initiation and progression of atherosclerosis. Short-term treatment with lipoic acid is shown in the current issue of the British Journal of Pharmacology to improve endothelial function of aortic rings of old rats. The age-related decrease in phosphorylation of nitric oxide synthase and Akt was improved by lipoic acid supplementation. The improved phosphorylation status may have been due to reduced activity of the phosphatase PPA2, associated with decreased levels of endothelial ceramide induced by lipoic acid. Neutral sphingomyelinase activity was also reduced by lipoic acid, which was due, at least in part, to increased glutathione levels in endothelial cells. The favourable antioxidant, anti-inflammatory, metabolic and endothelial effects of lipoic acid shown in rodents, in this and other recently published studies, warrant further assessment of its potential role for prevention and treatment of cardiovascular diseases.

18: J Altern Complement Med 2008 Mar;14(2):139-46

Restoration of blood total glutathione status and lymphocyte function following alpha-lipoic acid supplementation in patients with HIV infection.

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OBJECTIVES: To determine whether supplementation with alpha-lipoic acid (ALA), a glutathione-replenishing disulfide, modulates whole blood total glutathione (GSH + GSSG) levels and improves lymphocyte function in human immunodeficiency virus (HIV)-infected subjects with history of unresponsiveness to highly active antiretroviral treatment (HAART). DESIGN AND SETTING: Randomized, double-blinded, placebo-controlled trial conducted at two study sites: an eye clinic at a county hospital in San Jose and a research clinic in San Francisco, California. SUBJECTS: A total of 33 HIV-infected men and women with viral load >10,000 copies/cm(3), despite HAART, aged 44-47 years, approximately 36% nonwhite, were enrolled. INTERVENTION: Patients were randomly assigned to receive either ALA (300 mg three times a day) or matching placebo for 6 months. MAIN OUTCOME MEASURES: The change over 6 months in blood total glutathione status, lymphocyte proliferation response to T-cell mitogens, CD4 cell count, and viral load in patients

receiving ALA compared to placebo. RESULTS: The mean blood total glutathione level in ALA-supplemented subjects was significantly elevated after 6 months (1.34±0.79 vs. 0.81±0.18 mmol/L) compared to insignificant change (0.76±0.34 vs. 0.76±0.22 mmol/L) in the placebo group (ALA vs. placebo: p=0.04). The lymphocyte proliferation response was significantly enhanced or stabilized after 6 months of ALA supplementation compared to progressive decline in the placebo group (ALA vs. placebo: p<0.001 with phytohemagglutinin; p=0.02 with anti-CD3 monoclonal antibody). A positive correlation was seen between blood total glutathione level and lymphocyte response to anti-CD3 stimulation (R(2)=0.889). There was no significant change in either HIV RNA level or CD4 count over 6 months in the ALA-supplemented compared to the control group. CONCLUSION: Supplementation with alpha-lipoic acid may positively impact patients with HIV and acquired immune deficiency syndrome by restoring blood total glutathione level and improving functional reactivity of lymphocytes to T-cell mitogens.

19: Circulation 2008 Jan;117(3):421-8

Dietary alpha-lipoic acid supplementation inhibits atherosclerotic lesion development in apolipoprotein E-deficient and apolipoprotein E/low-density lipoprotein receptor-deficient mice.

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BACKGROUND: Vascular inflammation and lipid deposition are prominent features of atherosclerotic lesion formation. We have shown previously that the dithiol compound alpha-lipoic acid (LA) exerts antiinflammatory effects by inhibiting tumor necrosis factor-alpha- and lipopolysaccharide-induced endothelial and monocyte activation in vitro and lipopolysaccharide-induced acute inflammatory responses in vivo. Here, we investigated whether LA inhibits atherosclerosis in apolipoprotein E-deficient (apoE^{-/-}) and apoE/low-density lipoprotein receptor-deficient mice, 2 well-established animal models of human atherosclerosis. METHODS AND RESULTS: Four-week-old female apoE^{-/-} mice (n=20 per group) or apoE/low-density lipoprotein receptor-deficient mice (n=21 per group) were fed for 10 weeks a Western-type chow diet containing 15% fat and 0.125% cholesterol without or with 0.2% (wt/wt) R,S-LA or a normal chow diet containing 4% fat without or with 0.2% (wt/wt) R-LA, respectively. Supplementation with LA significantly reduced atherosclerotic lesion formation in the aortic sinus of both mouse models by approximately 20% and in the aortic arch and thoracic aorta of apoE^{-/-} and apoE/low-density lipoprotein receptor-deficient mice by approximately 55% and 40%, respectively. This strong antiatherogenic effect of LA was associated with almost 40% less body weight gain and lower serum and very low-density lipoprotein levels of triglycerides but not cholesterol. In addition, LA supplementation reduced aortic expression of adhesion molecules and proinflammatory cytokines and aortic macrophage accumulation. These antiinflammatory effects of LA were more pronounced in the aortic arch and the thoracic aorta than in the aortic sinus, reflecting the corresponding reductions in atherosclerosis. CONCLUSIONS: Our study shows that dietary LA supplementation inhibits atherosclerotic lesion formation in 2 mouse models of human atherosclerosis, an inhibition that appears to be due to the "antiobesity," antihypertriglyceridemic, and antiinflammatory effects of LA. LA may be a useful adjunct in the prevention and treatment of atherosclerotic vascular diseases.

20: Mol Med 2008 Mar-Apr;14(3-4):175-83

alpha-Lipoic acid modulates extracellular matrix and angiogenesis gene expression in non-healing wounds treated with hyperbaric oxygen therapy.

Alleva, Renata, Tomasetti, Marco, Sartini, Davide, Emanuelli, Monica, Nasole, Emanuele, Di Donato, Ferruccio, Borghi, Battista, Santarelli, Lory, Neuzil, Jiri

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alpha-Lipoic acid (LA) has been found previously to accelerate wound repair in patients affected by chronic wounds who underwent hyperbaric oxygen (HBO) therapy. Because proteinases are important in wound repair, we hypothesized that LA may regulate matrix metalloproteinase (MMP) expression in cells that are involved in wound repair. Patients undergoing HBO therapy were double-blind randomized into two groups: the LA group and the placebo group. Gene expression profiles for MMPs and for angiogenesis mediators were evaluated in biopsies collected at the first HBO session, at the seventh HBO session, and after 14 days of HBO treatment. ELISA tests were used to validate microarray expression of selected genes. LA supplementation in combination with HBO therapy downregulated the inflammatory cytokines and the growth factors which, in turn, affect MMPs expression. **The disruption of the positive autocrine feedback loops that maintain the chronic wound state promotes progression of the healing process.**

21: Nutr Clin Pract 2007 Dec;22(6):679-87

Nonvitamin, nonmineral dietary supplementation in HIV-positive people.

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BACKGROUND: Many consumers with chronic diseases attempt to take control of their health by using dietary supplements. The objective of this study was to describe current nonvitamin, nonmineral (NVNM) supplement use of HIV-infected persons in the Nutrition for Healthy Living (NFHL) cohort, the financial burden that buying these supplements might pose to this population, and to review current literature on potential interactions between NVNM supplements. **METHODS:** At baseline visit, participants were educated by a registered dietitian on keeping a complete 3-day food record (including all supplements) for 2 weekdays and 1 weekend day. Seventy-two subjects reported consumption of NVNM supplements, and their food records were reviewed in detail. **RESULTS:** Each of the 72 subjects in this study used a mean of 6 NVNM supplements, which may have been in the form of a pill, powder, bar, or liquid. The 6 most common were glutamine (51%), N-acetyl-cysteine (36%), fish oil (33%), alpha-lipoic acid (32%), acetyl-l-carnitine (28%), and coenzyme Q10 (28%). Participants were also taking an average of 4 vitamin/mineral supplements; the 6 most common were multivitamin/multimineral (83%), vitamin E (51%), vitamin C (47%), vitamin B complex (43%), calcium (29%), and selenium (28%). **CONCLUSIONS:** With a total of 107 different types of NVNM supplements, our estimated cost

examples indicated a weekly supplement regimen cost of between \$25 and \$40 dollars. According to literature review, taking an NVNM supplement may involve some risk because many components have not been studied and these products are not tightly regulated.

22: Chem Biol Interact 2008 Feb;171(3):306-11

Postmitotic tissue selenium and manganese levels in alpha-lipoic acid-supplemented aged rats.

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Redistribution of selenium and manganese in postmitotic tissues of alpha-lipoic acid-supplemented aged rats has been proposed to contribute to metal-catalyzed protein oxidation. DL-Alpha-lipoic acid (LA) (100 mg/[kg body wt.day]) was administered intraperitoneally to the Sprague-Dawley rats for 14 days. Serum selenium levels were lowered in the aged rats with LA supplementation compared with those of the rats without LA supplementation. Similarly, the selenium levels of the heart, brain and muscle were found to be significantly lower in LA-supplemented rats when compared to control rats. On the other hand, serum manganese levels were not changed in the aged rats with LA supplementation compared with those of the rats without LA supplementation. The heart manganese levels detected in LA-supplemented rats were significantly lower than controls. Manganese levels of the brain and muscle tissues were increased in the aged rats with LA supplementation compared with those of the rats without LA supplementation. Based on the findings of our study, we conclude that LA may exhibit pro-oxidant effect depending on the altered selenium and manganese homeostasis. Thus, our results stress the importance of monitoring the dose of LA supplementation and serum selenium levels, duration of treatment and its potential harmful pro-oxidant effects in the postmitotic tissues of aged rats.

23: Clin Exp Dermatol 2007 Nov;32(6):631-6

Antioxidants and narrow band-UVB in the treatment of vitiligo: a double-blind placebo controlled trial.

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BACKGROUND: Vitiligo is an acquired depigmenting disease with uncertain aetiopathogenesis, possibly associated with oxidative stress. Narrowband ultraviolet B phototherapy (NB-UVB) is the most widely used and effective treatment. AIM: To evaluate the clinical effectiveness of NB-UVB and the repairing of oxidative stress-induced damage, using oral supplementation with an antioxidant pool (AP). METHODS: Patients (n = 35) with nonsegmental vitiligo were enrolled in a randomized, double-blind, placebo-controlled multicentre trial. The treatment group received, for 2 months before and for 6 months during the NB-UVB treatment, a balanced AP containing alpha-lipoic acid, vitamins C and E, and polyunsaturated fatty acids. The area and number of lesions, as well as some parameters of the oxidation-reduction (redox) status of the peripheral blood mononuclear cells (PBMCs)

were estimated at the beginning, after 2 months, and at the end of the trial. RESULTS: In total, 28 patients completed the study. After 2 months of AP supplementation, the catalase activity and the production of reactive oxygen species (ROS) were 121% and 57% of the basal values ($P < 0.05$ and $P < 0.02$ vs. placebo, respectively). The AP increased the therapeutic success of NB-UVB, with 47% of the patients obtaining $> 75\%$ repigmentation vs. 18% in the placebo group ($P < 0.05$). An increase in catalase activity to 114% ($P < 0.05$ vs. placebo) and decrease in ROS level of up to 60% ($P < 0.02$ vs. placebo) of the basal value was observed in PBMCs. Finally, the AP intake maintained the membrane lipid ratio (saturated : unsaturated fatty acids 1.8 : 3.1; $P < 0.05$), counteracting phototherapy-induced saturation. CONCLUSIONS: Oral supplementation with AP containing alpha-lipoic acid before and during NB-UVB significantly improves the clinical effectiveness of NB-UVB, reducing vitiligo-associated oxidative stress.

24: J Environ Biol 2007 Apr;28(2 Suppl):333-47

Arsenic induced oxidative stress and the role of antioxidant supplementation during chelation: a review.

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Arsenic is a naturally occurring metalloid, ubiquitously present in the environment in both organic and inorganic forms. Arsenic contamination of groundwater in the West Bengal basin in India is unfolding as one of the worst natural geoenvironmental disaster to date. Chronic exposure of humans to high concentration of arsenic in drinking water is associated with skin lesions, peripheral vascular disease, hypertension, Blackfoot disease and high risk of cancer. The underlying mechanism of toxicity includes the interaction with the sulphhydryl groups and the generation of reactive oxygen species leading to oxidative stress. Chelation therapy with chelating agents like British Anti Lewisite (BAL), sodium 2,3-dimercaptopropane 1-sulfonate (DMPS), meso 2,3 dimercaptosuccinic acid (DMSA) etc., is considered to be the best known treatment against arsenic poisoning. The treatment with these chelating agents however is compromised with certain serious drawbacks/side effects. The studies show that supplementation of antioxidants along with a chelating agent prove to be a better treatment regimen. This review attempts to provide the readers with a comprehensive account of recent developments in the research on arsenic poisoning particularly the role of oxidative stress/free radicals in the toxic manifestation, an update about the recent strategies for the treatment with chelating agents and a possible beneficial role of antioxidants supplementation to achieve the optimum effects.

25: J Alzheimers Dis 2007 Sep;12(2):195-206

Lipoic acid and N-acetyl cysteine decrease mitochondrial-related oxidative stress in Alzheimer disease patient fibroblasts.

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In this study, we evaluated the effect of lipoic acid (LA) and N-acetyl cysteine (NAC) on oxidative [4-hydroxy-2-nonenal, N(epsilon)-(carboxymethyl)lysine and heme oxygenase-1] and apoptotic (caspase 9 and Bax) markers in fibroblasts from patients with Alzheimer disease (AD) and age-matched and young controls. AD fibroblasts showed the highest levels of oxidative stress, and the antioxidants, lipoic acid (1 mM) and/or N-acetyl cysteine (100 microM) exerted a protective effect as evidenced by decreases in oxidative stress and apoptotic markers. Furthermore, we observed that the protective effect of LA and NAC was more pronounced when both agents were present simultaneously. AD-type changes could be generated in control fibroblasts using N-methylprotoporphyrin to inhibit cytochrome oxidase assembly indicating that the oxidative damage observed was associated with mitochondrial dysfunction. The effects of N-methylprotoporphyrin were reversed or attenuated by both lipoic acid and N-acetyl cysteine. These data suggest mitochondria are important in oxidative damage that occurs in AD. As such, antioxidant therapies based on lipoic acid and N-acetyl cysteine supplementation may be promising.

26: Biochem Biophys Res Commun 2007 Nov;363(3):651-5

Thiol supplementation inhibits metalloproteinase activity independent of glutathione status.

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Matrix metalloproteinases (MMPs) are proteolytic enzymes that regulate both integrity and composition of the extracellular matrix (ECM). Excessive ECM breakdown by MMPs is implicated in many physiological and pathological conditions, such as atherosclerosis. Activated macrophages, especially in the atherosclerotic lesion, are a major source of reactive oxygen species (ROS). Antioxidants protect against ROS-induced MMPs activation and inhibit gelatinolytic activity. We sought to determine whether the antioxidants glutathione (GSH), N-acetylcysteine (NAC), or lipoic acid (LA) affect gelatinase production and secretion. The results show that thiol compounds affect MMPs expression and activity in different ways. MMP-2 activity is directly inhibited by NAC and GSH, while LA is ineffective. On the contrary, MMP-9 expression is inhibited by LA at a pretranscriptional level, and MMP-9 activity is stimulated by GSH through a direct interaction with the gelatinase itself. Although all thiols, these compounds have different properties and different cellular uptakes and metabolic characteristics, and this could explain, at least in part, their differential effects on MMPs.

27: Rev Port Cardiol 2007 Jun;26(6):609-19

Endothelial dysfunction in type 2 diabetes: effect of antioxidants.

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Individuals with insulin resistance and diabetes mellitus have increased cardiovascular morbidity and mortality, caused in part by vascular complications. Endothelial dysfunction has been implicated in the pathogenesis of vascular diabetic disease. This abnormal function of the vasculature precedes cardiovascular disease and is associated with impaired endothelium-dependent vasorelaxation. The main etiology of the increased mortality and morbidity of type 2 diabetic patients is atherosclerosis. Increased production of free radicals is associated with the pathophysiology of diabetes, resulting in oxidative damage to lipids and proteins. Reduction of oxidative stress in diabetic patients may delay the onset of atherogenesis and the appearance of micro- and macrovascular complications. Alpha-lipoic acid (LA) is a multifunctional antioxidant that has been shown to have beneficial effects on polyneuropathy and on markers of oxidative stress in various tissues. This study was conducted to investigate the effects of LA on endothelial function in diabetic and hyperlipidemic animal models. Carbohydrate and lipid metabolism, endothelial function, plasma malondialdehyde (MDA) and urinary 8-hydroxydeoxyguanosine (8-OHdG) were assessed in non-diabetic controls (Wistar rats), untreated diabetic Goto-Kakizaki (GK) rats and, atherogenic diet (AD)-fed GK rats (fed with atherogenic diet only, treated with alpha-lipoic acid and treated with vehicle, for 3 months). AD resulted in a 3-fold increase in both total and non-HDL serum cholesterol levels and in a 2-fold increase triglyceride levels while endothelial function was significantly reduced. MDA and 8-OHdG levels were higher in the GK and GK hyperlipidemic groups and were completely reversed by the antioxidant. Hyperlipidemic GK diabetic rats showed significantly reduced endothelial function that was partially improved with LA. Furthermore, lipoic acid significantly reduced serum cholesterol levels, without lowering HDL cholesterol. **Alpha-lipoic acid supplementation represents an achievable adjunct therapy to improve endothelial function and reduce oxidative stress, factors that are implicated in the pathogenesis of atherosclerosis in diabetes.**

28: FASEB J 2007 Nov;21(13):3756-62

Acetyl-L-carnitine and alpha-lipoic acid supplementation of aged beagle dogs improves learning in two landmark discrimination tests.

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Beagle dogs between 7.6 and 8.8 years of age administered a twice daily supplement of alpha-lipoic acid (LA) and acetyl-L-carnitine (ALC) over approximately 2 months made significantly fewer errors in reaching the learning criterion on two landmark discrimination tasks compared to controls administered a methylcellulose placebo. Testing started after a 5 day wash-in. The dogs were also tested on a variable delay version of a previously acquired spatial memory task; results were not significant. The improved performance on the landmark task of dogs supplemented with LA + ALC provides evidence of the effectiveness of this supplement in improving discrimination and allocentric spatial learning. We suggest that long-term maintenance on LA and ALC **may be effective in attenuating age-associated cognitive decline by slowing the rate of mitochondrial decay and cellular aging.**

29: J Altern Complement Med 2007 Jun;13(5):577-84

Effects of alpha-lipoic acid supplementation in peripheral arterial disease: a pilot study.

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OBJECTIVE: To examine whether 3 months of lipoic acid (LA) supplementation improved walking tolerance and delayed claudication pain onset in peripheral arterial disease (PAD). **DESIGN:** Randomized, double-blind, controlled study. **SETTING:** General Clinical Research Center. **SUBJECTS:** Twenty-eight (28) participants (15 men, 13 women) with PAD (ankle brachial index range 0.9-0.4, mean age 73.2 +/- 1.6 years). **INTERVENTION:** LA (600 mg/day) or placebo for 3 months. **OUTCOME MEASURES:** Walking tolerance was assessed by 6-minute walk test distance, 4-meter walk time, initial claudication pain time (ICT) and distance (ICD), and peak claudication pain. Serum was assessed for inflammation (C-reactive protein [CRP]) and oxidative stress (lipid hydroperoxides) as potential mechanisms for changes in walking tolerance. **RESULTS:** ICT increased 34.4% and 15%, ICD was reduced by 40.5% and 18%, and peak claudication pain ratings were reduced by 93% and 7% in LA and placebo groups, respectively. Although the improvements in peak pain and ICT achieved significance within the LA group (both $p < 0.05$), the interactions of group by time were not found to be significant ($p > 0.05$). Oxidative stress and CRP measures were not different between groups by month 3 ($p > 0.05$). **There were no serious side-effects associated with the LA. CONCLUSIONS:** LA may confer pain relief during exercise. However, longer and larger trials are warranted to determine long-term effects of LA alone or combined with other interventions on PAD symptoms.

30: Rejuvenation Res 2007 Sep;10(3):311-26

Cytochrome c oxidase rather than cytochrome c is a major determinant of mitochondrial respiratory capacity in skeletal muscle of aged rats: role of carnitine and lipoic acid.

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The release of mitochondrial cytochrome c followed by activation of caspase cascade has been reported with aging in various tissues, whereas little is known about the caspase-independent pathway involved in mitochondrial dysfunction. To determine the functional impact of cytochrome c loss on mitochondrial respiratory capacity, we monitored NADH redox transitions and oxygen consumption in isolated skeletal muscle mitochondria of 4- and 24-month-old rats in the presence and absence of exogenous cytochrome c; and assessed the efficacy of cosupplementation of carnitine and lipoic acid on age-related alteration in mitochondrial respiration. The loss of mitochondrial cytochrome c with age was accompanied with alteration in respiratory transition, which in turn was not rescued by exogenous addition of cytochrome c to isolated mitochondria. The analysis of mitochondrial and nuclear-encoded cytochrome c oxidase subunits suggests that the decreased levels of cytochrome c oxidase may be attributed for the irresponsiveness

to exogenously added cytochrome c on mitochondrial respiratory transitions, possibly through reduction of upstream electron carriers. Oral supplementation of carnitine and lipoic acid to aged rats help to maintaining the mitochondrial oxidative capacity by regulating the release of cytochrome c and improves cytochrome c oxidase transcript levels. Thus, carnitine and lipoic acid supplementation prevents the loss of cytochrome c and their associated decline in cytochrome c oxidase activity; thereby, effectively attenuating any putative decrease in cellular energy and redox status with age.

31: Med Chem 2007 May;3(3):297-300

Effect of alpha-lipoic acid supplementation on trace element levels in serum and in postmitotic tissue in aged rats.

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Redistribution of redox-active divalent metal ions (e.g. copper, zinc, and iron) in postmitotic tissues of lipoic acid supplemented aging rats has been proposed to contribute to metal-catalyzed protein oxidation. DL-alpha lipoic acid (LA) (100 mg/kg body wt/day) was administered intraperitoneally to the Sprague-Dawley rats for 14 days. Serum copper levels lowered in the aged rats with LA supplementation compared to the rats without LA supplementation. On the other hand, serum zinc and iron levels increased in the aged rats with LA supplementation compared to the rats without LA supplementation. Copper levels of the postmitotic tissues were not changed in the aged rats with LA supplementation compared to the controls. The heart zinc levels detected in LA supplemented rats were significantly lower than controls. Similarly, the iron levels of the heart were found to be significantly lower in LA supplemented rats when compared to control rats. LA supplementation did not affect brain and muscle iron levels. The brain and muscle zinc levels remained the same in both group of rats. Based on the findings of our study, we have concluded that LA may exhibit prooxidant effect depending on the altered trace element homeostasis. Therefore, our results emphasize the importance of monitoring the dose of LA supplementation, duration of treatment and its potential harmful effects in the postmitotic tissues of aged rats.

32: J Altern Complement Med 2007 Jan-Feb;13(1):159-75

Algorithm for complementary and alternative medicine practice and research in type 2 diabetes.

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OBJECTIVE: To develop a model to direct the prescription of nutritional and botanical medicines in the treatment of type 2 diabetes for both clinical and research purposes. METHODS: Available literature on nutritional and botanical medicines was reviewed and categorized as follows: antioxidant/anti-inflammatory; insulin sensitizer; and beta-cell protectant/insulin secretagogue. Literature describing laboratory assessment for glycemic control, insulin resistance, and beta-cell reserve

was also reviewed and a clinical decision tree was developed. RESULTS: Clinical algorithms were created to guide the use of nutritional and botanic medicines using validated laboratory measures of glycemic control, insulin sensitivity, and beta-cell reserve. Nutrient and botanic medicines with clinical trial research support include coenzyme Q10, carnitine, alpha-lipoic acid, N-acetylcysteine, vitamin D, vitamin C, vitamin E, chromium, vanadium, omega-3 fatty acids, cinnamon (*Cinnamomum cassia*), fenugreek (*Trigonella foenum-graecum*), and gymnema (*Gymnema sylvestre*). CONCLUSIONS: Clinical algorithms can direct supplementation in clinical practice and provide research models for clinical investigation. Algorithms also provide a framework for integration of future evidence as it becomes available. Research funding to investigate potentially beneficial practices in complementary medicine is critically important for optimal patient care and safety.

33: Antioxid Redox Signal 2007 Apr;9(4):497-506

Alpha-lipoic Acid modulates heat shock factor-1 expression in streptozotocin-induced diabetic rat kidney.

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Increased oxidative stress and impaired heat shock protein (HSP) synthesis may contribute to diabetic nephropathy. The question of whether 8-week thiol antioxidant alpha-lipoic acid (LA) supplementation modulates HSP response and oxidative stress was studied in the kidney of streptozotocin-induced diabetic (SID) and nondiabetic rats. SID caused a histological mesangial expansion, tubular dilatation, and increased levels of transforming growth factor-beta (TGF-beta), a mediator of glomerulosclerosis. SID increased 4-hydroxynonenal (4-HNE) protein adduct formation, a marker of lipid peroxidation, and heme oxygenase-1 (HO-1), also a marker of oxidative stress. Moreover, SID increased the DNA-binding activity of heat shock factor-1 (HSF-1) and expression of heat shock protein 60 (HSP60). In contrast, LA supplementation partially reversed histological findings of glomerulosclerosis and decreased TGF-beta. LA also increased HSF-1 and decreased HO-1 protein expression, without affecting 4-HNE protein adduct levels. At the mRNA level, LA increased expression of HSF-1, HSP90, and glucose-regulated protein (GRP75) in both control and diabetic animals and HSP72 in SID rats. However, LA supplementation did not affect these HSPs at the protein level. These findings suggest that in addition to its antiglomerulosclerotic effects, LA can induce cytoprotective response in SID.

34: Diabetes Educ 2007 Jan-Feb;33(1):111-7

Efficacy and safety of alpha-lipoic acid supplementation in the treatment of symptomatic diabetic neuropathy.

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PURPOSE: The purpose of this article is to review current evidence available for alpha-lipoic acid (ALA) and its ability to improve symptoms of peripheral diabetic neuropathy (PDN). **METHODS:** This article searched MEDLINE from 1966 to November 2005 to identify clinical trials that supplemented ALA to individuals with type 1 or type 2 diabetes and positive sensory symptoms of PDN. Clinical trials to be included in this review met specific criteria of randomization, double masking, and placebo-controlled design. **RESULTS:** The search results produced 5 clinical trials that met the prerequisites for this review. ALA appears to improve neuropathic symptoms and deficits when administered via parenteral supplementation over a 3-week period. Oral treatment with ALA appears to have more conflicting data whether it improves sensory symptoms or just neuropathic deficits alone. An oral regimen of ALA and optimal length of treatment remains unclear. Both parenteral and up to a 2-year time period of oral supplementation of ALA appears to be safe without affecting glycemic control. **CONCLUSIONS:** Based on these results, ALA should be considered as a treatment option for patients with PDN. When discussing supplementation with patients, it is important to discuss potential side effects; vitamin, mineral, and drug interactions; and current evidence available regarding efficacy.

35: Int J Vitam Nutr Res 2006 Sep;76(5):324-31

Effects of antioxidant supplementation and exercise training on erythrocyte antioxidant enzymes.

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Erythrocytes transport oxygen to tissues and exercise-induced oxidative stress increases erythrocyte damage and turnover. Increased use of antioxidant supplements may alter protective erythrocyte antioxidant mechanisms during training. **AIM OF STUDY:** To examine the effects of antioxidant supplementation (alpha-lipoic acid and alpha-tocopherol) and/or endurance training on the antioxidant defenses of erythrocytes. **METHODS:** Young male Wistar rats were assigned to (1) sedentary; (2) sedentary and antioxidant-supplemented; (3) endurance-trained; or (4) endurance-trained and antioxidant-supplemented groups for 14 weeks. Erythrocyte superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT) activities, and plasma malondialdehyde (MDA) were then measured. **RESULTS:** Antioxidant supplementation had no significant effect ($p > 0.05$) on activities of antioxidant enzymes in sedentary animals. Similarly, endurance training alone also had no effect ($p > 0.05$). GPX (125.9 ± 2.8 vs. 121.5 ± 3.0 U x gHb⁻¹), $p < 0.05$) and CAT (6.1 ± 0.2 vs. 5.6 ± 0.2 U x mgHb⁻¹), $p < 0.05$) activities were increased in supplemented trained animals compared to non-supplemented sedentary animals whereas SOD (61.8 ± 4.3 vs. 52.0 ± 5.2 U x mgHb⁻¹), $p < 0.05$) activity was decreased. Plasma MDA was not different among groups ($p > 0.05$). **CONCLUSIONS:** In a rat model, the combination of exercise training and antioxidant supplementation increased antioxidant enzyme activities (GPX, CAT) compared with each individual intervention.

36: J Nutr 2007 Feb;137(2):368-72

At low doses, a gamma-linolenic acid-lipoic acid conjugate is more effective than docosahexaenoic acid-enriched phospholipids in preventing neuropathy in diabetic rats.

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A deficiency in essential fatty acid metabolism has been reported in diabetes. Nutritional supplementations with (n-6) or (n-3) PUFA have differential efficiency on parameters of diabetic neuropathy, including nerve conduction velocity (NCV) and nerve blood flow (NBF). The aim of this study was to compare the neuroprotective effects of gamma-linolenic acid (GLA)-lipoic acid (LA) conjugate (GLA-LA) and docosahexaenoic acid (DHA)-enriched phospholipids (PL) supplementations on NCV and NBF. Streptozotocin-induced diabetic (D) and control (C) rats were supplemented for 8 wk with either DHA-enriched PL at a dose of 30 mg.kg⁻¹.d⁻¹ (DDHA and CDHA) or with corn oil enriched with GLA-LA at a dose of 30 mg.kg⁻¹.d⁻¹ (DGLA and CGLA). Moreover, a C and D group received no supplementation. After 8 wk, NCV (-30%) and NBF (-50%) were lower in the D group than in the C group. Supplementation with GLA-LA totally prevented the decrease in NCV and NBF in the DGLA group, in which values did not differ from group C. Supplementation with DHA only partially prevented the decrease in NCV in the DDHA group, in which value was different from groups C and D and did not affect NBF. We conclude that at the low doses used, supplementation with GLA-LA is more effective than supplementation with DHA in preventing experimental diabetic neuropathy. The difference could be due in part to an antioxidant protective effect of LA on GLA.

37: Mol Cell Biochem 2007 Jul;301(1-2):165-71

Beneficial effect of DL-alpha-lipoic acid on cyclosporine A induced hyperlipidemic nephropathy in rats.

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Cyclosporine A (CsA)-induced dyslipidemia is one of the most important risk factors for morbidity and mortality after solid organ transplantation. Reducing this side effect of CsA by dietary agents may be safe, cost-effective, and attractive to both patients and health professionals. Hence the present study was designed to evaluate the role of DL-alpha-Lipoic acid (LA) in deteriorating the lipid abnormalities induced by CsA in rat kidney. Male albino Wistar rats were divided into four groups. CsA administered at a dose of 25 mg/kg body weight, orally for 21 days showed abnormal changes in the levels of lipoprotein fractions (LDL, HDL and VLDL) and lipid profile in both plasma and renal tissue. Significant alterations were also observed in the activities of lipid metabolizing enzymes. Co-treatment with LA (20 mg/kg body weight, oral gavage, for 21 days) reverted the levels of lipid profile ($P < 0.001$, $P < 0.01$) and lipoprotein fractions ($P < 0.001$, $P < 0.01$) to near control. The activities of lipid metabolizing enzymes also showed considerable restoration on LA supplementation. The outcome of this study provides evidence that LA (a natural metabolic antioxidant) treatment acts as a potent antilipemic agent against CsA-induced lipid abnormalities.

38: Mech Ageing Dev 2007 Feb;128(2):206-12

Mitigation of age-dependent oxidative damage to DNA in rat heart by carnitine and lipoic acid.

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Endogenous damage to mtDNA by free radicals is believed to be a major contributory factor to aging. Mitochondrial DNA exists in a highly genotoxic environment created by exposure to reactive oxygen species and thus are more vulnerable to free radical attack. In the present study we have focused on the age associated alterations to DNA during aging and in parallel investigated the efficacy of carnitine (300 mg/kg bw) and lipoic acid (100 mg/kg bw) for 28 days in altering these changes. We observed a decline in the content of both mitochondrial and nuclear DNA during aging with an exponential increase in the 8-OHdG levels. We also observed an age-dependent increase in DNA protein crosslinks and double strand and single strand breaks. **Supplementation of carnitine and lipoic acid during aging process decreased the incidence of these DNA damage, therefore suggesting that this feeding regimen inhibits the accumulation of age-associated oxidative DNA damage.**

39: Cell Biol Toxicol 2007 Mar;23(2):129-37

alpha-Lipoic acid attenuates x-irradiation-induced oxidative stress in mice.

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The development of nontoxic but effective radioprotectors is needed because of the increasing risk of human exposure to ionizing radiation. We have reported that alpha-lipoic acid confers considerable radio-protective effect in mouse tissues when given prior to x-irradiation. In the present study, alpha-lipoic acid supplementation prior to x-irradiation with 4 and 6 Gy significantly inhibited the radiation-induced decline in total antioxidant capacity (TAC) of plasma. Radiation-induced decline in non-protein sulfhydryl content (NPSH) of different tissues, namely, brain, liver, spleen, kidney, and testis, was also ameliorated significantly at both 4 and 6 Gy doses. Maximal augmentation of radiation-induced protein carbonyl content was observed in spleen followed by brain, kidney, testis, and liver. Maximal protection in terms of carbonyl content was observed in spleen (116%) at 6 Gy dose, and minimal protection was found in liver (22.94%) at 4 Gy dose. Maximal increase in MDA (malondialdehyde) content was observed in brain, followed by testis, spleen, kidney, and liver. Protection by alpha-lipoic acid pretreatment in terms of MDA content was maximal in brain (51.67%) and minimal in spleen. The findings support the idea that alpha-lipoic acid is a free-radical scavenger and a potent antioxidant.

40: Am J Vet Res 2006 Jul;67(7):1192-8

Effect of dietary lipoic acid on metabolic hormones and acute-phase proteins during challenge with infectious bovine rhinotracheitis virus in cattle.

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OBJECTIVE: To determine the effect of dietary supplemental lipoic acid (LA) on serum concentrations of metabolic hormones and acute-phase proteins of steers challenged with infectious bovine rhinotracheitis virus (IBRV). **ANIMALS:** 32 steers. **PROCEDURES:** Steers were randomly assigned to 4 treatments: negative control (NC; no LA, no IBRV challenge), control (CON; no LA, IBRV challenge), 16 mg of LA/kg of body weight (BW)/d plus IBRV challenge (LA16), and 32 mg of LA/kg of BW/d plus IBRV challenge (LA32). Following a 21-day adaptation period, CON, LA16, and LA32 steers received IBRV (2 mL/nostril [day 0]); NC steers received saline (0.9% NaCl) solution. Blood samples, nasal swab specimens, BW, and rectal temperatures were obtained 0, 1, 3, 5, 7, 14, and 21 days after challenge. Serum was analyzed for concentrations of haptoglobin, amyloid-A, leptin, and anti-IBRV antibodies. **RESULTS:** Steers fed LA32 began gaining BW by day 7, whereas BW of CON and LA16 steers declined. Serum haptoglobin concentration of LA32 steers was lower than that of CON and LA16 steers on day 7. Serum neutralization titers for 30 of 32 steers were negative for anti-IBRV antibodies before challenge; however, all steers (including NCs) had antibodies on day 21. **CONCLUSIONS AND CLINICAL RELEVANCE:** Results suggested that LA supplementation augmented certain aspects of the immune response; LA32 steers had a more rapid recovery from IBRV viral challenge than did others.

41: Eur J Pharmacol 2006 Aug;543(1-3):92-6

Protective effect of DL-alpha-lipoic acid on cyclophosphamide induced hyperlipidemic cardiomyopathy.

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Cyclophosphamide is a potent alkylating agent used in cancer chemotherapy and immunosuppression. The present study is aimed at evaluating the role of a potent antioxidant lipoic acid in cyclophosphamide induced hyperlipidemic cardiomyopathy. Adult male Wistar rats were divided into four treatment groups. Two groups received single intraperitoneal injection of cyclophosphamide (200 mg/kg body weight) to induce cardiotoxicity, one of these groups received lipoic acid treatment (25 mg/kg body weight, orally for 10 days). A vehicle treated control group and a lipoic acid drug control were also included. Cyclophosphamide administration resulted in abnormal elevation of serum lipids. Similarly in the cardiac tissue, the levels of free cholesterol, esterified cholesterol, triglycerides were increased significantly ($P < 0.05$) while the levels of phospholipids and free fatty acids were reduced significantly unlike serum ($P < 0.05$). Serum Low Density Lipoprotein (LDL) and Very Low Density Lipoprotein (VLDL) cholesterol increased significantly ($P < 0.05$) while High Density Lipoprotein

(HDL) cholesterol ($P < 0.05$) decreased significantly when compared to controls. These changes corroborated with the abnormal distortion in the activities of lipid metabolizing enzymes in cyclophosphamide treated group. Supplementation of lipoic acid reverted these abnormalities in the lipid levels and activities of lipid metabolizing enzymes to near normalcy after cyclophosphamide administration.

42: Biogerontology 2006 Apr;7(2):101-9

Carnitine and lipoic acid alleviates protein oxidation in heart mitochondria during aging process.

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Oxidative modification alters the function of proteins and is thought to play an important role in the decline of cellular function during aging process. In the present study, we have evaluated the levels of oxidant production, protein oxidation, reduced and oxidized glutathione in young, middle aged and aged rats. The animals were divided into six groups, each group consisting of six animals each. Groups I and II were young rats, Groups III and IV were middle-aged rats and Groups V and VI were aged rats. Groups II, IV and VI were treated with carnitine (300 mg/kg bw) and Dl-alpha-Lipoic acid (100 mg/kg bw) for 28 days. Statistical significance was carried out using ANOVA. There was a significant reduction in the levels of reduced glutathione and Redox ratio ($P < 0.05$) in aged rats whereas elevation in the levels of oxidant production, protein carbonyls, advanced oxidation protein products and oxidized glutathione were observed. Co-supplementation of carnitine and lipoic acid improved these levels to near normalcy. Thus we conclude that the utilization of carnitine and lipoic acid will lead to an improvement in the quality of living during the later stages of life by preventing free radical induced damage to the proteins.

43: J Diabetes Complications 2006 Jul-Aug;20(4):257-61

Heat shock protein 60 response to exercise in diabetes: effects of alpha-lipoic acid supplementation.

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The pathophysiology of diabetes includes oxidative stress and impaired heat shock protein (HSP) expression. We studied the effects of alpha-lipoic acid (LA) supplementation for 8 weeks and acute exercise on HSP60 expression and the oxidative stress marker 4-hydroxynonenal adducts (4-HNE) in streptozotocin-induced diabetic (SID) and nondiabetic control rats. Diabetes was associated with decreased HSP60 in the heart and increased levels of HSP60 and 4-HNE in the liver. LA increased HSP60 in the liver of control and diabetic rats and decreased 4-HNE in the liver and heart. Acute exercise increased liver 4-HNE, which was offset by LA. In conclusion, diabetes induced oxidative stress and impaired myocardial HSP60 expression, while LA partially offsets these alterations in a tissue-specific manner.

44: Br J Nutr 2006 Jun;95(6):1094-101

Effects of dietary lipoic acid on plasma lipid, in vivo insulin sensitivity, metabolic response to corticosterone and in vitro lipolysis in broiler chickens.

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The present study consisted of two experiments. The first experiment was conducted to determine the effects of lipoic acid (ALA; 200 mg/kg) on plasma lipids and insulin sensitivity of whole-body tissue in broilers treated with or without corticosterone (5 mg/kg). Chickens received these agents from 2 to 5 weeks of age in a 2 x 2 factorial arrangement. Thereafter, from 39 to 42 d of age, insulin sensitivity was estimated using the euglycaemic and hyperinsulinaemic clamp technique. Experiment 2 examined whether ALA supplementation for 5 weeks (400 mg/kg) would alter short-chain acyl-CoA concentration in the liver and in vitro lipolysis of an adipose tissue slice, in relation to noradrenaline (10 microM) supplementation. In experiment 1, ALA had no effect on the corticosterone-induced negative growth performance. ALA lowered plasma glucose level ($P<0.05$) and, in contrast, increased triacylglycerol level ($P<0.05$). These responses to ALA had, however, no interrelationship with corticosterone. The rate of glucose uptake of whole-body tissue was enhanced in the ALA-fed chickens ($P<0.05$), regardless of corticosterone treatment. In experiment 2, ALA increased only the plasma free glycerol concentration ($P<0.01$). The rate of free glycerol release from an adipose tissue slice was enhanced by ALA feeding ($P<0.05$) but was not affected by noradrenaline supplementation. This study suggests that ALA stimulates the insulin sensitivity of tissues regardless of corticosterone-dependent metabolism and that the ALA-induced fatty acid metabolism of broilers differs between the liver and adipose tissue.

45: Clin Appl Thromb Hemost 2006 Apr;12(2):169-73

Vitamin E and alpha-lipoic acid supplementation increase bleeding tendency via an intrinsic coagulation pathway.

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Vitamin E and alpha-lipoic acid are potent nutritional antioxidants, and when used together, their antioxidant capabilities are improved as alpha-lipoic acid recycles vitamin E. Supplementation of vitamin E has been shown to prolong platelet aggregation but the effects of vitamin E and alpha-lipoic acid supplementation on bleeding tendency have yet to be reported. Young, male rats consumed either control diet (n=5) or vitamin E and alpha-lipoic acid-supplemented diet (n=5) for 14 weeks. Activated partial thromboplastin time (APTT) and prothrombin time (PT) were measured as markers of intrinsic and extrinsic coagulation pathways respectively in addition to lipid peroxidation (malondialdehyde). Supplementation significantly prolonged APTT (23.8 ± 1.5 vs 31.4 ± 1.2 s, $p<0.05$) compared to the control diet; however, there was no significant difference in PT

(27.8+/-1.5 vs 26.6+/-0.9s, p>0.05). While vitamin E was increased (p<0.05), there was no significant difference in plasma levels of malondialdehyde (p>0.05). Dietary supplementation of vitamin E and alpha-lipoic acid increases bleeding tendency via inhibition of the intrinsic coagulation pathway with no change in markers of lipid peroxidation. Such supplementation could benefit patients with cardiovascular disease who exhibit elevated levels of coagulation and oxidative stress.

46: Rejuvenation Res 2006;9(2):198-201

Protective efficacy of alpha-lipoic acid on acetylcholinesterase activity in aged rat brain regions.

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The purpose of the present investigation was to measure the activity of acetylcholinesterase in discrete regions of young and aged rat brain before and after DL-alpha-lipoic acid supplementation. Two groups of male albino rats were used in this study (4 and 24 months of age). DL-alpha-lipoic acid was administered intraperitoneally with a regimen of 100 mg/kg body weight per day using alkaline saline as a vehicle for 7 and 14 days. The activity was measured in the cerebral cortex, cerebellum, striatum, hippocampus and hypothalamus, and found to be significantly decreased in some of the brain regions in aged rats. Administration of lipoic acid into aged rats reversed the decrease in the activity in the discrete brain regions. These results suggest that lipoic acid is effective in restoration of the activity of acetylcholinesterase in aged rats.

47: Wien Klin Wochenschr 2006 Mar;118(3-4):100-7

Supply of R-alpha-lipoic acid and glutamine to casein-fed mice influences the number of B lymphocytes and tissue glutathione levels during endotoxemia.

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BACKGROUND: An overwhelming production of reactive oxygen species concomitant with a decrease in antioxidative capacity plays an important role in modulation of the immune system in critically ill patients. The purpose of this study was to assess the influence of a combined oral supply of the antioxidants R-alpha-lipoic acid (LA) and glutamine (GLN) on the immunity of endotoxemic mice, with a special focus on tissue glutathione levels. **METHODS:** Female Balb/c mice were fed diets enriched with GLN (3 g/100 kcal), LA (0.74 mg/100 kcal), a combination of GLN and LA, or an isocaloric and isonitrogenous control diet for 10 days. On day 7, the mice were challenged intraperitoneally with 25 microg lipopolysaccharide. Seventy-two hours later, the number and phenotype of lymphocytes in Peyer's patches (PP) and spleen of the endotoxemic mice were measured. In addition, glutathione levels were determined in the small intestine, spleen and liver. **RESULTS:** In PP only the combined supply of GLN and LA significantly increased the total cell yield (+19%), which was predominantly due to an

increased number of B cells. In the spleen, both LA (+17%) and the combination of GLN and LA (+22%) were able to enhance total cell yield. The glutathione content of the small intestine was increased by feeding LA alone, whereas in the spleen GLN plus LA was most effective. CONCLUSION: Supplying combined GLN and LA to endotoxemic mice is effective in selectively increasing the number of systemic and intestinal B lymphocytes. Furthermore, LA augmented the level of the main intracellular antioxidant glutathione in the small intestine. **On the basis of these data we recommend investigation of the effects of LA and GLN supplementation in patients with sepsis.**

48: Orv Hetil 2006 Apr;147(13):603-7

[The role of antioxidants in prevention]

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The imbalance between free radical formation and the mechanisms involved in eliminating them results in oxidative stress which lies at the baseline of many diseases. There are many pathological conditions that can be prevented or even be cured by the application of antioxidants. Food containing plenty of natural antioxidants is very important in the maintenance of health and in the prevention of many illnesses. In some diseases supplementation of antioxidants in the proper form and dosage may be irrelevant. According to nutrigenomics the biologically active components of nutrition, including **antioxidants, have an influence on the body in every single cell at all levels. Therefore the quality of nutrients is one of the important factors determining the appropriate cell function.**

49: J Hypertens 2006 May;24(5):947-56

Lipoic acid supplementation prevents cyclosporine-induced hypertension and nephrotoxicity in spontaneously hypertensive rats.

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BACKGROUND: Cyclosporine (CsA) has significantly improved long-term survival after organ transplantations. Hypertension and nephrotoxicity are common side effects during CsA treatment and are aggravated by high salt intake. OBJECTIVE: To examine whether lipoic acid (LA), a natural antioxidant that scavenges reactive oxygen species and regenerates/recycles endogenous antioxidants, could prevent CsA-induced hypertension and nephrotoxicity. METHODS: Six-week-old spontaneously hypertensive rats (SHR) on a high-sodium diet (NaCl 6%) received CsA [5 mg/kg subcutaneously (s.c.)] alone or in combination with LA (0.5% w/w) for 6 weeks. Blood pressure, arterial functions, and tissue morphology were determined. Immunohistochemistry, quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) and high-pressure liquid chromatography were used for kidney and heart samples. RESULTS: CsA induced severe hypertension, cardiac hypertrophy, endothelial dysfunction, and pronounced albuminuria.

Histologically, the kidneys showed severe thickening of the media of the afferent arteries with fibrinoid necrosis, perivascular monocyte/macrophage infiltration and nitrotyrosine overexpression. CsA induced the expression of fibrogenic connective tissue growth factor both in the heart and kidneys. The detrimental effects of CsA were associated with upregulation of myocardial atrial natriuretic peptide (ANP) mRNA expression, paradoxical activation of the renin-angiotensin system (RAS), induction of renal reduced nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase, and overexpression of oxidative stress-induced transcription factor NRF2. LA lowered blood pressure, ameliorated cardiac hypertrophy and endothelial dysfunction, and totally normalized albuminuria. In LA-treated rats, renal and cardiac morphologies were indistinguishable from those of SHR controls. CsA-induced myocardial ANP and connective tissue growth factor (CTGF) mRNA overexpression, RAS activation, NADPH oxidase induction, and NRF2 overexpression were prevented by LA. LA induced the mRNA expression of gamma-glutamylcysteine ligase, the rate-limiting enzyme in glutathione synthesis, and markedly increased hepatic cysteine and glutathione concentrations. CONCLUSIONS: Our findings suggest a salutary role for **lipoic acid supplementation in the prevention of CsA-induced hypertension and nephrotoxicity, and underscore the importance of increased oxidative stress in the pathogenesis of CsA toxicity.**

50: Radiat Res 2006 Apr;165(4):373-8

Effects of dietary supplements on the space radiation-induced reduction in total antioxidant status in CBA mice.

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In the present study, the total antioxidant status was used as a biomarker to evaluate oxidative stress induced by proton, HZE-particle and gamma radiation in CBA mice. The results demonstrated that the plasma level of TAS was significantly decreased ($P < 0.05$) in CBA mice after exposure to a 50-cGy dose of radiation from HZE particles or a 3-Gy dose of radiation from protons or gamma rays. Diet supplementation with Bowman-Birk Inhibitor Concentrate (BBIC), L-selenomethionine (L-SeM), or a combination of N-acetyl cysteine, sodium ascorbate, co-enzyme Q10 (CoQ10), alpha-lipoic acid, L-SeM and vitamin E succinate could partially or completely prevent the reduction in the plasma level of TAS in CBA mice exposed to proton or HZE-particle radiation. The selected antioxidant combination with or without CoQ10 has a comparable protective effect on the gamma-radiation-induced drop in TAS in CBA mice. These results indicate that BBIC, L-SeM and the selected antioxidant combinations may serve as countermeasures for space radiation-induced adverse biological effects.

51: Clin Chim Acta 2006 Jun;368(1-2):84-92

Oxidative stress-mediated macromolecular damage and dwindle in antioxidant status in aged rat brain regions: role of L-carnitine and DL-alpha-lipoic acid.

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BACKGROUND: The free radical theory of aging has significant relevance in a number of age-related neurological disorders. Too many free radicals create cellular pollution that shuts down energy levels. They have also been implicated in the loss of physiological functioning associated with the aging of post mitotic cells such as the brain. The activities of enzymatic antioxidative defenses decrease in rat brain may be possible causes of age-associated increase in oxidative damage to macromolecules. **METHODS:** We determined whether DL-alpha-lipoic acid (100 mg/kg body weight/day), and L-carnitine (300 mg/kg body weight/day) together when administered for 30 days declines the rate of oxidative stress-mediated macromolecular damages such as lipid peroxidation (LPO), protein carbonyl (PCO) and DNA protein cross-links in different anatomic regions (cortex, striatum and hippocampus). The activities of antioxidant enzymes in programmed aging were evaluated in the cortex, striatum and hippocampus of young and aged rat brain regions. **RESULTS:** Aged rats elicited a significant decline in the antioxidant status and increase in LPO, PCO and DNA protein cross-links as compared to young rats in all the 3 brain regions. The increase in LPO, PCO and DNA protein cross-links were (35.8%, 35.6%, 43.5%) in cortex, (32.5%, 40.3%, 29.8%) in striatum and (62.7%, 42.4%, 34.9%) in hippocampus, respectively, in aged rats as compared to young rats. Co-supplementation of carnitine and lipoic acid was found to be effective in reducing brain regional LPO, PCO and DNA protein cross-links and in increasing the activities of enzymatic antioxidants in aged rats to near normalcy. **CONCLUSION:** The combination of l-carnitine and lipoic acid overcame the oxidative stress induced rate of lipid peroxidation, protein carbonyl formation, accumulation of DNA protein cross-links and deficits in antioxidant enzyme activities in various brain regions of aged rats.

52: Basic Clin Pharmacol Toxicol 2006 Jan;98(1):68-73

Alpha-tocopherol and alpha-lipoic acid enhance the erythrocyte antioxidant defence in cyclosporine A-treated rats.

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The aim of this study was to determine the effects of dietary antioxidant supplementation with alpha-tocopherol and alpha-lipoic acid on cyclosporine A (cyclosporine)-induced alterations to erythrocyte and plasma redox balance. Rats were randomly assigned to either control, antioxidant (alpha-tocopherol 1000 IU/kg diet and alpha-lipoic acid 1.6 g/kg diet), cyclosporine (25 mg/kg/day), or cyclosporine + antioxidant treatments. Cyclosporine was administered for 7 days after an 8 week feeding period. Plasma was analysed for alpha-tocopherol, total antioxidant capacity, malondialdehyde, and creatinine. Erythrocytes were analysed for glutathione, methaemoglobin, superoxide dismutase, catalase, glutathione peroxidase, glucose-6-phosphate dehydrogenase, alpha-tocopherol and malondialdehyde. Cyclosporine administration caused a significant decrease in superoxide dismutase activity ($P < 0.05$ control versus cyclosporine) and this was improved by antioxidant supplementation ($P < 0.05$ cyclosporine versus cyclosporine + antioxidant; $P < 0.05$ control versus cyclosporine + antioxidant). Animals receiving cyclosporine and antioxidants showed

significantly increased ($P < 0.05$) catalase activity compared to both groups not receiving cyclosporine. Cyclosporine administration induced significant increases in plasma malondialdehyde and creatinine concentration ($P < 0.05$ control versus cyclosporine). Antioxidant supplementation prevented the cyclosporine induced increase in plasma creatinine ($P < 0.05$ cyclosporine versus cyclosporine + antioxidant; $P > 0.05$ control versus cyclosporine + antioxidant), however, supplementation did not alter the cyclosporine induced increase in plasma malondialdehyde concentration ($P > 0.05$ cyclosporine versus cyclosporine + antioxidant). Antioxidant supplementation resulted in significant increases ($P < 0.05$) in plasma and erythrocyte alpha-tocopherol in both of the supplemented groups compared to non-supplemented groups. In conclusion, dietary supplementation with alpha-tocopherol and alpha-lipoic acid enhanced the erythrocyte antioxidant defence and reduced nephrotoxicity in cyclosporine treated animals.

53: Am J Transplant 2006 Jan;6(1):41-9

Antioxidant supplementation enhances erythrocyte antioxidant status and attenuates cyclosporine-induced vascular dysfunction.

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The aim of this study was to determine the effects of dietary antioxidant supplementation with alpha-tocopherol and alpha-lipoic acid on cyclosporine-induced alterations to erythrocyte and plasma redox balance, and cyclosporine-induced endothelial and smooth muscle dysfunction. Rats were randomly assigned to either control, antioxidant, cyclosporine or cyclosporine + antioxidant treatments. Cyclosporine A was administered for 10 days after an 8-week feeding period. Plasma was analyzed for alpha-tocopherol, total antioxidant capacity, malondialdehyde and creatinine. Erythrocytes were analyzed for glutathione, methemoglobin, superoxide dismutase, catalase, glutathione peroxidase, glucose-6-phosphate dehydrogenase, alpha-tocopherol and malondialdehyde. Vascular endothelial and smooth muscle function was determined in vitro. Antioxidant supplementation resulted in significant increases in erythrocyte alpha-tocopherol concentration and glutathione peroxidase activity in both of the antioxidant-supplemented groups. Cyclosporine administration caused significant decreases in glutathione concentration, methemoglobin concentration and superoxide dismutase activity. Antioxidant supplementation attenuated the cyclosporine-induced decrease in superoxide dismutase activity. Cyclosporine therapy impaired both endothelium-independent and -dependent relaxation of the thoracic aorta, and this was attenuated by antioxidant supplementation. In summary, dietary supplementation with alpha-tocopherol and alpha-lipoic acid attenuated the cyclosporine-induced decrease in erythrocyte superoxide dismutase activity and attenuated cyclosporine-induced vascular dysfunction.

54: Mech Ageing Dev 2006 Apr;127(4):349-55

Mitochondrial membrane damage during aging process in rat heart: potential efficacy of L-carnitine and DL alpha lipoic acid.

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Mitochondria are the main intracellular source of oxidizing free radicals and these oxidants produced exhibit selectivity in damaging mitochondrial macromolecules and membrane functions. In the present study we have investigated the effect of co-supplementation of carnitine (300 mg/kg bw) and lipoic acid (100 mg/kg bw) for 28 days in young, middle aged and aged rats and evaluated the effect of these compounds on age-related alterations in mitochondrial membrane functions. The levels of H₂O₂ were increased in both middle aged and aged rats with a concomitant decrease in the levels of cardiolipin and mitochondrial membrane potential. The levels of membrane bound ATPases were also decreased in aged rats along with alterations in mitochondrial morphology. Supplementation of carnitine and lipoic acid to middle aged and aged rats brought these changes to near normalcy. Thus, lipoic acid acts with carnitine to improve mitochondrial-supported bioenergetics and also improves general antioxidant status, thereby effectively attenuating any putative increase in oxidative stress with age.

55: *Glia* 2006 Apr;53(6):669-74

Alpha-tocopherol (vitamin E) induces rapid, nonsustained proliferation in cultured rat microglia.

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Microglial cells undergo cell division in vitro, as well as in vivo after brain injury. Mitotic activity of microglia suggests that they have limited life spans and rely on self-renewal to replace senescent cells. In the current study we examined long-term effects of antioxidants vitamin E and alpha-lipoic acid on cultured rat microglia with respect to proliferative ability, telomere length, telomerase activity, and interleukin-1beta (IL-1beta) production. We report that vitamin E induces dramatic microglial proliferation, as measured by MTT assay and BrdU incorporation, surpassing that of the well-known microglial mitogen granulocyte macrophage-colony stimulating factor, and therefore establishing vitamin E as the most potent, known mitogen for microglia in vitro. The high rate of microglial proliferation resulted in a concomitant decrease in telomere length and telomerase activity. Production of IL-1beta was significantly decreased in vitamin E-treated microglia in vitro. Our findings provide an impetus to investigate potential benefits of vitamin E supplementation on microglial renewal capacity in vivo during aging or after brain injury.

56: *J Cardiovasc Nurs* 2006 Jan-Feb;21(1):9-16

Supplemental conditionally essential nutrients in cardiovascular disease therapy.

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Conditionally essential nutrients (CENs) are organic compounds that are ordinarily produced by the body in amounts sufficient to meet its physiological requirements. However, in disorders, such as cardiovascular disease (CVD), and in other physiologically stressful conditions, their biosynthesis may be inadequate. Under these circumstances, CENs become essential nutrients, comparable to vitamins. The CENs of primary importance in CVD, based on the quantity and quality of human clinical studies, are L-arginine, L-carnitine, propionyl-L-carnitine, and coenzyme Q10. Controlled studies of these CENs are reviewed in depth. Taurine is a CEN of secondary importance caused by a limited human database. Other putative CENs include alpha-lipoic acid, betaine, chondroitin sulfate, glutamine, and D-ribose, each of which is mentioned in passing. Collectively, CENs have demonstrated favorable clinical effects in CVDs, including chronic heart failure, myocardial infarction, angina pectoris, and in CVD risk factors, such as hypertension, hyperlipidemia, and lipoprotein(a). Limited research has pointed to possible benefits in CVD therapy accruing from supplementation with several CENs in combination. Additional controlled clinical studies of CENs in CVD are urgently needed. In view of the efficacy and safety of appropriate supplementation with CENs, it is strongly suggested that healthcare professionals become knowledgeable of these potentially important additions to the CVD therapeutic armamentarium.

57: Altern Med Rev 2005 Dec;10(4):268-93

Neurodegeneration from mitochondrial insufficiency: nutrients, stem cells, growth factors, and prospects for brain rebuilding using integrative management.

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Degenerative brain disorders (neurodegeneration) can be frustrating for both conventional and alternative practitioners. A more comprehensive, integrative approach is urgently needed. One emerging focus for intervention is brain energetics. Specifically, mitochondrial insufficiency contributes to the etiopathology of many such disorders. Electron leakages inherent to mitochondrial energetics generate reactive oxygen free radical species that may place the ultimate limit on lifespan. Exogenous toxins, such as mercury and other environmental contaminants, exacerbate mitochondrial electron leakage, hastening their demise and that of their host cells. Studies of the brain in Alzheimer's and other dementias, Down syndrome, stroke, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Friedreich's ataxia, aging, and constitutive disorders demonstrate impairments of the mitochondrial citric acid cycle and oxidative phosphorylation (OXPHOS) enzymes. Imaging or metabolic assays frequently reveal energetic insufficiency and depleted energy reserve in brain tissue in situ. Orthomolecular nutrients involved in mitochondrial metabolism provide clinical benefit. Among these are the essential minerals and the B vitamin group; vitamins E and K; and the antioxidant and energetic cofactors alpha-lipoic acid (ALA), ubiquinone (coenzyme Q10; CoQ10), and nicotinamide adenine dinucleotide, reduced (NADH). Recent advances in the area of stem cells and growth factors encourage optimism regarding brain regeneration. The trophic nutrients acetyl L-carnitine (ALCAR), glycerophosphocholine (GPC), and phosphatidylserine (PS) provide mitochondrial support and conserve growth factor receptors; all three improved cognition in double-blind trials. The omega-3 fatty acid docosahexaenoic acid (DHA) is enzymatically combined with GPC and PS to form membrane phospholipids for nerve cell expansion. Practical recommendations are presented for **integrating these safe and**

well-tolerated orthomolecular nutrients into a comprehensive dietary supplementation program for brain vitality and productive lifespan.