

# REPORT

## Reverse Mitochondrial Damage Potent Molecular Energizers for Lifelong Health

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### A COMPLEMENTARY COENZYME

Lipoic acid is a naturally occurring compound found in mitochondria. Like CoQ10, it is a **coenzyme** required for proper function of the mitochondrial energy chain.<sup>4</sup> Lipoic acid directly increases ATP production in mitochondria.<sup>79</sup> Clinical models indicate that lipoic acid may serve as a first-line defense for diseases involving impaired energy utilization, including diabetes and the nerve damage associated with it.<sup>80-82</sup>

R-alpha-lipoic acid is the most bioactive form of lipoic acid—and a powerful activator of mitochondrial energy complexes.<sup>83,84</sup> Studies in aging animals support the use of R-alpha-lipoic acid to improve mitochondrial function, decrease oxidative damage, and increase metabolic rate, all of which otherwise become impaired with aging.<sup>4</sup>

R-alpha-lipoic acid has been proven effective in reducing symptoms of diabetic neuropathy, without significant adverse reactions.<sup>81,85</sup> It also increases nerve conduction velocity in people with diabetic neuropathy, crucial to improved nerve signaling.<sup>86</sup> Experts attribute these effects to diminished fat oxidation in nerve cell membranes and improvements in local blood supply around nerves resulting from improved mitochondrial functioning.<sup>87,88</sup>

R-alpha-lipoic acid displays many protective effects. It reverses the age-related increase in liver cell damage caused by exogenous toxins, helping to protect liver function.<sup>89</sup> It prevents brain cells from becoming depleted of the natural antioxidant *reduced glutathione*, an important intracellular antioxidant in the body. Deficiency of reduced glutathione can predispose people to liver failure, Parkinson's disease, and other neurodegenerative conditions.<sup>90,91</sup> A therapeutic dose of **600 mg/day** even helped relieve migraine attack rates—an observation that may support the theory that migraines may be partially caused by impaired mitochondrial function.<sup>92</sup>



As you might expect of a mitochondrial energy booster, lipoic acid may also play a role in helping to ward off cardiovascular disease. Three months of lipoic acid supplementation provided pain relief to patients with peripheral vascular disease (PVD), extending the time they could walk before pain occurred.<sup>93</sup> Combined therapy with acetyl-L-carnitine improved blood vessel relaxation and blood flow, while reducing blood pressure, in patients with coronary artery disease.<sup>94</sup> And combined supplementation is a very good idea, as we'll see next.

### YOUR MITOCHONDRIAL FAT-BURNER

L-carnitine is a molecule required for helping transport fatty acids into the mitochondria, where they can be burned as fuel. Acetyl-L-carnitine (ALC) is the *form* of carnitine optimally absorbed through oral delivery. It has also been shown to boost mitochondrial health, facilitating fuel delivery to the electron transport chain, where supplements like CoQ10, shilajit, and lipoic acid take over.

Total carnitine levels diminish with age, a decline that may also be accelerated by overeating and diabetes.<sup>95</sup> As with other mitochondrial energy optimizers, ALC supplementation possesses distinct benefits across numerous physiological systems.<sup>96</sup>

A review of clinical studies shows that ALC may slow the natural course of Alzheimer's disease.<sup>97</sup> It has substantially increased Alzheimer's disease patients' responses to drug treatment, from **38%** to **50%** in one study.<sup>98</sup> ALC also protects brain tissue against destructive effects of hypoxia (low oxygen), by supporting cellular metabolism.<sup>99</sup> ALC and lipoic acid supplementation partially restored depleted brain mitochondrial activity in aged rats to that of young adults.<sup>100</sup>

The combination of ALC with lipoic acid improved cognitive function in a mouse model of Alzheimer's disease.<sup>101</sup> ALC alone has exhibited powerful effects, restoring aging animals' cardiac energy metabolism to that of young adults.<sup>102</sup> In combination with lipoic acid, ALC helps maintain heart muscle function in aging animals as well.<sup>103</sup>



## SUMMARY

Mitochondrial dysfunction is linked to a broad range of degenerative illness, from diabetes and neurological disorders to heart disease. Researchers have discovered that age-related mitochondrial dysfunction—which can ultimately lead to DNA damage and cell death—may be prevented and even *reversed*. The key lies in early and sustained interventions that support optimal mitochondrial health and function. CoQ10 in its superior form as **ubiquinol** may restore mitochondrial function. The organic adaptogen **shilajit** acts in synergy with ubiquinol, further enhancing mitochondrial function. R-alpha-lipoic acid and acetyl-L-carnitine have been shown in clinical studies to provide additional mitochondrial support.

*If you have any questions on the scientific content of this article, please call a Life Extension® Health Advisor at 1-866-864-3027.*

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## References

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1. Conley KE, Amara CE, Jubrias SA, Marcinek DJ. Mitochondrial function, fibre types and ageing: new insights from human muscle in vivo. *Exp Physiol*. 2007 Mar;92(2):333-9.
2. Lesnefsky EJ, Moghaddas S, Tandler B, Kerner J, Hoppel CL. Mitochondrial dysfunction in cardiac disease: ischemia—reperfusion, aging, and heart failure. *J Mol Cell Cardiol*. 2001 Jun;33(6):1065-89.
3. Conley KE, Marcinek DJ, Villarin J. Mitochondrial dysfunction and age. *Curr Opin Clin Nutr Metab Care*. 2007 Nov;10(6):688-92.
4. Hagen TM, Ingersoll RT, Lykkesfeldt J, et al. (R)-alpha-lipoic acid-supplemented old rats have improved mitochondrial function, decreased oxidative damage, and increased metabolic rate. *FASEB J*. 1999 Feb;13(2):411-8.
5. Shigenaga MK, Hagen TM, Ames BN. Oxidative damage and mitochondrial decay in aging. *Proc Natl Acad Sci U S A*. 1994 Nov 8;91(23):10771-8.
6. Genova ML, Pich MM, Bernacchia A, et al. The mitochondrial production of reactive oxygen species in relation to aging and pathology. *Ann N Y Acad Sci*. 2004 Apr;1011:86-100.
7. Sohal RS, Weindruch R. Oxidative stress, caloric restriction, and aging. *Science*. 1996 Jul 5;273(5271):59-63.
8. Hagen TM, Yowe DL, Bartholomew JC, et al. Mitochondrial decay in hepatocytes from old rats: membrane potential declines, heterogeneity and oxidants increase. *Proc Natl Acad Sci U S A*. 1997 Apr 1;94(7):3064-9.
9. Sanz N, Diez-Fernandez C, Alvarez A, Cascales M. Age-dependent modifications in rat hepatocyte antioxidant defense systems. *J Hepatol*. 1997 Sep;27(3):525-34.
10. Erdinçler DS, Seven A, Inci F, Beger T, Candan G. Lipid peroxidation and antioxidant status in experimental animals: effects of aging and hypercholesterolemic diet. *Clin Chim Acta*. 1997 Sep 8;265(1):77-84.
11. DiMauro S, Tanji K, Bonilla E, Pallotti F, Schon EA. Mitochondrial abnormalities in muscle and other aging cells: classification, causes, and effects. *Muscle Nerve*. 2002 Nov;26(5):597-607.

12. Sullivan PG, Brown MR. Mitochondrial aging and dysfunction in Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005 Mar;29(3):407-10.
13. Choksi KB, Nuss JE, Boylston WH, Rabek JP, Papaconstantinou J. Age-related increases in oxidatively damaged proteins of mouse kidney mitochondrial electron transport chain complexes. *Free Radic Biol Med*. 2007 Nov 15;43(10):1423-38.
14. Baines CP. The mitochondrial permeability transition pore and ischemia-reperfusion injury. *Basic Res Cardiol*. 2009 Mar;104(2):181-8.
15. Di Lisa F, Kaludercic N, Carpi A, Menabo R, Giorgio M. Mitochondria and vascular pathology. *Pharmacol Rep*. 2009 Jan-Feb;61(1):123-30.
16. Sohal RS, Forster MJ. Coenzyme Q, oxidative stress and aging. *Mitochondrion*. 2007 Jun;7 Suppl:S103-11.
17. Aberg F, Appelkvist EL, Dallner G, Ernster L. Distribution and redox state of ubiquinones in rat and human tissues. *Arch Biochem Biophys*. 1992 Jun;295(2):230-4.
18. Kalen A, Appelkvist EL, Dallner G. Age-related changes in the lipid compositions of rat and human tissues. *Lipids*. 1989 Jul;24(7):579-84.
19. Bliznakov EG. Immunological senescence in mice and its reversal by coenzyme Q10. *Mech Ageing Dev*. 1978 Mar;7(3):189-97.
20. Rosenfeldt FL, Pepe S, Linnane A, et al. The effects of ageing on the response to cardiac surgery: protective strategies for the ageing myocardium. *Biogerontology*. 2002;3(1-2):37-40.
21. Rosenfeldt FL, Pepe S, Linnane A, et al. Coenzyme Q10 protects the aging heart against stress: studies in rats, human tissues, and patients. *Ann N Y Acad Sci*. 2002 Apr;959:355-39; discussion 463-35.
22. Aejmelaeus R, Metsa-Ketela T, Laippala P, Solakivi T, Alho H. Ubiquinol-10 and total peroxy radical trapping capacity of LDL lipoproteins during aging: the effects of Q-10 supplementation. *Mol Aspects Med*. 1997;18 Suppl:S11320.
23. Quiles JL, Ochoa JJ, Huertas JR, Mataix J. Coenzyme Q supplementation protects from age-related DNA double-strand breaks and increases lifespan in rats fed on a PUFA-rich diet. *Exp Gerontol*. 2004 Feb;39(2):189-94.
24. Ochoa JJ, Quiles JL, Huertas JR, Mataix J. Coenzyme Q10 protects from aging-related oxidative stress and improves mitochondrial function in heart of rats fed a polyunsaturated fatty acid (PUFA)-rich diet. *J Gerontol A Biol Sci Med Sci*. 2005 Aug;60(8):970-5.
25. Ochoa JJ, Quiles JL, Lopez-Frias M, Huertas JR, Mataix J. Effect of lifelong coenzyme Q10 supplementation on age-related oxidative stress and mitochondrial function in liver and skeletal muscle of rats fed on a polyunsaturated fatty acid (PUFA)-rich diet. *J Gerontol A Biol Sci Med Sci*. 2007 Nov;62(11):1211-8.
26. Kaikkonen J, Tuomainen TP, Nyssonen K, Salonen JT. Coenzyme Q10: absorption, antioxidative properties, determinants, and plasma levels. *Free Radic Res*. 2002 Apr;36(4):389-97.
27. Hosoe K, Kitano M, Kishida H, Kubo H, Fujii K, Kitahara M. Study on safety and bioavailability of ubiquinol (Kaneka QH) after single and 4-week multiple oral administration to healthy volunteers. *Regul Toxicol Pharmacol*. 2007 Feb;47(1):19-28.
28. Shults CW, Flint Beal M, Song D, Fontaine D. Pilot trial of high dosages of coenzyme Q10 in patients with Parkinson's disease. *Exp Neurol*. 2004 Aug;188(2):491-4.
29. Soukoulis V, DiHu JB, Sole M, et al. Micronutrient deficiencies an unmet need in heart failure. *J Am Coll Cardiol*. 2009 Oct 27;54(18):1660-73.
30. Langsjoen PH, Langsjoen AM. Supplemental ubiquinol in patients with advanced congestive heart failure. *Biofactors*. 2008;32(1-4):119-28.

31. Available at: [http://www.abouthf.org/questions\\_stages.htm](http://www.abouthf.org/questions_stages.htm). Accessed October 9, 2009.
32. Belardinelli R, Mucaj A, Lacalaprice F, et al. Coenzyme Q10 improves contractility of dysfunctional myocardium in chronic heart failure. *Biofactors*. 2005;25(1-4):137-45.
33. Morisco C, Trimarco B, Condorelli M. Effect of coenzyme Q10 therapy in patients with congestive heart failure: a long-term multicenter randomized study. *Clin Investig*. 1993;71(8 Suppl):S134-6.
34. Jeejeebhoy F, Keith M, Freeman M, et al. Nutritional supplementation with MyoVive repletes essential cardiac myocyte nutrients and reduces left ventricular size in patients with left ventricular dysfunction. *Am Heart J*. 2002 Jun;143(6):1092-100.
35. Singh RB, Neki NS, Kartikey K, et al. Effect of coenzyme Q10 on risk of atherosclerosis in patients with recent myocardial infarction. *Mol Cell Biochem*. 2003 Apr;246(1-2):75-82.
36. Makhija N, Sendasgupta C, Kiran U, et al. The role of oral coenzyme Q10 in patients undergoing coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth*. 2008 Dec;22(6):832-9.
37. Kuettner A, Pieper A, Koch J, Enzmann F, Schroeder S. Influence of coenzyme Q(10) and cerivastatin on the flow-mediated vasodilation of the brachial artery: results of the ENDOTACT study. *Int J Cardiol*. 2005 Feb 28;98(3):413-9.
38. Graham D, Huynh NN, Hamilton CA, et al. Mitochondria-targeted antioxidant MitoQ10 improves endothelial function and attenuates cardiac hypertrophy. *Hypertension*. Aug 2009;54(2):322-8.
39. Tiano L, Belardinelli R, Carnevali P, Principi F, Seddaiu G, Littarru GP. Effect of coenzyme Q10 administration on endothelial function and extracellular superoxide dismutase in patients with ischaemic heart disease: a double-blind, randomized controlled study. *Eur Heart J*. 2007 Sep;28(18):2249-55.
40. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA*. 2002 May 15;287(19):2570-81.
41. Watts GF, Playford DA, Croft KD, Ward NC, Mori TA, Burke V. Coenzyme Q(10) improves endothelial dysfunction of the brachial artery in Type II diabetes mellitus. *Diabetologia*. 2002 Mar;45(3):420-6.
42. Marcoff L, Thompson PD. The role of coenzyme Q10 in statin-associated myopathy: a systematic review. *J Am Coll Cardiol*. 2007 Jun 12;49(23):2231-7.
43. Hamilton SJ, Chew GT, Watts GF. Coenzyme Q10 improves endothelial dysfunction in statin-treated type 2 diabetic patients. *Diabetes Care*. 2009 May;32(5):810-2.
44. Di Meo S, Venditti P. Mitochondria in exercise-induced oxidative stress. *Biol Signals Recept*. 2001 Jan-Apr;10(1-2):125-40.
45. Powers SK, Jackson MJ. Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. *Physiol Rev*. 2008 Oct;88(4):1243-76.
46. Yegutkin GG, Samburski SS, Mortensen SP, Jalkanen S, Gonzalez-Alonso J. Intravascular ADP and soluble nucleotidases contribute to acute prothrombotic state during vigorous exercise in humans. *J Physiol*. 2007 Mar 1;579(Pt 2):553-64.
47. Hellsten Y, Nielsen JJ, Lykkesfeldt J, et al. Antioxidant supplementation enhances the exercise-induced increase in mitochondrial uncoupling protein 3 and endothelial nitric oxide synthase mRNA content in human skeletal muscle. *Free Radic Biol Med*. 2007 Aug 1;43(3):353-61.
48. Cooke M, Iosia M, Buford T, et al. Effects of acute and 14-day coenzyme Q10 supplementation on exercise performance in both trained and untrained individuals. *J Int Soc Sports Nutr*. 2008;5:8.
49. Kon M, Tanabe K, Akimoto T, et al. Reducing exercise-induced muscular injury in kendo athletes with supplementation of coenzyme Q10. *Br J Nutr*. 2008 Oct;100(4):903-9.
50. Gokbel H, Gul I, Belviranli M, Okudan N. The Effects Of Coenzyme Q10 Supplementation on Performance During Repeated Bouts of Supramaximal Exercise in Sedentary Men. *J Strength Cond Res*. 2009 Jul 28.

51. Mizuno K, Tanaka M, Nozaki S, et al. Antifatigue effects of coenzyme Q10 during physical fatigue. *Nutrition*. 2008 Apr;24(4):293-9.
52. Langsjoen PH, Langsjoen JO, Langsjoen AM, Lucas LA. Treatment of statin adverse effects with supplemental Coenzyme Q10 and statin drug discontinuation. *Biofactors*. 2005;25(1-4):147-52.
53. Kidd PM. Neurodegeneration from mitochondrial insufficiency: nutrients, stem cells, growth factors, and prospects for brain rebuilding using integrative management. *Altern Med Rev*. 2005 Dec;10(4):268-93.
54. Matthews RT, Yang L, Browne S, Baik M, Beal MF. Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. *Proc Natl Acad Sci U S A*. 1998 Jul 21;95(15):8892-7.
55. Ayaz M, Tuncer S, Okudan N, Gokbel H. Coenzyme Q(10) and alpha-lipoic acid supplementation in diabetic rats: conduction velocity distributions. *Methods Find Exp Clin Pharmacol*. 2008 Jun;30(5):367-74.
56. Russo R, Cavaliere F, Rombola L, et al. Rational basis for the development of coenzyme Q10 as a neurotherapeutic agent for retinal protection. *Prog Brain Res*. 2008;173:575-82.
57. Feher J, Papale A, Mannino G, Gualdi L, Balacco Gabrieli C. Mitotropic compounds for the treatment of age-related macular degeneration. The metabolic approach and a pilot study. *Ophthalmologica*. 2003 Sep-Oct;217(5):351-7.
58. Qu J, Kaufman Y, Washington I. Coenzyme Q10 in the human retina. *Invest Ophthalmol Vis Sci*. 2009 Apr;50(4):1814-8.
59. Feher J, Kovacs B, Kovacs I, et al. Improvement of visual functions and fundus alterations in early age-related macular degeneration treated with a combination of acetyl-L-carnitine, n-3 fatty acids, and coenzyme Q10. *Ophthalmologica*. 2005 May-Jun;219(3):154-66.
60. Prah S, Kueper T, Biernoth T, et al. Aging skin is functionally anaerobic: importance of coenzyme Q10 for anti aging skin care. *Biofactors*. 2008;32(1-4):245-55.
61. Inui M, Ooe M, Fujii K, Matsunaka H, Yoshida M, Ichihashi M. Mechanisms of inhibitory effects of CoQ10 on UVB-induced wrinkle formation in vitro and in vivo. *Biofactors*. 2008;32(1-4):237-43.
62. Hoppe U, Bergemann J, Diembeck W, et al. Coenzyme Q10, a cutaneous antioxidant and energizer. *Biofactors*. 1999;9(2-4):371-8.
63. Blatt T, Lenz H, Koop U, et al. Stimulation of skin's energy metabolism provides multiple benefits for mature human skin. *Biofactors*. 2005;25(1-4):179-85.
64. Passi S, De Pità O, Grandinetti M, Simotti C, Littarru GP. The combined use of oral and topical lipophilic antioxidants increases their levels both in sebum and stratum corneum. *Biofactors*. 2003;18(1-4):289-97.
65. Schepetkin IA, Xie G, Jutila MA, Quinn MT. Complement-fixing activity of fulvic acid from Shilajit and other natural sources. *Phytother Res*. 2009 Mar;23(3):373-84.
66. Goel RK, Banerjee RS, Acharya SB. Antiulcerogenic and antiinflammatory studies with shilajit. *J Ethnopharmacol*. 1990 Apr;29(1):95-103.
67. Agarwal SP, Khanna R, Karmarkar R, Anwer MK, Khar RK. Shilajit: a review. *Phytother Res*. 2007 May;21(5):401-5.
68. Bhattacharyya S, Pal D, Gupta AK, Ganguly P, Majumder UK, Ghosal S. Beneficial effect of processed shilajit on swimming exercise induced impaired energy status of mice. *Pharmacologyonline*. 2009;1:817-25.
69. Piotrowska D, Dlugosz A, Witkiewicz K, Pajak J. The research on antioxidative properties of TOLPA Peat Preparation and its fractions. *Acta Pol Pharm*. 2000 Nov;57 Suppl:127-9.
70. Ghosal S. *Shilajit in Perspective*. Oxford, U.K.: Narosa Publishing House; 2006.
71. Visser SA. Effect of humic substances on mitochondrial respiration and oxidative phosphorylation. *Sci Total Environ*. 1987 Apr;62:347-54.

72. Royer RA, Burgos WD, Fisher AS, Unz RF, Dempsey BA. Enhancement of biological reduction of hematite by electron shuttling and Fe(II) complexation. *Environ Sci Technol*. 2002 May 1;36(9):1939-46.
73. Kang SH, Choi W. Oxidative degradation of organic compounds using zero-valent iron in the presence of natural organic matter serving as an electron shuttle. *Environ Sci Technol*. 2009 Feb 1;43(3):878-83.
74. Islam A, Ghosh R, Banerjee D, Nath P, Mazumder U, Ghosal S. Biotransformation of 3-hydroxydibenzo—pyrone into 3,8 dihydroxydibenzo—pyrone and aminoacyl conjugates by *Aspergillus niger* isolated from native “shilajit.” *Electronic Journal of Biotechnology*. 2008 Jul 15;11(3):2-10.
75. Bhattacharyya S, Pal D, Banerjee D, et al. Shilajit dibenzo—pyrones: Mitochondria targeted antioxidants. *Pharmacologyonline*. 2009; 2:690-8.
76. Pal D, Bhattacharya S. Pilot Study on the Improvement of Human Performance with ReVitalETM as Energy Booster: Part-IV. 2006. Data on file. Natreon, Inc.
77. Clinical study for evaluation of safe use in purified and standardized shilajit in normal volunteers. J. B. Roy State Ayurvedic Medical College and Hospital, Kolkata. 2007. Data on file. Natreon, Inc.
78. Clinical study for evaluation of plasma antioxidant capacity and safe use of purified and standardized Shilajit (ReVitalET) in normal volunteers. J. B. Roy State Ayurvedic Medical College and Hospital, Kolkata. 2007. Data on file. Natreon, Inc.
79. Zimmer G, Mainka L, Kruger E. Dihydrolipoic acid activates oligomycin-sensitive thiol groups and increases ATP synthesis in mitochondria. *Arch Biochem Biophys*. 1991 Aug 1;288(2):609-13.
80. Jacob S, Henriksen EJ, Schiemann AL, et al. Enhancement of glucose disposal in patients with type 2 diabetes by alpha-lipoic acid. *Arzneimittelforschung*. 1995 Aug;45(8):872-4.
81. Ziegler D, Hanefeld M, Ruhnau KJ, et al. Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant alpha-lipoic acid. A 3-week multicentre randomized controlled trial (ALADIN Study). *Diabetologia*. 1995 Dec;38(12):1425-33.
82. Sachse G, Willms B. Efficacy of thioctic acid in the therapy of peripheral diabetic neuropathy. *Horm Metab Res Suppl*. 1980;9:105-7.
83. Loffelhardt S, Bonaventura C, Locher M, Borbe HO, Bisswanger H. Interaction of alpha-lipoic acid enantiomers and homologues with the enzyme components of the mammalian pyruvate dehydrogenase complex. *Biochem Pharmacol*. 1995 Aug 25;50(5):637-46.
84. Carlson DA, Smith AR, Fischer SJ, Young KL, Packer L. The plasma pharmacokinetics of R-(+)-lipoic acid administered as sodium R-(+)-lipoate to healthy human subjects. *Altern Med Rev*. 2007 Dec;12(4):343-51.
85. Tankova T, Koev D, Dakovska L. Alpha-lipoic acid in the treatment of autonomic diabetic neuropathy (controlled, randomized, open-label study). *Rom J Intern Med*. 2004;42(2):457-64.
86. Negrisanu G, Rosu M, Bolte B, Lefter D, Dabelea D. Effects of 3-month treatment with the antioxidant alpha-lipoic acid in diabetic peripheral neuropathy. *Rom J Intern Med*. 1999 Jul-Sep;37(3):297-306.
87. Androne L, Gavan NA, Veresiu IA, Orasan R. In vivo effect of lipoic acid on lipid peroxidation in patients with diabetic neuropathy. *In Vivo*. 2000 Mar-Apr;14(2):327-30.
88. Haak E, Usadel KH, Kusterer K, et al. Effects of alpha-lipoic acid on microcirculation in patients with peripheral diabetic neuropathy. *Exp Clin Endocrinol Diabetes*. 2000;108(3):168-74.
89. Hagen TM, Vinarsky V, Wehr CM, Ames BN. (R)-alpha-lipoic acid reverses the age-associated increase in susceptibility of hepatocytes to tert-butylhydroperoxide both in vitro and in vivo. *Antioxid Redox Signal*. 2000 Fall;2(3):473-83.
90. Bharat S, Cochran BC, Hsu M, Liu J, Ames BN, Andersen JK. Pre-treatment with R-lipoic acid alleviates the effects of GSH depletion in PC12 cells: implications for Parkinson's disease therapy. *Neurotoxicology*. 2002 Oct;23(4-5):479-86.
91. Suh JH, Wang H, Liu RM, Liu J, Hagen TM. (R)-alpha-lipoic acid reverses the age-related loss in GSH redox status in post-

mitotic tissues: evidence for increased cysteine requirement for GSH synthesis. Arch Biochem Biophys. 2004 Mar 1;423(1):126-35.

92. Magis D, Ambrosini A, Sandor P, Jacquy J, Laloux P, Schoenen J. A randomized double-blind placebo-controlled trial of thioctic acid in migraine prophylaxis. Headache. 2007 Jan;47(1):52-7.

93. Vincent HK, Bourguignon CM, Vincent KR, Taylor AG. Effects of alpha-lipoic acid supplementation in peripheral arterial disease: a pilot study. J Altern Complement Med. 2007 Jun;13(5):577-84.

94. McMackin CJ, Widlansky ME, Hamburg NM, et al. Effect of combined treatment with alpha-Lipoic acid and acetyl-L-carnitine on vascular function and blood pressure in patients with coronary artery disease. J Clin Hypertens (Greenwich). 2007 Apr;9(4):249-55.

95. Noland RC, Koves TR, Seiler SE, et al. Carnitine insufficiency caused by aging and overnutrition compromises mitochondrial performance and metabolic control. J Biol Chem. 2009 Aug 21;284(34):22840-52.

96. Rosca MG, Lemieux H, Hoppel CL. Mitochondria in the elderly: Is acetylcarnitine a rejuvenator? Adv Drug Deliv Rev. 2009 Aug 29.

97. Carta A, Calvani M. Acetyl-L-carnitine: a drug able to slow the progress of Alzheimer's disease? Ann N Y Acad Sci. 1991;640:228-32.

98. Bianchetti A, Rozzini R, Trabucchi M. Effects of acetyl-L-carnitine in Alzheimer's disease patients unresponsive to acetylcholinesterase inhibitors. Curr Med Res Opin. 2003;19(4):350-3.

99. Corbucci GG, Melis A, Piga M, Marchionni A, Calvani M. Influence of acetyl-carnitine on some mitochondrial enzymic activities in the human cerebral tissue in conditions of acute hypoxia. Int J Tissue React. 1992;14(4):183-94.

100. Long J, Gao F, Tong L, Cotman CW, Ames BN, Liu J. Mitochondrial decay in the brains of old rats: ameliorating effect of alpha-lipoic acid and acetyl-L-carnitine. Neurochem Res. Apr 2009 Apr;34(4):755-63.

101. Shenk JC, Liu J, Fischbach K, et al. The effect of acetyl-L-carnitine and R-alpha-lipoic acid treatment in ApoE4 mouse as a model of human Alzheimer's disease. J Neurol Sci. 2009 Aug 15;283(1-2):199-206.

102. Lesnefsky EJ, He D, Moghaddas S, Hoppel CL. Reversal of mitochondrial defects before ischemia protects the aged heart. FASEB J. 2006 Jul;20(9):1543-5.

103. Hagen TM, Moreau R, Suh JH, Visioli F. Mitochondrial decay in the aging rat heart: evidence for improvement by dietary supplementation with acetyl-L-carnitine and/or lipoic acid. Ann N Y Acad Sci. 2002 Apr;959:491-507.

104. Rahbar S. Novel inhibitors of glycation and AGE formation. Cell Biochem Biophys. 2007;48(2-3):147-57.

105. Adegate E. Molecular and cellular basis of the aetiology and management of diabetic cardiomyopathy: a short review. Mol Cell Biochem. 2004 Jun;261(1-2):187-91.

106. Schleicher E, Friess U. Oxidative stress, AGE, and atherosclerosis. Kidney Int Suppl. 2007 Aug;(106):S17-26.

107. Tan AL, Forbes JM, Cooper ME. AGE, RAGE, and ROS in diabetic nephropathy. Semin Nephrol. 2007 Mar;27(2):130-43.

108. Gasser A, Forbes JM. Advanced glycation: implications in tissue damage and disease. Protein Pept Lett. 2008;15(4):385-91.

109. Peppas M, Uribarri J, Vlassara H. Aging and glycoxidant stress. Hormones (Athens). 2008 Apr-Jun;7(2):123-32.

110. Reddy VP, Garrett MR, Perry G, Smith MA. Carnosine: a versatile antioxidant and antiglycating agent. Sci Aging Knowledge Environ. 2005 May 4;2005(18):pe12.

111. Hipkiss AR. Would carnosine or a carnivorous diet help suppress aging and associated pathologies? Ann N Y Acad Sci. 2006 May;1067:369-74.

112. Hipkiss AR. Could carnosine or related structures suppress Alzheimer's disease? *J Alzheimers Dis.* 2007 May;11(2):229-40.

113. Kotanidou A, Xagorari A, Bagli E, et al. Luteolin reduces lipopolysaccharide-induced lethal toxicity and expression of proinflammatory molecules in mice. *Am J Respir Crit Care Med.* 2002 Mar 15;165(6):818-23.

114. Kim JS, Jobin C. The flavonoid luteolin prevents lipopolysaccharide-induced NF-kappaB signalling and gene expression by blocking IkappaB kinase activity in intestinal epithelial cells and bone-marrow derived dendritic cells. *Immunology.* 2005 Jul;115(3):375-87.

115. Wu CH, Yen GC. Inhibitory effect of naturally occurring flavonoids on the formation of advanced glycation endproducts. *J Agric Food Chem.* 2005 Apr 20;53(8):3167-73.

116. Psotova J, Chlopcikova S, Miketova P, Hrbac J, Simanek V. Chemoprotective effect of plant phenolics against anthracycline-induced toxicity on rat cardiomyocytes. Part III. Apigenin, baicalein, kaempferol, luteolin and quercetin. *Phytother Res.* 2004 Jul;18(7):516-21.

117. Wu CH, Wu CF, Huang HW, Jao YC, Yen GC. Naturally occurring flavonoids attenuate high glucose-induced expression of proinflammatory cytokines in human monocytic THP-1 cells. *Mol Nutr Food Res.* 2009 Aug;53(8):984-95.

118. Volvert ML, Seyen S, Piette M, et al. Benfotiamine, a synthetic S-acyl thiamine derivative, has different mechanisms of action and a different pharmacological profile than lipid-soluble thiamine disulfide derivatives. *BMC Pharmacol.* 2008;8:10.

119. Du X, Edelstein D, Brownlee M. Oral benfotiamine plus alpha-lipoic acid normalises complication-causing pathways in type 1 diabetes. *Diabetologia.* 2008 Oct;51(10):1930-2.

120. Stirban A, Negrean M, Stratmann B, et al. Benfotiamine prevents macro- and microvascular endothelial dysfunction and oxidative stress following a meal rich in advanced glycation end products in individuals with type 2 diabetes. *Diabetes Care.* 2006 Sep;29(9):2064-71.

121. Pomeroy F, Molinar Min A, La Selva M, Allione A, Molinatti GM, Porta M. Benfotiamine is similar to thiamine in correcting endothelial cell defects induced by high glucose. *Acta Diabetol.* 2001;38(3):135-8.

122. Marchetti V, Menghini R, Rizza S, et al. Benfotiamine counteracts glucose toxicity effects on endothelial progenitor cell differentiation via Akt/FoxO signaling. *Diabetes.* 2006 Aug;55(8):2231-7.

123. Hammes HP, Du X, Edelstein D, et al. Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. *Nat Med.* 2003 Mar;9(3):294-9.

124. Khatami M, Suldan Z, David I, Li W, Rockey JH. Inhibitory effects of pyridoxal phosphate, ascorbate and aminoguanidine on nonenzymatic glycosylation. *Life Sci.* 1988;43(21):1725-31.

125. Higuchi O, Nakagawa K, Tsuzuki T, Suzuki T, Oikawa S, Miyazawa T. Aminophospholipid glycation and its inhibitor screening system: a new role of pyridoxal 5'-phosphate as the inhibitor. *J Lipid Res.* 2006 May;47(5):964-74.

126. Nakamura S, Niwa T. Pyridoxal phosphate and hepatocyte growth factor prevent dialysate-induced peritoneal damage. *J Am Soc Nephrol.* 2005 Jan;16(1):144-50.

127. Nakamura S, Li H, Adijiang A, Pischetsrieder M, Niwa T. Pyridoxal phosphate prevents progression of diabetic nephropathy. *Nephrol Dial Transplant.* 2007 Aug;22(8):2165-74.

128. Mehta R, Shangari N, O'Brien PJ. Preventing cell death induced by carbonyl stress, oxidative stress or mitochondrial toxins with vitamin B anti-AGE agents. *Mol Nutr Food Res.* 2008 Mar;52(3):379-85.



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