AGELOC SCIENCE: THE GENETICS OF YOUTH

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INTRODUCTION: THE GENETICS OF YOUTH

Nu Skin brings together a world-class team of scientists who have conducted pioneering research in their respective fields of anti-aging research for over 30 years. Collectively, they have published over 300 scientific papers, and their insights have changed the understanding of aging. Their work details the genetic basis of aging while demonstrating that biological aging is no longer considered an inexorable or inevitable process.

Together with these scientists we have developed ageLOC science, which targets the ultimate sources of aging. With ageLOC science we better understand functional groups of genes related to aging (what we call Youth Gene Clusters or YGCs) and how to reset them to reflect a more youthful gene expression pattern.

The loss of vitality is one of the first signs of feeling older that people notice. By the time they reach their mid to late thirties, most adults report a decline in youthful vitality—reporting it even before they notice their first wrinkle. Loss of physical energy, reduced mental acuity, and the lack of sexual health are common signs of aging—what we call the loss of vitality.

Deep inside each of our cells mitochondria create the energy that fuels our bodies. Mitochondria are the key source of youthful vitality and are most highly concentrated in the brain, heart, and muscle. As we age, the efficiency and number of our mitochondria decline, and energy production doesn't always meet the demands of our bodies. Nu Skin's ageLOC scientific approach identifies how this source of vitality can be influenced—through our research we have learned how to target and reset the mitochondrial related YGC to promote a more youthful expression pattern.

The following collection of scientific publications and presentations includes the work of Nu Skin scientists, Nu Skin Anti-Aging Scientific Advisory Board members, and academic partners and represents important research from which we have gained key insights into the genetics of vitality and aging. Ongoing research is being conducted to further enhance ageLOC science into the future.

TRANSCRIPTIONAL BIOMARKERS OF AGE AND THEIR MODULATION BY DIETARY INTERVENTIONS

Presented at: International Congress on Controversies in Longevity, Health and Aging (CoLONGY) Barcelona, Spain. June 26, 2010.

Authors: Barger JL[1], Wood SM[2], Weindruch R[1], Prolla TA[1].

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Studies using whole-genome transcriptional profiling have identified thousands of genes that are changed in expression with age. However, many of these age-related changes are not universal, but instead are specific to the genetic background of the organism being studied. Thus, there is great interest in identifying robust biomarkers of age across multiple experimental models that are applicable to human aging. We use gene expression profiling to identify transcripts that were consistently changed in expression with age (5 vs. 28–30 month old) in seven mouse strains. This analysis was performed in four tissues (heart, cerebral cortex, gastrocnemius and adipose tissue) and RT-qPCR was used to confirm a panel of 10–20 genes in each tissue. Interestingly, we found minimal overlap across the four tissues studied, suggesting that aging at the individual gene level is tissue-specific. We then assessed whether the age-related change in these biomarkers was effected by caloric restriction (CR), the only intervention known to extend lifespan by slowing the aging process. Depending of the tissue studied, CR opposed 3–24% of the overall aging change. Finally, we assessed the ability of dietary ingredients to attenuate age-related changes in these biomarkers. An extract of pomegranate was the most effective compound tested, opposing 32–65% of the overall aging change depending on the tissue studied. In summary, we have identified robust, tissue-specific panels of the transcriptional biomarkers that are relevant to human aging. We are currently using these biomarkers in a large-scale screen of compounds to determine if they have efficacy in preventing aging at the transcriptional level.

ANTIOXIDATION AND LIFESPAN EXTENSION ACTIVITIES OF CORDYCEPS SINENSIS CS-4 IN OXIDATIVE STRESS AND AGING MODELS

Presented at: Oxygen Club of California 2010 World Congress at Santa Barbara, CA. March 17–20, 2010, and was awarded the prestigious DSM Nutraceutical Research Award.

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Cordyceps sinensis is traditionally believed as an anti-aging herb in China. We have reported the effects of Cordyceps sinensis Cs-4 (Cs-4), a mycelia fermentation product of C. sinensis, in glucose-lipidenergy metabolisms, anti-fatigue and endurance enhancement. In this study we examined the effect of Cs-4 in antioxidant and lifespan extension in mice. The antioxidant activity was tested in mice (6 months old) that received 60 days of vehicle or Cs-4 (0.5, 1.0, or 1.5 g/kg) and a single dose of 11 Gry 60Co gamma-radiation on Day 60. Compared to controls, Cs-4 increased plasma total thiolgroups, GSH and GSH- eroxidase, and liver CAT, SOD and GSHreductase ($p < 0.05$). Cs-4 reduced liver protein carbonyl-groups and 8-OHdG ($p < 0.05$). For examining the lifespan-extension effect of CM, 250 mice of 12 months of age (both sexes) were received either vehicle or Cs-4 (0.5, 1.0, or 1.5 g/kg) mixed with the forage. Calorie intake was adjusted to match the levels for controls twice per week. Compared to controls, the 75% survival time was extended 94-108 days in the Cs-4 dosage groups, the 50% survival time extended 10–66 days, the 25% survival time extended 29-44 days and the 12.5% survival time extended 7-50 days (86 wks so far; treatment continues). The Kaplan-Meier Survivor analysis revealed the extended lifespan and the reduced risks of death by Cs-4 ($p < 0.05$). In conclusion, Cs-4 therapy significantly improves the body's antioxidant capacity and extends the lifespan in mice, supporting the traditional belief on the anti-aging function of Cs-4 in humans.

TRANSCRIPTIONAL BIOMARKERS OF MITOCHONDRIAL AGING AND MODULATION BY CORDYCEPS SINENSIS CS-4

Presented at: Biology of Aging, Determinants of Health-Span: From Cells to Humans. Gordon Research Conferences. Les Diablerets, Switzerland. August 22-27, 2010.

Authors: SM Wood[1], JL Barger[2], TA Prolla[2], R Weindruch[2], A Mastaloudis[1], SB Ferguson[1].

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Introduction: One of the earliest manifestations of human aging is a decline in energy which begins as early as 30 years of age. The source of this decline is multi-factorial yet changes in mitochondria (ie. function and number) have been implicated as an integral component of the age-associated decline in humans. Therefore, we set out to identify mitochondrial-related nuclear encoded genes that consistently change in expression with aging. Cordyceps sinensis Cs-4 (Cs-4) is a natural ingredient that has been shown to have anti-aging properties and positive effects on energy including maximal oxygen consumption (VO2max). Therefore, we examined whether age-related gene expression changes could be opposed by Cs-4.

Methods: Mice (C57Bl/6), aged 5 (n = 5; young control (YC)) and 22 (n = 10; old) months of age were fed an AIN 93M diet. The old animals were divided into two groups and fed either the diet alone (old control (OC)) or supplemented with Cs-4 (300 mg/kg body weight)(old supplemented (OS)), for three months. Tissues were collected from skeletal muscle (gastrocnemius) and brain (cerebral cortex); gene expression was analyzed using microarrays. Gene expression profiling was used to identify mitochondrial-related transcripts that consistently changed with age in brain and muscle. Gene ontology terms were used and Parametric Analysis of Gene set Enrichment (PAGE) performed to determine effects of age (YC vs. OC) and supplementation with Cs-4 (OC vs. OS).

Results: We identified 393 out of 1241 mitochondria-related nuclear encoded transcripts in the muscle (220) and brain (173) that changed in expression with age. Cs-4 opposed the age-related changes in 48 of the genes ($P<0.05$). In addition, Cs-4 opposed the effects of aging in several gene ontology pathways.

Conclusion: We identified mitochondrial-related nuclear encoded genes which changed consistently in expression with age. Using this methodology, we found that Cs-4 opposed many of these changes in aging brain and muscle. Ongoing studies are utilizing this technique to investigate the effects of a variety of natural ingredients in brain, muscle and other tissues.

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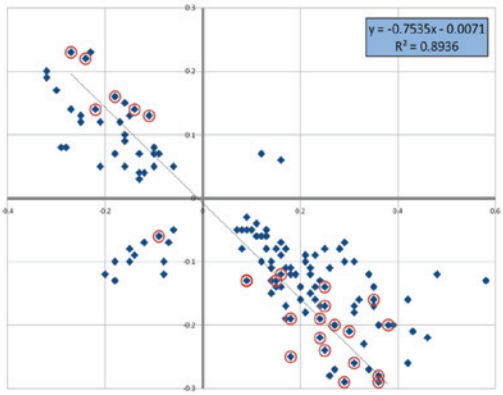
MUSCLE MITOCHONDRIAL RELATED NUCLEAR ENCODED GENE CHANGES, AGING VS. CS-4



Brain Mitochondrial Related Nuclear Encoded Gene Changes, Aging vs. Cs-4

Figure Description: Gene Expression (fold change) as influenced by aging (x-axis) vs. Cs-4 (y-axis). Each point represents one gene. Those that are statistically different ($p<0.05$) with Cs-4 supplementation are circled in red.

MITOCHONDRIA YGC HEATMAP

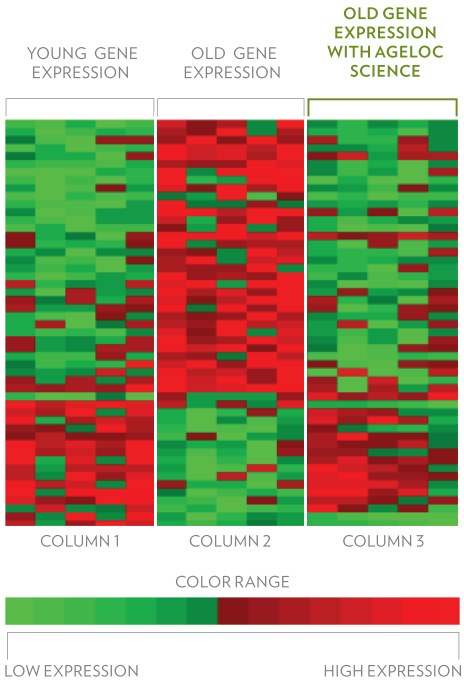


Figure Description: This heatmap illustrates gene expression of three groups from a pre-clinical test with one of the ageLOC Vitality ingredients: young (column 1), old (column 2), and old with ageLOC science (column 3). Each row represents one of 52 genes comprising the mitochondrial Youth Gene Cluster (mtYGC). Columns 1 and 2 show that each of the 52 genes became more or less active during the aging process. In column 3, the YGC activity pattern of the old with ageLOC science group has been reset to a gene expression pattern similar to the young group in column 1[1].

[1] *Transcriptional Biomarkers of Mitochondrial Aging and Modulation by Cordyceps Sinensis Cs-4*. Gordon Research Conference, Biology of Aging, Determinants of Health-Span: From Cells to Humans, August 22-27, 2010. Les Diablerets Conference Center, Les Diablerets, Switzerland.

A NUTRITIONAL STRATEGY TO OPPOSE THE GENETIC EXPRESSION OF AGING AND LOSS OF VITALITY

Presented at: 1st World Congress on Targeting Mitochondria, Strategies, Innovations & Clinical Applications. Berlin, Germany; November 18-19, 2010.

Authors: Wood SM[1]; Ferguson SB[1], Barger JL[2]; Prolla TA[2]; Weindruch R[2]; Bartlett M[1].

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Introduction: One of the earliest manifestations of human aging is a decline in vitality. Age-related mitochondrial dysfunction yields bioenergetic defects within the cell that influence physical and mental vitality. The purpose of this study was to identify and target tissue-specific transcriptional biomarkers (Super Markers of aging) and functional youth gene clusters associated with the mitochondria (mtYGCs) in mouse brain (cerebral cortex) and skeletal muscle (gastrocnemius) tissues. Furthermore, we screened natural ingredients using Super Markers of aging and mtYGCs to identify candidates for a nutritional formula to oppose age-related gene expression changes that influence vitality.

Methods: *Study 1. Super Markers of Aging:* Seven strains of mice (six inbred and one F1 hybrid strain: 129sv, BALB/c, CBA, DBA, C57bl/6, C3H, and B6C3F1) aged 5 mo (young;Y) and 25 mo (old;O) were compared for consistent age-related changes in gene expression in select tissues including the brain and skeletal muscle. Once age-related gene expression changes were identified, common to all seven strains (Super Markers of aging), several natural ingredients were screened for activity that opposed aging effects.

Study 2. mtYGC Identification: Brain and skeletal muscle tissues were collected from mice (C57Bl/6) aged 5 mo (young control;YC) and 25 mo (old control;OC) of age and gene expression profiles were compared. Nuclear mitochondrial-associated genes whose expression changed with age (OC vs. YC, $p<0.05$) were grouped and defined as a mtYGC. Old supplemented (OS) mice were fed Cordyceps sinensis Cs-4 (Cs-4) at 300 mg/kg body weight from age 22–25 mo. Tissues from OS were compared to OC for gene expression differences and whether changes were towards a more youthful (YC) gene expression pattern.

Results: *Study 1.* Super Markers of aging were identified by their consistency of change in all strains of mice and included 10–15 genes per tissue. Pomegranate fruit (PFE) was one of the most potent natural ingredients that opposed changes in the Super Markers of aging muscle and brain tissue, respectively (32–65%; $p<0.05$).

Study 2. Of the 20,687 gene transcripts measured, 1241 were classified with the mitochondria in some fashion (structural, enzymatic, etc). Of these genes, 172 changed in expression with aging in brain and 220 in muscle tissues (OC vs. YC). Cs-4 strongly opposed ($p<0.05$) the age-related changes in mtYGCs in both tissues.

Conclusion: We identified Super Markers of aging as well as mtYGCs whose expression changed with age. We then screened ingredients which opposed these changes and identified PFE and Cs-4 as potent

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mitochondrial anti-aging ingredients. The gene expression changes we observed following supplementation provide mechanistic evidence of anti-aging effects noted by other researchers. Studies designed to elucidate the functional benefits (i.e. vitality) of resetting mtYGC as well as a novel formula containing PFE and Cs-4 are ongoing.

TARGETING AGE-RELATED GENE EXPRESSION IMPROVES MENTAL AND PHYSICAL VITALITY

Presented at: 1st World Congress on Targeting Mitochondria, Strategies, Innovations & Clinical Applications. Berlin, Germany; November 18-19, 2010.

Authors: Ferguson SB[1], Tan NZ[2], Dong YZ[2], Lu JH[2], Fisk NA[1], Wood SM[1], Zhu JS[1,2] Bartlett M[1].

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Introduction: Vitality loss is a universal complication of the aging process. Age-related mitochondrial dysfunction yields bioenergetic defects within the cell, having profound effects on physical and mental vitality. We previously identified functional groups of genes, or gene clusters associated with mitochondrial aging, and transcriptional biomarkers of aging in multiple tissues. Using these as targets, we performed large scale screening of natural products and identified two ingredients in particular which were able to restore the transcriptional profile of these genes to a more youthful pattern. For example, a unique pomegranate fruit extract (PFE) opposed 32–65% of the overall aging changes depending on the tissue studied. Cordyceps sinensis Cs-4 (Cs-4), a natural ingredient, was also shown to significantly restore the expression pattern of mitochondrial gene clusters to a more youthful level.

Published studies have established that Panax Ginseng Root Extract (PG) improves mitochondrial function by increasing key transcriptional factors (AMPK, PGC-1 alpha, nrf2). These findings, coupled with our own transcriptional profiling experiments on Cs-4 and PFE have led us to our present objective: to better understand the functional benefits of targeting age related gene expression changes, via dietary supplementation with combinations of Cs-4, PFE, and PG.

Methods: Female ICR mice (8 and 18 months of age) were fed either control or a blend of Cs-4+PG +/- PFE; 400 or 800 mg/kg) (n=15). Treadmill exercise to exhaustion was examined at Week 5, and swim to exhaustion tested at Week 7. After two weeks of Cs-4+PG+PFE supplementation, the following parameters were tested: plasma lactate, muscle and liver glycogen, muscle mitochondria enzyme activities and muscle superoxide. In a separate human cognitive study, male and female human subjects aged 28–50 were randomized into 4 independent arms (n=10/group): 1. Positive-control: 200mg Phosphatidylserine DHA, 300mg Bacopan, 30mg Vinpocetine; 2. Vitality blend: 2270 mg/day (Cs-4+PG+PFE); 3. Placebo: mono-crystalline cellulose, caramel color; 4. No-supplementation. Subjects underwent cognitive testing (designed by MyBrainTrainer.com) twice a week for 12 weeks. Parameters measured: 3-choice reaction time, short term memory, executive function, information processing, pattern recognition, and working memory. The six scores were averaged to generate a Composite Cognition Index (CCI).

Results: In mice, Cs-4+PG treatment increased treadmill time to exhaustion by 63% ($p<0.01$) increased activities of mitochondrial complexes I+III and II+III ($p<0.05$), and decreased blood lactate by 25% ($p<0.01$). Treatment with Cs-4+PG+PFE increased swim time to exhaustion by 22% ($p=0.02$), spared glycogen in muscle ($p=0.003$), and lowered muscle superoxide production by 32% ($p=0.005$). In humans, treatment with Cs-4+PG+PFE (vitality blend) improved overall cognitive function by 20% (as measured by the CCI), and improved reaction time by 110 ms (14%) vs. placebo ($p<0.05$).

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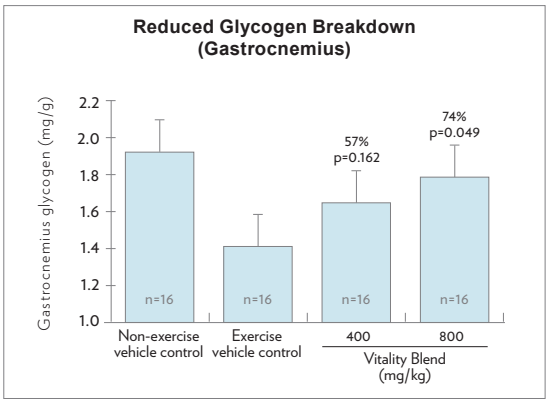
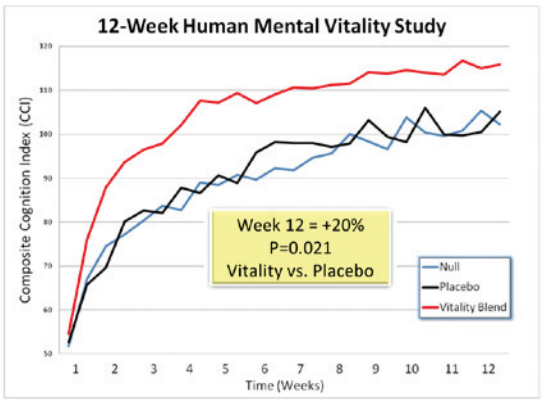
Conclusion: We report improvements in treadmill performance, swimming performance and glycogen sparing in mice. Considerable enhancement in cognitive performance was achieved in a blinded human clinical study. These results demonstrate that targeting the genetic basis of the aging process (changes in gene expression), can yield powerful anti-aging benefits. This work indicates that a blend of Cs-4, PG, and PFE can alleviate some of the physical and mental symptoms of age-related vitality loss.





ROLE OF MITOCHONDRIA IN AGE-RELATED HEARING LOSS AND ITS PREVENTION BY CALORIC RESTRICTION

Presented at: International Symposium on Aging and Anti-Aging; Tokyo, Japan. Sept 24, 2010.

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Age-related hearing loss (AHL, also known as presbycusis) is a universal feature of mammalian aging and is the most common sensory disorder in the elderly population, affecting 50% of individuals over 60 years of age. AHL is a complex disorder, but it is widely accepted that AHL is generally caused by degeneration of the inner ear (cochlea). AHL is associated with age-dependent loss of sensory hair cells, which function as mechanosensory transducers, and spiral ganglion neurons, which relay information from the hair cells to the CNS. Because these cells do not regenerate in mammals, cochlear cell loss eventually leads to AHL.

We have recently demonstrated that AHL can be prevented in mice by deletion of Bak, a mitochondrial pro-apoptotic protein. Bak-mediated cell death of cochlear cells is induced by oxidative stress, and prevented by overexpression of a mitochondrial-targeted catalase, or dietary antioxidants that target mitochondria.
We have also shown that caloric restriction can prevent AHL, and that prevention is associated with the induction of mitochondrial transcripts, and reduction in the expression of genes involved in the mitochondrial apoptotic pathway. Induction of the mitochondrial sirtuin Sirt3 appears to be essential for the positive effects of CR, since sirt3 gene deletion prevents the beneficial effects of CR. These findings suggest novel pathways for intervention in aging and AHL through the development of CR mimetic compounds.

SECTION 2: BACKGROUND RESEARCH COMPLETED BY INDEPENDENT PARTIES

PHYSICAL VIGOR

1. Weindruch R, Prolla TA, Barger JL. Effect of the ageLOC ingredient Cordyceps Cs-4 on gene expression profiles, and effects of caloric restriction and the ageLOC ingredient pomegranate on supermarkers of aging. LifeGen Technologies, unpublished work, 2010.
2. Aviram M, Volkova N, Coleman R et al. Pomegranate phenolics from the peels, arils, and flowers are antiatherogenic: studies in vivo in atherosclerotic apolipoprotein e-deficient (E 0) mice and in vitro in cultured macrophages and lipoproteins. J Agric Food Chem 2008;56:1148–57.
3. Bentler SE, Hartz AJ, Kuhn EM. Prospective observational study of treatments for unexplained chronic fatigue. J Clin Psychiatry 2005;66:625–32.
4. Kim SH, Park KS, Chang MJ, Sung JH. Effects of Panax ginseng extract on exercise-induced oxidative stress. J Sports Med Phys Fitness 2005;45:178–82.
5. Kaneko H, Nakanishi K. Proof of the mysterious efficacy of ginseng: basic and clinical trials: clinical effects of medical ginseng, korean red ginseng: specifically, its anti-stress action for prevention of disease. J Pharmacol Sci 2004;95:158–62.
6. Tesch BJ. Herbs commonly used by women: an evidence-based review. Am J Obstet Gynecol. 2003 May ;188 (5 Suppl):S44–55.
7. Li, C. L., Nicodemus, K. J., Baker, C., Hagan, R. D., Chang, J., and Zhu, J. S. CordyMax improves aerobic, cardiovascular, and metabolic capacity during exercise in endurance-conditioned athletes. 2002. 11-28-2005.
8. Zhao CS, Yin WT, Wang JY et al. CordyMax Cs-4 improves glucose metabolism and increases insulin sensitivity in normal rats. J Altern Complement Med 2002;8:309–14.
9. Zhu J-S, Nicodemus KJ, Hagan RD, Baker C. CordyMax Cs-4 improves cardiovascular and metaboic capacity during exercise in highly fit athletes. FASEB J 2002; (abstr).
10. Dai G, Bao T, Xu C, Cooper R, Zhu JS. CordyMax Cs-4 improves steady-state bioenergy status in mouse liver. J Altern Complement Med. 2001 Jun;7(3):231–40.
11. Nicodemus KJ, Hagan RD, Zhu J, Baker C. Supplementation with Cordyceps Cs-4 fermentation product promotes fat metabolism during prolonged exercise. Medicine and Science in Sports and Exercise 2001;33:S 164 (abstr).
12. Talbott SM, Zhu JS, Rippe JM. CordyMax(tm) Cs-4 enhances endurance in sedentary individuals. Med Sci Sports Exerc 2001;33 (abstr).
13. Aviram M, Dornfeld L, Rosenblat M et al. Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL, and platelet aggregation: studies in humans and in atherosclerotic apolipoprotein E-deficient mice. Am J Clin Nutr 2000;71:1062–76.
14. Zhu JS., Halpern GM, and Jones K. The scientific rediscovery of an ancient Chinese herbal medicine: Cordyceps sinensis. Part I. J Altern Complement Med. 1998; 4(3), 289–303.
15. Zhu JS, Halpern GM, Jones K. The scientific rediscovery of a precious ancient Chinese herbal regimen: Cordyceps sinensis: part II. J Altern Complement Med 1998;4:429–57.
16. Xi, J and TCM Drugs Factory. Clinical study of Cordyseps sinensis capsules on the treatment of chronic bronchitis. Original Applications Material XX, 1–6. 1997.
17. Qiuo, Y. and Xianchuo, M. Treatment of 32 tussive asthma patients with JinShuiBao (Cordyceps sinensis Cs-4). 1996.
18. Han S-R. Experience with Jin Shui Bao in the treatment of chronic bronchitis and other pulmonary disorders. J Administration Traditional Chinese Med 1995;5:33–4.
19. Jiang J, Gao Y. Summary of treatment of 37 chronic renal dysfunction patients with Jin Shui Bao (Cordyceps sinensis Cs-4). J Management Traditional Chinese Medicine 1995;5:23–4.
20. Mao-lu L, Jianping W. Jin Shui Bao capsule as adjuvant treatment for acute stage pulmonary heart disease: Analysis of therapeutic effect of 50 clinical cases. J Management Traditional Chinese Medicine 1995;5:28–9.
21. Wang WQ. Observations of The Effects of Jin-Shui-Bao on the Activities of SOD of COED Patients. Journal of administration of TCM 1995;5:24.
22. Yin QZ, Kang S, Lu CW, Jun T. Evaluation of therapeutic effect of Jin-Shui Bao capsule for treatment of respiratory disease. J Management Traditional Chinese Medicine 1995;5:29–30.
23. Zhang, Z., Huang, W., Liao, S., Jinsheng, L., Lei, L., and Et Al. Clinical and laboratory studies of JinShuiBao in eliminating oxygen free radicals in elderly senescent Xu-Zheng patients. Journal of Management of Traditional Chinese Medicine 5(supplement), 14–18. 1995.
24. Cao, Z. and Wen, Y. Therapeutic effect analysis of JinShuiBao capsule in treatment of 33 elderly senescent Xu-Zheng (Asthenia syndrome) patients. Journal of Applied TCM 1, 32–33. 1993.
25. Fei X. Chinese version: Medicinal use of chinese deep-layer mycelia fermentation product of Cordyceps. Chinese Pharmaceutical J 1992;27:195–8.

MENTAL ACUITY

1. Weindruch R, Prolla TA, Barger JL. Effect of the ageLOC ingredient Cordyceps Cs-4 on gene expression profiles, and effects of caloric restriction and the ageLOC ingredient pomegranate on supermarkers of aging. LifeGen Technologies, unpublished work, 2010.
2. Zhao H, Li Q, Pei X et al. Long-term ginsenoside administration prevents memory impairment in aged C57BL/6J mice by up-regulating the synaptic plasticity-related proteins in hippocampus. Behav Brain Res 2009;201:311–7.
3. Hartman RE, Shah A, Fagan AM et al. Pomegranate juice decreases amyloid load and improves behavior in a mouse model of Alzheimer's disease. Neurobiol Dis 2006;24:506–15.
4. Rausch WD, Liu S, Gille G, Radad K. Neuroprotective effects of ginsenosides. Acta Neurobiol Exp (Wars) 2006;66:369–75.
5. Reay JL, Kennedy D, Scholey A. Effects of Panax ginseng, consumed with and without glucose, on blood glucose levels and cognitive performance during sustained 'mentally demanding' tasks. J Psychopharmacol 2006;20:771–81.
6. Cheng Y, Shen LH, Zhang JT. Anti-amnestic and anti-aging effects of ginsenoside Rg1 and Rb1 and its mechanism of action. Acta Pharmacol Sin 2005;26:143–9.
7. Reay JL, Kennedy DO, Scholey AB. Single doses of Panax ginseng (G115) reduce blood glucose levels and improve cognitive performance during sustained mental activity. J Psychopharmacol 2005;19:357–65.
8. Kaneko H, Nakanishi K. Proof of the mysterious efficacy of ginseng: basic and clinical trials: clinical effects of medical ginseng, korean red ginseng: specifically, its anti-stress action for prevention of disease. J Pharmacol Sci 2004;95:158–62.
9. Kennedy DO, Scholey AB. Ginseng: potential for the enhancement of cognitive performance and mood. Pharmacol Biochem Behav 2003;75:687–700.
10. Zhu, J. S., Halpern, G. M., and Jones, K. The scientific rediscovery of an ancient Chinese herbal medicine:Cordyceps sinensis. Part I. J Altern.Complement Med 4(3); 1998; 289–303.

SEXUAL HEALTH

1. Oh KJ, Chae MJ, Lee HS, Hong HD, Park K. Effects of Korean red ginseng on sexual arousal in menopausal women: placebo-controlled, double-blind crossover clinical study. J Sex Med 2010;7:1469–77.
2. Zhang Q, Radisavljevic ZM, Siroky MB, Azadzoi KM. Dietary antioxidants improve arteriogenic erectile dysfunction. Int J Androl. 2010 Jun 24.
3. Jia L, Zhao Y, Liang XJ. Current evaluation of the millennium phytomedicine- ginseng (II): Collected chemical entities, modern pharmacology, and clinical applications emanated from traditional Chinese medicine. Curr Med Chem 2009;16:2924–42.
4. Choi KT. Botanical characteristics, pharmacological effects and medicinal components of Korean Panax ginseng C A Meyer. Acta Pharmacol Sin 2008;29:1109–18.
5. Kiefer D, Pantuso T. Panax ginseng. Am Fam Physician 2003;68:1539–42.
6. Zhu, J. S., Halpern, G. M., and Jones, K. The scientific rediscovery of an ancient Chinese herbal medicine:Cordyceps sinensis. Part I. J Altern.Complement Med 4(3), 289–303. 1998.
7. Da Guang, C. Effects of Cs-4, Jinshuibao capsules on the life qualities of patients with chronic heart failure. Journal of administration of Traditional Chinese Medicine (TCM) 5 (additional issue), 40–43. 1995.
8. Jiang J, Gao Y. Summary of treatment of 37 chronic renal dysfunction patients with Jin Shui Bao (Cordyceps sinensis Cs-4). J Management Traditional Chinese Medicine 1995;5:23–4.
9. Fei X. Chinese version: Medicinal use of chinese deep-layer mycelia fermentation product of Cordyceps. Chinese Pharmaceutical J 1992;27:195–8.
10. Yang W, Deng X, Hu W. Clinical study of fermentation product of cordyceps sinensis on treatment of hyposexuality. Jiangxi Traditional Chinese Medicine 1985;5:46–7.