



FOUR PILLARS COGNITIVE

Complete daily nutritional supplement*

Complete daily nutrition emphasizing cognitive health*

- Includes the four major cornerstones of nutrition: vitamins and minerals, omega-3 fatty acids, antioxidants, and human-sourced probiotics
- Helps support cognitive function*
- Helps the body respond to mental and physical stress*
- Promotes energy metabolism, physical working capacity and general mental wellness*



Four Pillars Cognitive is a unique combination of over 20 vitamins and minerals, omega-3 fatty acids, herbs, and probiotics. With a blend of standardized adaptogenic herbal extracts and polyphenols, Four Pillars Cognitive concentrates on supporting cognitive health and mental performance after occasional stress.* Rhodiola mediates neurotransmitter activity, while eleuthero regulates nervous system responses to help the body respond to mental and physical stress.* The grape and organic blueberry fruit blend provides polyphenols, which may also help promote cognitive health in adults.* Four Pillars Cognitive contains the omega-3 fatty acids DHA and EPA, which further support brain function, including memory.* The vitamins and minerals in this blend support cellular energy production, healthy glucose metabolism and muscle function, as well as skin, immune and bone health.* Probiotics are also included to support a healthy gastrointestinal tract, which may communicate with the brain and influence cognitive health.*

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

This information is intended for use by healthcare practitioners only and does not establish a doctor-patient relationship. Please be sure to consult your physician before taking this or any other product.

Copyright © 2016 Seroyal. All rights reserved. No part of this information may be used or reproduced in any form or by any means, or stored in a database or retrieval system, or be distributed or replicated without express permission of Seroyal. Making copies of any part of this information for any purposes other than your own personal use is a violation of copyright law.

SUPPLEMENT FACTS

Serving Size 1 Tablet

| Amount per serving | | %DV |
|---|---------|-------|
| Vitamin A (as vitamin A acetate) | 1000 IU | 20% |
| Vitamin C (ascorbic acid) | 180 mg | 300% |
| Vitamin D ₃ (as cholecalciferol) | 1000 IU | 250% |
| Vitamin E (as <i>d</i> -alpha tocopheryl succinate) | 30 IU | 100% |
| Vitamin K ₂ (as Menaquinone-7) | 120 mcg | 150% |
| Thiamin (as thiamin mononitrate) | 12.5 mg | 833% |
| Riboflavin | 12.5 mg | 735% |
| Niacin (as niacinamide) | 25 mg | 125% |
| Vitamin B ₆ (as pyridoxal-5-phosphate) | 12.5 mg | 625% |
| Folate (as calcium L-5-methyltetrahydrofolate, Metafolin®▲) | 400 mcg | 100% |
| Vitamin B ₁₂ (as methylcobalamin) | 400 mcg | 6667% |
| Biotin | 100 mcg | 33% |
| Pantothenic acid (as calcium <i>d</i> -pantothenate) | 25 mg | 250% |
| Calcium (as calcium citrate malate) | 50 mg | 5% |
| Iodine (as potassium iodide) | 150 mcg | 100% |
| Magnesium (as magnesium citrate) | 25 mg | 6% |
| Zinc (as zinc citrate) | 11 mg | 73% |
| Selenium (as selenomethionine) | 100 mcg | 143% |
| Copper (as copper gluconate) | 1 mg | 50% |
| Manganese (as manganese gluconate) | 2.3 mg | 115% |
| Chromium (as chromium polynicotinate) | 60 mcg | 50% |
| Molybdenum (as potassium molybdate) | 45 mcg | 60% |
| Potassium (as potassium citrate monohydrate) | 50 mg | 1% |
| Lutein (from Aztec marigold flower) | 5 mg | † |
| Zeaxanthin (from Aztec marigold flower) | 1 mg | † |

† % Daily Value (DV) not established

Other ingredients: Cellulose, hypromellose, croscarmellose sodium, ascorbyl palmitate, silica, glycerin

▲ Metafolin® is a registered trademark of Merck KGaA, Darmstadt, Germany.

Recommended intake

Adults: Contents of one serrated blister pack strip: 1 tablet, 1 softgel, 1 capsule (brown), 1 capsule (off-white), all taken once daily with a meal, at least two to three hours before or after taking medications, or as professionally directed. Not to be taken immediately before bedtime.

Pack Size

30 Day Supply
(30 strips of 1 tablet, 2 capsules and 1 softgel)

Product Code

FP04-30



SUPPLEMENT FACTS

Serving Size 1 Softgel

| Amount per serving | | %DV |
|--|--------|-----|
| Calories | 15 | |
| Calories from Fat | 10 | |
| Total Fat | 1 g | 2%◆ |
| Cholesterol | 10 mg | 4%◆ |
| Eicosapentaenoic acid (EPA) | 395 mg | † |
| Docosahexaenoic acid (DHA) | 265 mg | † |
| Total omega-3 (EPA, DHA & other omega-3's provided as sardine & anchovy oil) | 750 mg | † |

◆ % Daily Values (DV) are based on a 2,000 calorie diet
† % Daily Value not established

Other ingredients: Fish gelatin (tilapia, striped catfish, Nile perch, carp, shad, grunt, catfish), glycerin, orange oil, natural mixed tocopherols

SUPPLEMENT FACTS

Serving Size 1 Capsule (brown powder-filled)

| Amount per serving | | %DV |
|---|--------|-----|
| Rhodiola (<i>Rhodiola rosea</i>) root std. extract (3% rosavin, 1% salidroside) | 144 mg | † |
| Ashwagandha (<i>Withania somnifera</i>) root std. extract (5-8:1) (equivalent to 675 - 1080 mg dried root/7% withanolides) | 135 mg | † |
| Eleuthero (<i>Eleutherococcus senticosus</i>) root std. extract (15:1) (equivalent to 1500 mg dried root/0.8% eleutherosides) | 100 mg | † |
| Neurophenol™ Proprietary Blend Grape (<i>Vitis vinifera</i>) fruit extract Organic blueberry (<i>Vaccinium angustifolium</i>) fruit extract | 91 mg | † |

† % Daily Value (DV) not established

Other ingredients: Hypromellose, silica, ascorbyl palmitate

SUPPLEMENT FACTS

Serving Size 1 Capsule (off-white powder-filled)

| Amount per serving | | %DV |
|---|----------------|-----|
| HLC Consortium | 10 billion CFU | † |
| <i>Lactobacillus acidophilus</i> (CUL-60) | | |
| <i>Lactobacillus acidophilus</i> (CUL-21) | | |
| <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> (CUL-34) | | |
| <i>Bifidobacterium bifidum</i> (CUL-20) | | |

† % Daily Value (DV) not established

Other ingredients: Cellulose, hypromellose

Scientific Rationale:

Pillar 1: Vitamins and Minerals

Multivitamin and mineral supplements help individuals to obtain recommended levels of essential nutrients.¹ Dietary supplementation may be especially important to specific populations, including pregnant or lactating women, individuals who avoid specific food groups, or those who regularly consume processed and fast food.¹ Pillar 1 provides a combination of more than 20 vitamins and minerals, plus lutein and zeaxanthin which provides support for cognitive function and ocular health.^{2-6*} It has been reformulated to provide additional nutritional support, as compared to the original Four Pillars product.

B vitamins are critical for cognitive health as they support cellular energy metabolism and neurotransmitter synthesis.^{2*} Four Pillars Cognitive provides Metafolin[®], a proprietary and bioavailable form of the naturally occurring form of folate.^{3*} It can be used directly by the body and does not depend on the genotype of folate-dependent enzymes.^{3*} Metafolin[®] may be more appropriate for supplementation than folic acid as it does not mask the symptoms of vitamin B₁₂ deficiency.^{3*} Also included is vitamin C, which is prevalent in the brain and spinal cord as a scavenger of free radicals produced by neurotransmission.⁶ In addition, Four Pillars Cognitive contains lutein and zeaxanthin, natural carotenoid pigments that are highly concentrated within the lens and macula of the retina.^{4*} As the primary carotenoids in these areas, they have a unique ability to protect the eye against oxidative damage produced by metabolic activity and light exposure.^{4*} Clinical trials have also shown that daily supplementation with lutein and zeaxanthin promotes healthy macular pigment optical density in older adults.^{5,6*} Vitamin K has an important role in maintaining bone health through the carboxylation of osteocalcin, a protein that regulates calcium uptake and bone mineral maturation.^{7*} Vitamin K₂ is provided as menaquinone-7, a highly bioavailable (compared to vitamin K₁ and menaquinone-4) and effective form of the vitamin, likely due to its long half-life time.^{8-10*} This blend also supports healthy glucose metabolism, proper muscle and thyroid gland function, and the maintenance of eyesight, skin, membranes and immune function.^{11-16*}

Randomized, placebo-controlled trials have found that daily multivitamin and mineral supplementation improves cognitive health in adults.^{17,18*} Studies have reported that multivitamin and mineral supplementation improved the accuracy and performance of tasks, such as mathematical calculations and the Stroop Color-Word Task (naming font colour when incongruent with color name).^{17,18*} It also improved scores of general mental health/vigor, mood, stress and mental fatigue.^{17,18*} Similarly, a multivitamin, mineral, herbal and probiotic supplement was found to promote spatial working memory performance (measured by remembering the location of squares in a grid) as well as healthy levels of vitamins B₆ and B₁₂ in elderly females.¹⁹ Multivitamin supplementation was also found to significantly promote healthy homocysteine metabolism.^{17,19*}

Pillar 2: Omega-3 Fatty Acids

Pillar 2 contains omega-3 fatty acids, including DHA and EPA. Research demonstrates that omega-3 fatty acids are incorporated into neural membranes and help promote their function.^{20*} Omega-3 fatty acids increase membrane fluidity, support proper receptor and neurotransmitter signalling, and maintain ion flow and membrane-bound enzyme activity.^{20*}

As a result of their role in maintaining neuron function, supplementation with fish oils has been associated with beneficial effects on cognitive health.^{20*} Supplementation with DHA has been found to promote long-term potentiation, a form of synaptic plasticity associated with learning and memory.^{20*} Similarly, randomized, double-blind trials have found that daily supplementation with fish oils significantly enhances episodic memory (measured by remembering or recognizing words/pictures) and working memory (measured by sequencing tasks), and improves cognitive age in older adults.^{21,22*}

Pillar 3: Phytonutrients

Herbal extracts

Rhodiola is a plant found at high altitudes in the Arctic, Asia and Europe.²³ By decreasing the activity of enzymes that degrade neurotransmitters and by prolonging neurotransmitter activity in the brain, rhodiola elevates bio-electrical brain activity.^{23*} This results in increased cognitive function as well as improved attention, memory and learning abilities.^{15*} Rhodiola helps modulate occasional stress by influencing mediators of stress responses, including the stress hormone cortisol and neuropeptide Y, which regulates energy balance, memory, learning and mood.^{23,24*} Rhodiola also provides antioxidants to promote optimal health.^{25*} Clinical research demonstrates that daily supplementation with 100-200 mg of rhodiola extract significantly supports mental and physical wellbeing during occasional stress, promotes coordination and regulates fatigue in stressful situations, and provides antioxidant protection.^{25-28*}

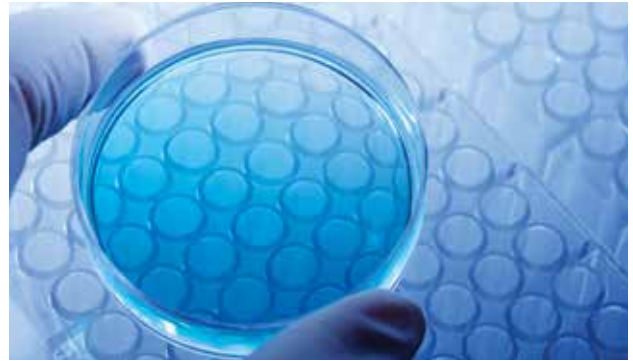
Eleuthero supplementation during periods of stress has been found to significantly decrease the activity of the sympathetic nervous system (which controls the body's fight or flight response) and increase the activity of the parasympathetic nervous system (which controls the body's rest and digest activities).^{24*} Similarly, research has shown that eleuthero promotes mental performance after periods of physical or mental exertion by mediating the signalling of hormones involved in stress responses, including cortisol and norepinephrine.^{28,29*} This promotes the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which controls various homeostatic processes in the body.^{29*} Eleuthero also raises the consumption and use of oxygen to help the body adjust in times of mental, physical, and metabolic stress.^{28*} Supplementation with eleuthero has been shown to provide support for physical and mental stress in adults with moderate fatigue.^{30*} In a trial involving male athletes, eleuthero intake also promoted physical working capacity during physical stress.^{31*} Specifically, eleuthero significantly improved four measures of working capacity: maximal oxygen uptake, oxygen pulse, total work and exhaustion time.^{31*}

Ashwagandha is a shrubby plant traditionally used in Ayurvedic and Unani medicine.^{32*} The roots contain withanolides, the primary bioactive compounds of the plant.³² Randomized, double-blind, placebo-controlled trials have found that daily supplementation with ashwagandha extract significantly promotes mental wellbeing, including support for cognitive function and occasional stress.^{33-35*} This neuroprotection may result from the free radical scavenging ability of ashwagandha, or from its ability to promote normal levels of adrenal hormones in times of stress, including cortisol and dehydroepiandrosterone (DHEA).^{34-37*} This is important to note as the ratio of cortisol to DHEA may be a clinical marker of HPA axis functioning.^{38*}

Fruit polyphenols

Research using aged rats has found that supplementation with blueberry helps to promote cognitive health, including object memory recognition.^{39,40*} In one trial, the antioxidant-rich blueberry diet also promoted healthy levels of NFκB, the cytokine-mediating transcription factor, in four areas of the brain associated with cognitive and motor performance.^{40*} Berry polyphenols may promote healthy vasculature in the brain, including increased cerebral blood flow, maintenance of endothelial cell health and regulation of platelet activity.^{41*} Polyphenols may also support neurotransmitter activity, mediate the metabolism of amyloid protein and increase antioxidant enzymes in the brain.^{41*}

A review of clinical trials has found that supplementation with flavonols supports cognitive function, including memory and information processing.^{42*} In a clinical trial involving older adults, daily supplementation with grape juice was found to promote memory as measured by a test of verbal learning and retention.^{43*} Similarly, daily supplementation with blueberry juice promoted memory function in older adults as measured by word recall and the formation of word associations.^{44*}



Pillar 4: Probiotics

The human intestinal tract contains more than 400 bacterial species, although its composition can be altered by diet, stress, medication and age.⁴⁵ Bacterial balance needs to be maintained for healthy intestines, which selectively allow absorbance and promote the excretion of dangerous substances.^{45,46*} Probiotics mediate microbial colonization the gastrointestinal tract by reducing the pH and stimulating the production of antimicrobial peptides in the intestine.^{46*} In addition to controlling bacterial survival, probiotics strengthen the epithelial barrier.^{46*} They mediate the integrity of tight junctions and increase mucin release, which regulates permeability and reduces microbial adherence to cells.^{47*} Additionally, approximately 80% of the body's immunologically active cells are located in gut-associated lymphoid tissue, demonstrating an important interaction between the intestines and the immune system.^{48*} Supplementation with a combination of microorganisms helps maximize intestinal colonization, promoting the growth of beneficial bacteria.^{47*} Four Pillars Cognitive is formulated using Seroyal's Lactobacillus and Bifidobacterium probiotic consortium. These microorganisms have been used in a wide body of clinical research, and have been found to promote gastrointestinal comfort and immune health (when combined with vitamin C).^{49-53*}

Recent research has demonstrated a close relationship between the brain and gut, known as the "gut-brain axis".^{54*} Studies show that the gastrointestinal tract and brain communicate using four main information carriers (neurons, cytokines, gut hormones and microbial factors) to send neural, immune and endocrine messages.^{54*} This connection appears to be bi-directional, as the brain may influence microflora composition and gastrointestinal function, while gut health may impact cognition, mood, appetite and stress.^{54*}

REFERENCES

- National Institutes of Health: Office of Dietary Supplements. (2015). Multivitamin/mineral Supplements Fact Sheet for Health Professionals. Retrieved from: <https://ods.od.nih.gov/factsheets/MVMMS-HealthProfessional/>
- Combs, GF. (2012). The Vitamins (4th ed.). USA: Elsevier.
- EMD Millipore Corporation. (2015). Key benefits of Metafolin®. Retrieved from: <http://www.emdmillipore.com/CA/en/products/small-molecule-pharmaceuticals/bulk-apl/olates/metafolin/key-benefits/830bqBMZEAFAAFNTW/ltHt_navgid=xptMKfaY5ZSRpEoNdlgbj720000gbiXydlol:sid=egfulohvDBeiqwog3R_BewKvWVOH11_WbZtasT6mmj-ryWNOiWtmxSCtq2LbOCazR0Pu4i1QsZYCID5bktFV_2r41o1q7TsuuV2Fu79lPoMOfG4WlXG6tb6vCdRPOZFUsYJmC0sZyCpj-eFOPu4i1>
- Ma, L, Lin, XM. J Sci Food Agric. 2010; 90: 2-12.
- Huang, YM, Yan, SF, Ma, L, Zou, ZY, Xu, XR, Dou, HL, Lin, XM. Nutrition. 2013; 29: 387-392.
- Huang, YM, Dou, HL, Huang, FF, Xu, XR, Zou, ZY, Lu, XR, Lin, XM. British Journal of Ophthalmology. 2015; 99: 371-375.
- Plaza, SM, Lamson, DW. Altern Med Rev. 2005; 10(1): 24-35.
- Schurgers, LJ, Teunissen, KJF, Hamulyak, K, Knapen, MHJ, Vik, H, Vermeer, C. Blood. 2007; 109(8): 3279-3283.
- Saito, T, Schurgers, LJ, Uenishi, K. Nutrition Journal. 2012; 11: 93.
- Knapen, MHJ, Drummen, NE, Smit, E, Vermeer, C, Theuvsissen, E. 2013; 24: 2499-2507.
- Hua, Y, Clark, S, Ren, J, Sreejayan, N. J Nutr Biochem. 2012; 23(4): 313-319.
- Holick, MF, Binkley, NC, Bischoff-Ferrari, HA, Gordon, CM, Hanley, DA, Heaney, RP, Murad, MH, Weaver, CM. J Clin Endocrinol Metab. 2011; 96(7):1911-1930.
- de Baaij, JHF, Hoenderop, JGJ, Bindels, RJM. Physiol Rev. 2015; 95: 1-46.
- Schomburg, L, Kohle, J. Mol. Nutr. Food Res. 2008; 52: 1235-1246.
- Mukherjee, S, Datta, A, Patravala, V, Korting, HC, Roeder, A, Weindl, G. Clinical Interventions in Aging. 2006; 1(4): 327-348.
- Ruhl, R. Proceedings of the Nutrition Society. 2007; 66: 458-469.
- Haskell, CF, Robertson, B, Jones, E, Forster, J, Jones, R, Wilde, A, Maggini, S, Kennedy, DO. Hum. Psychopharmacol Clin Exp. 2010; 25: 448-461.
- Kennedy, DO, Veasey, R, Watson, A, Dodd, F, Jones, E, Maggini, S, Haskell, CF. Psychopharmacology. 2010; 211: 55-68.
- Macpherson, H, Ellis, KA, Sali, A, Pipingas, A. Psychopharmacology. 2012; 220: 351-365.
- Horrocks LA, Farooqui AA. Prostaglandins Leukotrienes Essent Fatty Acids. 2004; 70: 361-372.
- Stonehouse, W, Conlon, CA, Podd, J, Hill, SR, Minihane, SM, Haskell, C, Kennedy, D. Am J Clin Nutr. 2013; 97: 1134-43.
- Yurko-Mauro, J, McCarthy, D, Rom, D, Nelson, EB, Ryan, AS, Blackwell, A, Salem Jr, N, Stedman, M. 2010; 6: 456-464.
- Hung, SK, Perry, R, Ernst, E. Phytomedicine. 2011; 18: 235-244.
- Panosian, A, Wikman, G. Pharmaceuticals. 2010; 3: 188-224.
- Skarpanska-Slejnborn, A, Piliaczynska-Szczesiak, L, Basta, P, Deskur-Smielecka, E. International Journal of Sport Nutrition and Exercise Metabolism. 2009; 19: 186-199.
- Spassov, AA, Wikman, GK, Mandrikov, VB, Mironova, A, Neumoin, VV. Phytomedicine. 2000; 7(2): 85-89.
- Darbinyan, V, Kleyan, A, Panossian, A, Gabrielyan, E, Wikman, G, Wagner, H. Phytomedicine. 2000; 7(5): 365-371.
- Stansbury, J, Saunders, P, Winston, D. Journal of Restorative Medicine. 2012; 1: 76-82.
- Panosian, AG. Psychiatr Clin N Am. 2013; 36: 49-64.
- Hartz, AJ, Noyes, BR, Hoehns, J, Logemann, C, Sinitz, S, Butani, Y, Wang, W, Brake, K, Ernst, M, Kautzman, H. Psychological Medicine. 2004; 34: 51-61.
- Asanot, K, Takahashi, T, Miyashita, M, Matsuzaka, A, Muramatsu, S, Kuboyama, M, Kugo, H, Imai, J. Planta Med. 1986; (3): 175-177.
- Singh, G, Sharma, PK, Dudhe, R, Singh, S. Annals of Biological Research. 2010; 1(3): 56-63.
- Chengappa, KNR, Bowie, CR, Schlicht, FJ, Fleet, D, Brar, JS, Jindal, R. J Clin Psychiatry. 2013; 74(11): 1076-1083.
- Auddy, B, Hazra, J, Mitra, A, Abedon, B, Ghosal, S. JANA. 2008; 11(1): 50-56.
- Chandrasekhar, K, Kapoor, J, Anishetty, S. Indian J Psychol Med. 2012; 34(3): 255-262.
- Naidu, PS, Singh, A, Kulkarni, SK. Phytother. Res. 2006; 20: 140-146.
- Konar, A, Shah, N, Singh, R, Saxena, N, Kaul, SC, Wadhwa, R, Thakur, MK. PLoS ONE 6(11): e27265.
- Guilliams, TG, Edwards, L. The Standard. 2010; 9(2): 1-12.
- Malin, DL, Lee, DR, Goyarzu, P, Chang, YH, Ennis, LJ, Beckett, E, Shukitt-Hale, B, Joseph, JA. Nutrition. 2011; 27: 338-342.
- Goyarzu, P, Malin, DH, Lau, FC, Tagliatalata, G, Moon, WD, Jennings, R, Moy, E, Lippold, S, Shukitt-Hale, B, Joseph, JA. Nutritional Neuroscience. 2004; 7(2): 75-83.
- Cherniack, EP. British Journal of Nutrition. 2012; 108: 794-800.
- Macready, AL, Kennedy, OB, Ellis, JA, Williams, CM, Spencer, JPE, Butler, LT. Genes Nutr. 2009; 4: 227-242.
- Krikorian, R, Nash, TA, Shidler, MD, Shukitt-Hale, B, Joseph, JA. British Journal of Nutrition. 2010; 103: 730-734.
- Krikorian, R, Shidler, MD, Nash, TA, Kalt, W, Vinquist-Tymchuk, MR, Shukitt-Hale, B, Joseph, JA. J Agric Food Chem. 2010; 58(7): 3996-4000.
- Nagpal, R, Yadav, H, Kumar, M, Jain, S, Yamashiro, Y, Marotta, F. (2013). Chapter 1. Probiotics, Prebiotics and Synbiotics. In Otlles, S. (Ed.), Probiotics and Prebiotics in Food, Nutrition and Health (pp. 1-24). Boca Raton, FL: CRC Press.
- Saulnier, N, Zocco, MA, Di Caro, S, Gasbarrini, G, Gasbarrini, A. Genes & Nutrition. 2006; 1(2): 107-116.
- Allen, SJ, Wareham, K, Bradley, C, Harris, W, Dhar, A, Brown, H, Foden, A, Cheung, WY, Gravenor, MB, Plummer, S, Phillips, CJ, Mack, D. 2012; 12: 108.
- Saavedra, JM. Use of Probiotics in Pediatrics: Rationale, Mechanisms of Action, and Practical Aspects. Nutrition in Clinical Practice. 2007; 22: 351-365.
- Allen, SJ, Jordan, S, Storey, M, Thornton, CA, Gravenor, M, Garaiova, I, Plummer, SF, Wang, D, Morgan, G. J Nutr. 2010; 140(3): 483-488.
- Williams, EA, Stimpson, J, Wang, D, Plummer, S, Garaiova, I, Barker, ME, Corfe, BM. Aliment Pharmacol Ther. 2009; 29(1): 97-103.
- Madden, JA, Plummer, SF, Tang, J, Garaiova, I, Plummer, NT, Heribson, M, Hunter, JO, Shimada, T, Cheng, L, Shirakawa, T. Int Immunopharmacol. 2005; 5(6): 1091-1097.
- Plummer, SF, Garaiova, I, Sarvotham, T, Cottrell, SL, Le Scoullier, S, Weaver, MA, Tang, J, Dee, P, Hunter, J. Int J Antimicrob Agents. 2005; 26(1): 69-74.
- Plummer, S, Weaver, MA, Harris, JC, Dee, P, Hunter, J. Int Microbiol. 2004; 7(1): 59-62.
- Holzer, P, Farzi, A. Adv Exp Med Biol. 2014; 817: 195-219.