

A Flood of Health Functional Foods: What Is to Be Recommended?

Eun Sil Lee

Department of Obstetrics and Gynecology, Soonchunhyang University College of Medicine, Seoul, Korea

Health functional food is referred to a food prepared or processed from specific components or ingredients for functionality beneficial to the body through extraction, concentration, purification, blending and other methods. The demand for health functional foods is steadily increasing, and red ginseng is the most demanded food among women in the 50s, followed by multivitamin, omega-3, glucosamine and aloe. To date, there is insufficient evidence on the effect of red ginseng on exercise capacity, somatic symptom and cognitive performance in healthy individuals. Moreover, evidence is insufficient that a nutritional dose of vitamin or mineral reduces the incidence of cardiovascular disease and cancer, or mortality rate. A steady intake of oily fish is recommended to prevent the incidence of cardiovascular disease for postmenopausal women. Consumption of omega-3 fatty acids is expected to prevent cardiovascular disease in postmenopausal women with almost no intake of oily fish and those not taking statins. It still remains controversial whether glucosamine is effective in the treatment of osteoarthritis. Hence, physicians should fully inform patients with all controversial information about the effectiveness of glucosamine when prescribing glucosamine for patients with osteoarthritis. (**J Menopausal Med 2015;21:12-18**)

Key Words: Fatty acids omega-3, Functional foods, Glucosamine, Red ginseng, Vitamins

Introduction

The term “health functional food” means food manufactured or processed in a form of tablet, capsule, powder, granule, liquid or pill, etc. with ingredients or components, that possess the functionality useful for human body in accordance with Article 3 of the Korean Health Functional Food Act. About 25 different supplements including chitosan, squalene and others are approved as supplementary health foods, and they have been sold as medicine or food. The term “health food supplements” used until 2002 is now currently converted to “health functional foods.” This term is used interchangeably as dietary supplements in the United States, food for specific health use in Japan, and food supplements in Europe.¹ Even though accurate

statistics have not been available in Korea, the scale of Korea’s health functional food market was estimated to be worth 3.9 trillion won in 2011. Some reports have suggested that sharp rise in demand for health functional foods has been observed as external environmental factors such as avian influenza and severe acute respiratory syndrome (SARS) have increasingly drawn much attention since 2008. Red ginseng is one of the most widely consumed health functional foods, in addition to multivitamin, omega-3, glucosamine and others. The most commonly consumed food is red ginseng, followed by multivitamin, omega-3, glucosamine and aloe in women in the 50’s.² The amounts of thiamin, riboflavin, niacin, and vitamin C, as well as omega-3 and omega-6, consumed are found to show a decreasing trend in Korean postmenopausal women

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Address for Correspondence: Eun Sil Lee, Department of Obstetrics and Gynecology, Soonchunhyang University College of Medicine 59 Daesagwan-ro, Yongsan-gu, Seoul 140-743, Korea
Tel: +82-2-703-9320, Fax: +82-2-709-9332, E-mail: eslee165@schmc.ac.kr

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as they age.³ This study is aimed to review four health functional foods most commonly consumed by women in the 50s.

Red Ginseng

Ginseng is divided into fresh ginseng, white ginseng, and red ginseng depending on the processing method. Fresh ginseng is a term used to refer to ginseng plant that has been cultivated for less than 4 years. While ginseng is usually grown for 4 to 6 years, peeled and then dried to reduce the water content to 12% or less. White ginseng may contain less of the therapeutic constituents. Red ginseng is made from 6-year-old fresh ginseng that is steamed at 100°C and then sun-dried. Through this process, ginseng starch begins to gelatinize, increasing the amount of saponin content. Therefore, red ginseng is more widely used as herbal medicine compared to white ginseng. The pharmacological action of red ginseng is mostly generated by ginsenosides, known as ginseng saponins, and polysaccharides. In addition, polyacetylenes, sesquiterpenes and peptidoglycans are identified to have pharmacological effect.⁴

In traditional medicine, red ginseng is known as an adaptogen that restores and enhances normal well-being. Moreover, red ginseng is believed to improve immune function, physical performance and sexual function, and manage cancer, diabetes (DM) and hypertension. In a study of Hwang et al.⁵ 1 g/kg of red ginseng was given to mice orally daily during two weeks of exercise. Consequently, fat oxidation during the initial exercise period significantly increased in the red ginseng group compared to the non-red ginseng group. Furthermore, the liver glycogen stores significantly decreased immediately after the one-hour exercise but compared to at rest in the red ginseng group, but did not differ between immediately after the one-hour exercise and at rest in the red ginseng group. These findings suggest that the administration of mice with red ginseng during two weeks of exercise boosts fat oxidation and has glycogen-sparing effect, and red ginseng is involved in delaying peripheral fatigue during exercise.⁵

Lee et al.⁶ performed a study on the effect of red ginseng extract (RGE) on influenza infection by administrating

RGE to A549 cells and being infected with H1N1 influenza viruses 24 hours later. When they observed human alveolar epithelial cells infected with H1N1, RGE did not increase the viability of cells prior to infection, but reduced the cytopathogenic effect of H1N1 infection with RGE level and cell death caused by influenza virus infection.

Yin et al.⁷ administered mice with saponin, polysaccharide, total RGE and antiviral medication orally to identify which components of red ginseng have anti influenza effect, and observed survival after injecting the lethal dose of influenza A virus. As a result, they verified that polysaccharides are main components for antiviral effect. Oh et al.⁸ demonstrated that red ginseng supplements has the potential to improve postprandial plasma glucose level and they suggested that red ginseng supplementation may be beneficial for individual with impaired glucose tolerance or type 2 DM.

Some reports have proposed that red ginseng can improve erectile dysfunction in men.^{9,10} With respect to the effect of red ginseng on sexual dysfunction, animal tests have shown that red ginseng has a relaxing effect on rabbit vaginal smooth muscles through NO pathway and hyperpolarization via Ca²⁺ activated K⁺ channels.¹¹ Moreover, red ginseng has found to improve sexual arousal in postmenopausal women.¹²

According to Choi et al.⁴ there is insufficient evidence on the effect of red ginseng on exercise capacity, somatic symptom and cognitive performance in healthy individuals. Evidence is also insufficient that red ginseng can serve as an immune modulator in patients with gastric or colon cancer. Moreover, they addressed that red ginseng has no favorable effect on DM.

Multivitamin

People take multivitamin and mineral supplements with an expectation to reduce the incidence rate of chronic disease or cancer as an insufficient intake of antioxidant vitamins and minerals has been identified to increase the occurrence of cardiovascular disease and cancer. The Linxial trial is the leading study that supports this statement. Multivitamin and mineral supplements were given to nutrition-deficient individuals in Linxial area based on the fact that their incidence rates of esophageal and gastric cardia cancers

were high. This study was performed to examine whether esophageal and gastric cardia cancers were reduced in patients with esophageal dysplasia that appeared to be a precancerous lesion. According to the results, although multivitamin supplementation did not decrease the incidence of esophageal, gastric and other cancers and cerebrovascular disease and mortality rate in overall, mortality rate was reduced in the group administered with selenium, vitamin E and beta carotene in combination compared with other groups administered with other components.¹³ During the 10-year follow-up after stopping multivitamin and mineral supplementation, the effect of combined administration of selenium, vitamin E and beta-carotene persisted in reducing mortality rate, but this effect lasted only in subjects aged below 55 years.¹⁴

In contrast, the intake of antioxidant vitamins and minerals did not lower the incidence of cancer or ischemic heart disease in healthy individuals according to the SU.VI. MAX study developed in France.^{15,16} In the analysis of American healthy male physicians in the Physicians' Health Study, multivitamin intake did not reduce cardiovascular or coronary heart disease mortality.¹⁷

To sum up the above findings of several cohort studies, although the Nurses' Health Study suggested that multivitamin use had a weak favorable effect on colon and breast cancers, there was no impact of multivitamin use on the risk of cardiovascular disease or cancer in overall.¹⁸⁻²⁰

In the 2012 Cochrane review, there was no evidence to support antioxidants supplements for primary or secondary prevention, and beta-carotene, vitamin E and vitamin A seem to increase mortality rate. For these reasons, antioxidants supplements need to be considered as medicinal products rather than supplements. Thus, sufficient evaluation is necessary before marketing.²¹ In 2013, the U.S. Preventive Services Task Force reported that there are no proofs that taking a nutritional dose of vitamins or minerals reduces the risk of cardiovascular disease or cancer and mortality rate in healthy individuals without known nutritional deficiencies.²²

Omega-3

Omega-3 fatty acids have the first double bond three carbons from the methyl terminal, whereas omega-6 fatty acids have their first double bond six carbons from the methyl terminal. Major types of omega-3 fatty acids are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Omega-6 fatty acids include linoleic acid (LA) and arachidonic acid (AA). Mammals require the two essential fatty acid, ALA and LA to yield more bioactive derivatives through elongation and desaturation, and longer chain derivatives, EPA and DHA as well as AA can be obtained through oral intake of diet.²³ LA is elongated and desaturated to form AA which encourages the production of proinflammatory cytokines, setting the stage for inflammation. ALA is elongated to EPA and DHA which are major components of the phospholipid membranes of the brain and retina and have anti-inflammatory effect.²⁴ Omega-3 rich foods are salmon, herring, anchovi, sablefish, whitefish, tuna and others. Common vegetable oils have a higher content of omega-6 than omega-3. Although flaxseed, canola, mustard, walnut, soybean and other vegetable oils are rich in omega-3 fatty acids, vegetable oils abundantly contain ALA and have low levels of EPA or DHA. Since the conversion of ALA contained in vegetable oil to DHA or EPA is very inefficient, there is weaker evidence that ALA intake decreases cardiovascular events compared with DHA or EPA. Thus, it is almost impossible that taking flaxseed oil may influence cardiovascular disease progression.²² The mechanisms by which omega-3 fatty acids may reduce risk for cardiovascular disease are thought to be attributable to lowered serum triglyceride levels and antithrombotic, anti-inflammatory and antihypertensive activities.²⁴

Several clinical studies identified that intake of fish oil reduces serum triglyceride level and blood pressure in both normal individuals and patients with hypertriglyceridemia, and lowers the frequency of arrhythmia and the progression of atherosclerosis. Thus, we have arrived at a conclusion that daily intake of 0.5 to 1.8 g of EPA/DHA decreases mortality rate caused by cardiovascular disease, and the sufficient amount of omega-3 fatty acids can be achieved by eating fatty fish at least twice a week.²⁵

The American Heart Association recommends that adults

eat fish (particularly fatty fish) at least twice a week, and foods rich in ALA such as tofu, soybeans, walnuts, flaxseeds and their oil, and canola oil. Moreover, 1 g of EPA and DHA daily is recommended when coronary artery disease is already present, and 2 to 4 g of EPA and DHA daily is suggested to decrease triglyceride levels by 20% to 40%.²⁶

In the analysis results of the Nurses' Health Study on postmenopausal women, the incidence rate of coronary artery disease was significantly reduced with an increasing intake frequency of fish at once a month, 1 to 3 times a month, once a week, 2 to 4 times a week, and more than 5 times a week. In particular, mortality rate caused by cardiovascular disease was reduced at a greater rate.²⁷ Moreover, the incidence of ischemic stroke was also decreased with increasing fish intake.²⁸

The effect of concurrent use of EPA with lipid-lowering agent has been also proved by the Japan EPA Lipid Intervention Study (JELIS). In the study, more than 18,000 Japanese patients with hypercholesterolaemia were recruited. The incidence rate of cardiovascular disease was reduced by 19% in the group consumed 1.8 g of EPA with statins daily for 5 years compared to that of the group with statins alone.²⁹

According to a recent meta-analysis of 20 randomized clinical trials (RCTs) performed on about 68,000 subjects, omega-3 supplements did not reduce overall mortality rate, and mortality rate caused by cardiovascular disease, and the risk of myocardial infarction or stroke.³⁰ However, several limitations have been pointed out in the results of those studies.³¹

Therefore, consistent consumption of fatty fish is recommended to prevent the risk of cardiovascular disease in postmenopausal women. Taking omega-3 supplement is expected to prevent cardiovascular disease in postmenopausal women almost not eating oily fish and not taking statins.³² The results from literature reviews provide that omega-3 intake, beside cardiovascular disease, has preventive effect on osteoporosis, cognitive dysfunction, cancer and inflammation.³³

Glucosamine

Glucosamine is an endogenous aminomonosaccharide synthesized from glucose, and is a precursor for the synthesis of glycosaminoglycans and glycoproteins. Glucosamine naturally found in all human tissues is particularly found at high concentrations in connective tissues, and at highest concentration in articular cartilage.³⁴ Glucosamine is made in the body from glucose using adenosine triphosphate (ATP) and the amine from glutamine. However, most glucosamine supplements are made from chitosans obtained from crustacean sources prepared using sulfate. After oral administration of glucosamine sulfate, 90% is absorbed and helps to build articular cartilage. Glucosamine exists in a number of different forms including sulfate, hydrochloride, N-acetyl-glucosamine, chlorohydrate salt, and as a dextrorotatory isomer, but it remains controversial which form is most effective. Glucosamine sulfate has showed effective clinical results to date, but many clinical studies have reported ineffectiveness of glucosamine sold in other forms.³⁵ Even though the potential mechanisms of glucosamine are known to be direct stimulation of chondrocytes, incorporation of sulfur into cartilage, and protection against degradative processes, the exact mechanism is unclear.³⁶ In addition, the effect of glucosamine in the treatment of osteoarthritis still remains controversial.

In the 2001 Belgian study, 212 persons with osteoarthritis were treated with 1,500 mg of glucosamine sulfate daily for 3 years, and were evaluated using the WOMAC osteoarthritis index. The study showed that patients taking glucosamine sulfate had modest pain reduction and reduced joint space narrowing compared with placebo.³⁷ In a similar trial conducted in Prague, 202 persons with osteoarthritis were given 1,500 mg of glucosamine sulfate daily for 3 years. Patients receiving glucosamine sulfate showed improvement in symptoms of pain and stiffness and radiographic findings showed reduced joint space narrowing.³⁸ After these two long-term studies presented favorable results, glucosamine has attracted much attention in managing osteoarthritis.

Meanwhile, a meta-analysis of 20 randomized trials performed on 2,570 patients concluded that glucosamine was not effective in improving pain function.³⁵

The GAIT study presented in 2006 is a large scale comparative study that firstly compared the effects of glucosamine, chondroitin, glucosamine+chondroitin, cyclooxygenase inhibitor and placebo.³⁹ A total of 1583 patients were followed for 6 months, and a 20% relative reduction for each primary endpoint of WOMAC score was observed. In conclusion, the use of glucosamine alone or combination of glucosamine and chondroitin for 6 months did not relieve pain in patients with osteoarthritis of the knee, and showed the same outcome of placebo.

A 500 mg of glucosamine three times daily is recommended, and common side effects are epigastric pain (3.5%), heartburn (2.7%), diarrhea (2.5%), nausea (1%) and others.⁴⁰ Although there is a concern that glucosamine may decrease the effects of antidiabetic medications, there is no report that glucosamine can reduce insulin sensitivity or increase insulin resistance. Nevertheless, patients with DM should monitor their blood glucose level more frequently when taking glucosamine supplements. Moreover, glucosamine made from crustacean shells is strictly forbidden in people with shellfish allergy or asthma. Physicians should fully inform patients with osteoarthritis about the effects and controversies of glucosamine when prescribing glucosamine supplements. Glucosamine with potential benefits can be taken into consideration especially when other drugs are not usable. Since most positive results are noticed 30 to 90 days after taking glucosamine sulfate, patients will decide whether they should continue treatment after trying glucosamine sulfate for 60 days.³⁴

In conclusion, although some study results suggest that red ginseng can boost immunity against influenza infection and improve erectile dysfunction, but its beneficial effects are unclear in healthy persons. Moreover, there is insufficient evidence that multivitamin intake prevents the risk of chronic disease or cancer and reduces mortality rate in healthy adults on a balanced diet. Eating fishy oil more than twice a week or taking omega-3 on a regular basis lowers the risk of cardiovascular disease. It still remains controversial glucosamine is effective in osteoarthritis, so it can be taken into account in patients who are unable to take other osteoarthritis medicines after detailed consultation.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Korea Agency of Education, Promotion & Information Service in Food, Agriculture, Forestry & Fisheries. Patent analysis report of health functional foods. Anyang: Korea Agency of Education, Promotion & Information Service in Food, Agriculture, Forestry & Fisheries; 2014.
2. Korea Agro-Fisheries & Food Trade Corporation. 2013 health functional food market report. Naju: Korea Agro-Fisheries & Food Trade Corporation; 2013.
3. Heo J, Park Y, Park HM. Dietary intake of nutrients and food in postmenopausal Korean women. *J Korean Soc Menopause* 2011; 17: 12-20.
4. Choi J, Kim TH, Choi TY, Lee MS. Ginseng for health care: a systematic review of randomized controlled trials in Korean literature. *PLoS One* 2013; 8: e59978.
5. Hwang H, Kim J, Park J, Yun H, Cheon WK, Kim B, et al. Red ginseng treatment for two weeks promotes fat metabolism during exercise in mice. *Nutrients* 2014; 6: 1874-85.
6. Lee JS, Hwang HS, Ko EJ, Lee YN, Kwon YM, Kim MC, et al. Immunomodulatory activity of red ginseng against influenza A virus infection. *Nutrients* 2014; 6: 517-29.
7. Yin SY, Kim HJ, Kim HJ. A comparative study of the effects of whole red ginseng extract and polysaccharide and saponin fractions on influenza A (H1N1) virus infection. *Biol Pharm Bull* 2013; 36: 1002-7.
8. Oh MR, Park SH, Kim SY, Back HI, Kim MG, Jeon JY, et al. Postprandial glucose-lowering effects of fermented red ginseng in subjects with impaired fasting glucose or type 2 diabetes: a randomized, double-blind, placebo-controlled clinical trial. *BMC Complement Altern Med* 2014; 14: 237.
9. de Andrade E, de Mesquita AA, Claro Jde A, de Andrade PM, Ortiz V, Paranhos M, et al. Study of the efficacy of Korean Red Ginseng in the treatment of erectile

- dysfunction. *Asian J Androl* 2007; 9: 241–4.
10. Lee NH, Son CG. Systematic review of randomized controlled trials evaluating the efficacy and safety of ginseng. *J Acupunct Meridian Stud* 2011; 4: 85–97.
 11. Kim SO, Kim MK, Lee HS, Park JK, Park K. The effect of Korean red ginseng extract on the relaxation response in isolated rabbit vaginal tissue and its mechanism. *J Sex Med* 2008; 5: 2079–84.
 12. 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.
 13. Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* 1993; 85: 1483–92.
 14. Qiao YL, Dawsey SM, Kamangar F, Fan JH, Abnet CC, Sun XD, et al. Total and cancer mortality after supplementation with vitamins and minerals: follow-up of the Linxian General Population Nutrition Intervention Trial. *J Natl Cancer Inst* 2009; 101: 507–18.
 15. Herberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, et al. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med* 2004; 164: 2335–42.
 16. Herberg S, Kesse-Guyot E, Druesne-Pecollo N, Touvier M, Favier A, Latino-Martel P, et al. Incidence of cancers, ischemic cardiovascular diseases and mortality during 5-year follow-up after stopping antioxidant vitamins and minerals supplements: a postintervention follow-up in the SU.VI.MAX Study. *Int J Cancer* 2010; 127: 1875–81.
 17. Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C, MacFadyen J, et al. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA* 2008; 300: 2123–33.
 18. Prentice RL. Clinical trials and observational studies to assess the chronic disease benefits and risks of multivitamin-multimineral supplements. *Am J Clin Nutr* 2007; 85: 308S–13S.
 19. Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC. Vitamin E consumption and the risk of coronary disease in women. *N Engl J Med* 1993; 328: 1444–9.
 20. Rimm EB, Willett WC, Hu FB, Sampson L, Colditz GA, Manson JE, et al. Folate and vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women. *JAMA* 1998; 279: 359–64.
 21. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst Rev* 2008: CD007176.
 22. Fortmann SP, Burda BU, Senger CA, Lin JS, Whitlock EP. Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer: An updated systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2013; 159: 824–34.
 23. Deckelbaum RJ, Torrejon C. The omega-3 fatty acid nutritional landscape: health benefits and sources. *J Nutr* 2012; 142: 587S–91S.
 24. Sudheendran S, Chang CC, Deckelbaum RJ. N-3 vs. saturated fatty acids: effects on the arterial wall. *Prostaglandins Leukot Essent Fatty Acids* 2010; 82: 205–9.
 25. Miles JM, Park YS, Walewicz D, Russell-Lopez C, Windsor S, Isley WL, et al. Systemic and forearm triglyceride metabolism: fate of lipoprotein lipase-generated glycerol and free fatty acids. *Diabetes* 2004; 53: 521–7.
 26. Stone NJ. Fish consumption, fish oil, lipids, and coronary heart disease. *Circulation* 1996; 94: 2337–40.
 27. Hu FB, Bronner L, Willett WC, Stampfer MJ, Rexrode KM, Albert CM, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *JAMA* 2002; 287: 1815–21.
 28. Iso H, Rexrode KM, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, et al. Intake of fish and omega-3 fatty acids and risk of stroke in women. *JAMA* 2001; 285: 304–12.
 29. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* 2007; 369: 1090–8.
 30. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA* 2012; 308: 1024–33.
 31. Lewis EJ. Omega-3 fatty acid supplementation and cardiovascular disease events. *JAMA* 2013; 309: 27.
 32. DiNicolantonio JJ, Niaz AK, McCarty MF, O'Keefe JH, Meier P, Lavie CJ. Omega-3s and cardiovascular health. *Ochsner J* 2014; 14: 399–412.
 33. Kim TH, Byun DW, Park Y. Omega-3 and menopause. *J Korean Soc Menopause* 2012; 18: 75–80.
 34. Dahmer S, Schiller RM. Glucosamine. *Am Fam Physician* 2008; 78: 471–6.
 35. Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, et al. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev* 2005: CD002946.

36. D'Ambrosio E, Casa B, Bompani R, Scali G, Scali M. Glucosamine sulphate: a controlled clinical investigation in arthrosis. *Pharmatherapeutica* 1981; 2: 504-8.
37. Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001; 357: 251-6.
38. Pavelká K, Gatterová J, Olejarová M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med* 2002; 162: 2113-23.
39. Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006; 354: 795-808.
40. Tapadinhas MJ, Rivera IC, Bignamini AA. Oral glucosamine sulphate in the management of arthrosis: report on a multi-centre open investigation in Portugal. *Pharmatherapeutica* 1982; 3: 157-68.