LifeExtension®
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COVER STORY

The Disease-Preventive Power of the Mediterranean Diet

By Dale Kiefer

Earlier this year, news headlines extolled the health and anti-aging benefits of the Mediterranean diet, characterized by fish that provide omega-3 fatty acids, relatively copious amounts of olive oil, and antioxidant-rich fruits, vegetables, and herbs.

Epidemiological evidence has long suggested that the Mediterranean diet offers life-extending benefits. Recent studies associate this diet with lowered cardiovascular risk and increased life span.1 This is especially true among Greeks and Spaniards, who adhere most closely to the "classic" Mediterranean diet that is believed to specifically reduce cancer risk and protect cardiovascular health.2-8

The traditional Mediterranean diet is closely associated with the olive-growing regions of the Mediterranean Sea. Monounsaturated fats from olive oil and omega-3 fatty acids from fish are the predominant fats in the Mediterranean diet. Saturated fat, which is far more common in the diets of North Americans, makes up a relatively small portion of the Mediterranean diet.

An EPIC Study

Earlier this spring, scientists involved in Europe's massive EPIC-elderly study released key findings from nearly a decade of research. EPIC (European Prospective Investigation into Cancer and Nutrition) is the largest study to date to provide convincing evidence that diet directly affects life span.

More than 74,000 healthy seniors aged 60 years or older from nine European countries participated in this eight-year study of factors affecting the incidence of cancer and other chronic diseases. Biological, dietary, lifestyle, and environmental factors were examined in relation to overall health. Researchers assessed the impact on health and longevity of omega-3 essential fatty acids such as those found in fatty fish like salmon and mackerel, as well as of monounsaturated fats obtained almost exclusively from olive oil.

The researchers developed a 10-point scale to quantify degree of adherence to the modified diet, and then compared scores with mortality data. Subjects who adhered most closely to the classic Mediterranean diet while consuming the least saturated fat earned the highest scores. Higher scores were clearly associated with longer life span. As the scientists noted, ". . . adherence to a

modified Mediterranean diet . . . was associated with a significantly longer life expectancy in apparently healthy elderly people . . .”9

In essence, the data from this enormously important study show that adherence to a Mediterranean-type diet can extend life. Individuals who improved their scores by just two points on the 10-point scale increased their life expectancy by 7%. As an example, a 60-year-old man who adhered to the diet could expect to live a year longer than another man of the same age who did not follow the diet. According to the researchers, “The reduction in mortality in relation to a dietary score was more striking than expected . . .”9

In a further study, the EPIC scientists found that the longevity-promoting effects of the Mediterranean diet were even more dramatic in adults with coronary heart disease. When individuals with prevalent coronary heart disease at the time of enrollment improved their adherence to the Mediterranean diet by two points on the 10-point scale, they experienced a 27% lower rate of mortality and a 31% lower rate of cardiac death.10

The great question associated with the anti-aging benefits ascribed to the Mediterranean diet is how, exactly, the diet is responsible for the impressive, observed effects on longevity. Five years earlier, researchers had estimated that up to 25% of the incidence of colorectal cancer, about 15% of the incidence of breast cancer, and roughly 10% of the incidence of prostate, pancreatic, and endometrial cancers could be prevented by replacing the typical Western diet—high in saturated fat and low in omega-3 fatty acids, phytonutrients, and antioxidants—with the Mediterranean diet.11

To gain a better understanding of how the Mediterranean diet prolongs life, we need to examine the diet’s fundamental components, which include fatty acid-rich fish, antioxidants, phytonutrients, and olive oil.

Dangers of Polyunsaturated Fats

An enormous amount of scientific data documents the health risks associated with excess consumption of polyunsaturated fatty acids. While the polyunsaturated fats known as omega-6 fatty acids are essential to optimal health, most Americans and citizens of other Western nations consume far too many omega-6 polyunsaturated fatty acids and not enough omega-3 polyunsaturated fatty acids. Although a roughly 2:1 ratio of omega-6 to omega-3 fatty acids is considered optimal, most Americans consume these fats in a lopsided ratio that approaches 10:1.12,13 For optimal health and longevity, it is critical to achieve a dietary balance of these important nutrients. Given that the vast majority of people in Western countries consume excessive amounts of omega-6 fatty acids, attention should be focused on consuming adequate amounts of omega-3 fatty acids.

Omega-3 polyunsaturated fatty acids have been shown to have anti-cancer, anti-inflammatory, and antihypertensive effects, and to reduce the risk of stroke, heart arrhythmias, dementia, and heart attack when consumed in balance with omega-6 fatty acids.14-21

Omega-3 fatty acids influence health and well-being through a variety of mechanisms. These include modulation of cell membranes’ physical and chemical properties, and regulation of the metabolism of immune system components that are involved in inflammation.

Evidence also suggests omega-3 polyunsaturated fatty acids regulate body functions through the modulation of specific genes.17,22

The omega-3 fatty acids EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid) are found in abundance in fatty fish and some marine mammals, as well as in the algae (seaweed) upon which they feed. A third polyunsaturated fatty acid, alpha-linolenic acid, can be converted into DHA and EPA. While alpha-linolenic acid is available from sources such as canola oil, flaxseed oil, and walnuts, its conversion to DHA is slow and inefficient.23,24 Scientists believe that direct consumption of DHA and EPA is the best way to obtain adequate omega-3 polyunsaturated fatty acids.16,25-32

The importance of DHA and EPA cannot be overstated. For example, adequate intake of omega-3 fatty acids during early childhood is thought to play a role in preventing attention deficit hyperactivity disorder (ADHD) and in improving learning and academic performance.30 In older adults, consuming omega-3 fats such as DHA and EPA may reverse signs of brain aging and protect against development of Alzheimer's disease and other causes of age-associated dementia and decline.18,27-29,33-36

Power of Olive Polyphenols

For millennia, olives have provided a staple source of high-energy food and critical nutrients for the many civilizations that have thrived in the Mediterranean area.

Researchers in Barcelona and other southern European cities lead the world in investigating the remarkable health benefits of olives.37-41 While the monounsaturated fats in olive oil are clearly a crucial component of the Mediterranean diet, a lesser known but no less important component is the rich mixture of antioxidant polyphenols in olives.5 Once discarded as a by-product of the olive oil-extraction process, olive polyphenols concentrated in the watery juice of the olive fruit have an impressive array of beneficial properties.37,41-62

For example, laboratory studies of cells grown in culture have shown that the primary olive oil polyphenol—hydroxytyrosol—scavenges the dangerous free radical hydrogen peroxide, which is a by-product of normal cellular respiration.42 As Life Extension members are well aware, the damage caused by free radicals includes DNA damage that can lead to premature aging, cancer, and other degenerative conditions.63-65

In addition to in-vitro experiments, tests with hydroxytyrosol-rich polyphenols in vivo have also yielded impressive results. For example, scientists in the Netherlands fed animals either polyphenol-rich extra-virgin olive oil or extra-virgin olive oil with the polyphenol components removed. Levels of the antioxidant vitamin E were significantly increased in the animals that received the polyphenols, indicating that olive oil polyphenols improved antioxidant defense systems.59 Removal of hydroxytyrosol-rich polyphenols from the diet also rendered LDL (low-density lipoprotein) more susceptible to oxidation. As Life Extension members are aware, LDL oxidation is thought to play an important role in the development of atherosclerosis and cardiovascular disease.
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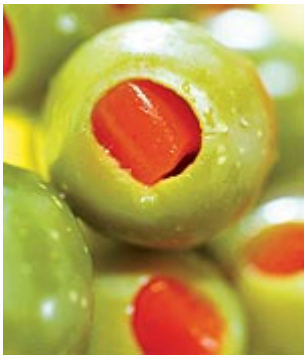
Olive Polyphenols and Cholesterol



Wondering whether hydroxytyrosol's LDL-protective effect could be reproduced in humans, researchers in Spain solicited healthy volunteers to participate in a randomized, double-blind, controlled crossover study. Subjects consumed three different extra-virgin olive oils with incrementally greater levels of polyphenols. At the end of each study period, blood plasma levels of LDL were examined for degree of oxidation. Levels of beneficial HDL (high-density lipoprotein) were also assayed. As the polyphenol content of the olive oil increased, LDL oxidation decreased. Polyphenol-rich olive oil also raised HDL levels. Both effects are associated with an improved cardiovascular risk profile.37 Other researchers have observed similar results demonstrating the ability of olive oil polyphenols to prevent damaging oxidative processes.52-54,58

In a variation of this study, Spanish researchers tested the effects of feeding three olive oils with incrementally greater levels of polyphenols to a group of healthy male volunteers. Subjects in this randomized, double-blind study consumed standardized doses of polyphenol-rich olive oil. After a washout period, subjects were blindly switched to another polyphenol-rich olive oil formulation. The researchers assessed plasma LDL oxidation and the activity of glutathione peroxidase and other markers of antioxidant status. Oxidized LDL decreased, glutathione antioxidant activity increased, and HDL levels increased in the participants. These effects were proportionally greater as olive polyphenol content increased. All of these changes reflect improvements in surrogate markers of cardiovascular health.39

Another study conducted by researchers at the same Barcelona medical research facility showed similar results. Markers of oxidative stress, implicated in the development of cardiovascular disease,41 were assessed after ingestion of a single dose of polyphenol-rich extra-virgin olive oil. LDL's resistance to oxidation improved after consumption of the polyphenol-rich olive oil,40 while glutathione-related enzyme activities also improved.40 Other studies have reported similar results.38

Sesame Lignans: Phytonutrient Power

Like polyphenols from olives, sesame seeds are rich in compounds with powerful antioxidant properties. Sesame seeds contain lignans, a class of chemicals known as phytonutrients that are responsible for a range of health benefits.

For example, lignans have the ability to modulate immunity and may prevent various types of cancer.66-73 When Scandinavian researchers fed the sesame lignan sesamin to laboratory animals, they documented an increase in bioavailable levels of the important antioxidant gamma tocopherol, a potent and biologically active form of vitamin E.74 Japanese researchers have shown that when sesamin is added to the diets of animals bred for their susceptibility to hypertension and stroke, various markers of cardiovascular damage are significantly improved, especially among salt-sensitive hypertensive animals.75

In a similar experiment, scientists fed vitamin E, sesamin, or both to animals prone to hypertension and stroke. A control group received normal feed. As they aged, the control animals developed high blood pressure and elevated levels of an oxidative stress marker, and exhibited an increased tendency to develop clots that could precipitate stroke. By contrast, the animals fed sesamin, vitamin E, or a combination of the two nutrients were significantly

protected from these deadly conditions.76

Reducing Inflammation

More recent work on the mechanisms underlying these effects indicates that sesamin reduces levels of inflammatory prostaglandins and leukotrienes, immune system components that are associated with pathological inflammatory conditions.77 Many scientists now believe that low-grade inflammation is an underlying condition that contributes to a broad range of degenerative diseases such as atherosclerosis, heart disease, arthritis, cancer, Alzheimer's disease, and Parkinson's disease.78-84 Omega-3 fatty acids are also known to reduce inflammation,14,85 and recent research indicates that they may increase levels of anti-inflammatory compounds in the bloodstream.21,86-87

Sesame seed components, including sesamin and sesamolin, may also reduce the effects of reactive oxygen species, a class of highly reactive, damaging free radicals that are generated in response to injuries such as those caused by stroke. In an experiment designed to simulate stroke damage, Chinese scientists deprived nerve cells of oxygen in the laboratory. In cells treated with sesamin and sesamolin, cell death was reduced significantly compared to untreated cells. The scientists concluded that the sesame seed lignans may have suppressed the generation of reactive oxygen species and inhibited the release of mitogen-activated protein kinases,88 a family of immune system proteins responsible for inducing programmed cell death, or apoptosis.89 Recently, Taiwanese researchers reported findings that appear to confirm this ability of sesame lignans to intervene in apoptosis by modulating immune system signaling events.90

Lowering Blood Pressure

Sesame seed lignans may also reduce blood pressure. In an effort to document sesame's antihypertensive effects, Japanese researchers worked with animals bred to serve as a model of human hypertension. One group of animals was fed a normal diet supplemented with sesamin, while the other group received only the normal diet. After five weeks, aortic superoxide, an indicator of cardiovascular stress, was measured in both groups. Sesamin-fed animals had lower superoxide levels and lower blood pressure; conversely, animals fed a normal diet developed hypertension and elevated levels of superoxide. The scientists concluded that sesamin may inhibit production of aortic superoxide, and that sesamin's antioxidant activity may contribute to its ability to reduce blood pressure.91,92

Preventing Lipid Peroxidation

Sesame lignans also reduce the peroxidation of lipids. Lipid peroxidation produces harmful free radicals that can have damaging, disease-promoting effects in the body, and may precede the development of atherosclerosis. Preventing peroxidation may make lipids less likely to adhere to the lining of blood vessels, an important goal of preventive medicine.93 Researchers in Japan determined that, when fed to laboratory animals, the sesame seed lignans sesamin and sesaminol decrease lipid peroxidation and raise levels of alpha tocopherol, aform of vitamin E. Other researchers have confirmed this effect.94-96

Indian scientists found a similar effect when animals were fed sesame oil and sesamin. Despite induced oxidative stress, the animals fed sesame oil and sesamin retained high levels of tocopherols, or vitamin E antioxidants. The researchers suggested that sesame lignans may regenerate oxidized tocopherols, essentially sparing them in the body.96

Controlling Inflammation Synergistically

Synergy refers to effects produced by two or more agents that are greater than the sum of their respective individual effects. As an example, consider the benefits of adding omega-3 fatty acids to standard chemotherapy for cancer treatment. Studies have shown that omega-3 polyunsaturated fatty acids may be cancer preventive, but that they also synergize with some anti-cancer drugs to enhance tumor-killing activity.15

Recently, scientists in Brazil reported a synergistic effect on rheumatoid arthritis of DHA- and EPA-rich fish oil combined with polyphenol-rich olive oil.16 Forty-three middle-aged patients undergoing rheumatoid arthritis treatment were randomly assigned to one of three groups. In addition to standard treatment for their pain, stiffness, and inflammation, patients in group one received a placebo oil. Patients in group two received DHA- and EPA-rich omega-3 fatty acids from fish oil, while patients in group three were given a combination of fish oil and polyphenol-rich olive oil. Disease status was assessed before the beginning of the study and at three and six months. At the study's end, fish oil was found to significantly relieve various indicators of disease progression. Duration of morning stiffness decreased, joint pain intensity was reduced, handgrip strength increased, and fatigue was lessened.

Most impressive, however, were the effects observed in the group that received both fish oil and olive oil. These patients exhibited an "accentuated improvement" when DHA- and EPA-rich fish oil supplements were used in combination with polyphenol-rich olive oil.16 While fish oil improved various parameters of inflammation, only fish oil and olive oil together provided additional improvements in duration of morning stiffness, the ability to turn faucets on and off, and patients' subjective assessments of satisfaction with their daily living activities.
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Summary

The Mediterranean diet has well-substantiated health- and longevity-promoting effects.

Critical components of this diet that may account for the impressive benefits described in scientific studies include potent antioxidants from phytonutrients, the critical omega-3 fatty acids DHA and EPA, and health-enhancing polyphenols derived from olive fruit.

While the remarkable health benefits associated with antioxidant-rich phytonutrients and the omega-3 fatty acids DHA and EPA are well established, emerging research supporting the benefits of olive polyphenols is equally impressive. Particularly striking is the study just described, in which a combination of EPA/DHA and hydroxytyrosol-rich olive polyphenols produced synergistic benefitsin controlling inflammation in rheumatoid arthritis patients.

Hydroxytyrosol, a potent antioxidant, is the major polyphenol present in olive extract. This and other olive polyphenols are most concentrated in water-soluble olive fruit extract, not in the oil itself. Concentrated, standardized extracts of olive fruit enable health-conscious people to consume high concentrations of these

powerful nutrients without ingesting servings of extra-virgin olive oil containing inadvisably large amounts of dietary fat and calories.

Extensive research strongly supports phytonutrients, omega-3 polyunsaturated fatty acids, and olive polyphenols as critical nutrients that likely account for many of the remarkable anti-aging and health benefits of the Mediterranean diet.

References

1. Eposito K, Marfella R, Ciotola M, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA. 2004 Sep 22;292(12):1440-6.

2. Osler M, Heitmann BL, Gerdes LU, Jorgensen LM, Schroll M. Dietary patterns and mortality in Danish men and women: a prospective observational study. Br J Nutr. 2001 Feb;85(2):219-25.

3. Osler M, Schroll M. Diet and mortality in a cohort of elderly people in a north European community. Int J Epidemiol. 1997 Feb;26(1):155-9.

4. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003 Jun 26;348(26):2599-608.

5. Trichopoulou A, Vasilopoulou E. Mediterranean diet and longevity. Br J Nutr. 2000 Dec;84 Suppl 2:S205-9.

6. Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, et al. Diet and overall survival in elderly people. BMJ. 1995 Dec 2;311(7018):1457-60.

7. Knoops KT, de Groot LC, Kromhout D, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. JAMA. 2004 Sep 22;292(12):1433-9.

8. Lasheras C, Fernandez S, Patterson AM. Mediterranean diet and age with respect to overall survival in institutionalized, nonsmoking elderly people. Am J Clin Nutr. 2000 Apr;71(4):987-92.

9. Trichopoulou A, Orfanos P, Norat T, et al. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. BMJ. 2005 Apr 30;330(7498):991.

10. Trichopoulou A, Bania C, Trichopoulos D. Mediterranean diet and survival among patients with coronary heart disease in Greece. Arch Intern Med. 2005 Apr 25;165(8):929-35.

11. Trichopoulou A, Lagiou P, Kuper H, Trichopoulos D. Cancer and Mediterranean dietary traditions. Cancer Epidemiol Biomarkers Prev. 2000 Sep;9(9):869-73.

12. Zamaria N. Alteration of polyunsaturated fatty acid status and metabolism in health and disease. Reprod Nutr Dev. 2004 May-Jun;44(3):273-82.

13. Kris-Etherton PM, Taylor DS, Yu-Poth S, et al. Polyunsaturated fatty acids in the food chain in the United States. Am J Clin Nutr. 2000 Jan;71(1 Suppl):179S-88S.

14. Mori TA, Beilin LJ. Omega-3 fatty acids and inflammation. Curr Atheroscler Rep. 2004 Nov;6(6):461-7.

15. Hardman WE. n-3 fatty acids and cancer therapy. J Nutr. 2004 Dec;134(12 Suppl):3427S-

430S.

16. Berbert AA, Kondo CR, Almendra CL, Matsuo T, Dichi I. Supplementation of fish oil and olive oil in patients with rheumatoid arthritis. Nutrition. 2005 Feb;21(2):131-6.

17. Guesnet P, Alessandri JM, Vancassel S, Zamaria N. Analysis of the 2nd symposium "Anomalies of fatty acids, ageing and degenerating pathologies." Reprod Nutr Dev. 2004 May-Jun;44(3):263-71.

18. Conquer JA, Tierney MC, Zecevic J, Bettger WJ, Fisher RH. Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. Lipids. 2000 Dec;35(12):1305-12.

19. Horrocks LA, Yeo YK. Health benefits of docosahexaenoic acid (DHA) Pharmacol Res. 1999 Sep;40(3):211-25.

20. Hjerkinn EM, Seljeflot I, Ellingsen I, et al. Influence of long-term intervention with dietary counseling, long-chain n-3 fatty acid supplements, or both on circulating markers of endothelial activation in men with long-standing hyperlipidemia. Am J Clin Nutr. 2005 Mar;81(3):583-9.

21. Nettleton JA, Katz R. n-3 long-chain polyunsaturated fatty acids in type 2 diabetes: a review. J Am Diet Assoc. 2005 Mar;105(3):428-40.

22. Jayasooriya AP, Weisinger RS, Weisinger HS, et al. Influence of dietary omega-3 polyunsaturated fatty acid (PUFA) supply on brain gene expression. Asia Pac J Clin Nutr. 2004;13(Suppl):S77.

23. Goyens PL, Spilker ME, Zock PL, Katan MB, Mensink RP. Development of a compartmental model to quantify alpha-linolenic acid conversion after longer-term intake of multiple tracer boluses. J Lipid Res. 2005 Apr 16.

24. Gerster H. Can adults adequately convert alpha-linolenic acid (18:3n-3) to eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3)? Int J Vitam Nutr Res. 1998;68(3):159-73.

25. Ismail HM. The role of omega-3 fatty acids in cardiac protection: an overview. Front Biosci. 2005 May 1;10:1079-88.

26. Carrero JJ, Martin-Bautista E, Baro L,

et al. Cardiovascular effects of omega-3-fatty acids and alternatives to increase their intake. Nutr Hosp. 2005 Jan-Feb;20(1):63-9.

27. Bourre JM. Omega-3 fatty acids in psychiatry. Med Sci (Paris). 2005 Feb;21(2):216-21.

28. Bourre JM. Dietary omega-3 fatty acids and psychiatry: mood, behaviour, stress, depression, dementia and aging. J Nutr Health Aging. 2005;9(1):31-8.

29. Bourre JM. The role of nutritional factors on the structure and function of the brain: an update on dietary requirements. Rev Neurol (Paris). 2004 Sep;160(8-9):767-92.

30. Singh M. Essential fatty acids, DHA and human brain. Indian J Pediatr. 2005 Mar;72(3):239-42.

31. Oh R. Practical applications of fish oil (omega-3 fatty acids) in primary care. J Am Board

Fam Pract. 2005 Jan-Feb;18(1):28-36.

32. Seo T, Blaner WS, Deckelbaum RJ. Omega-3 fatty acids: molecular approaches to optimal biological outcomes. Curr Opin Lipidol. 2005 Feb;16(1):11-8.

33. Youdim KA, Martin A, Joseph JA. Essential fatty acids and the brain: possible health implications. Int J Dev Neurosci. 2000 Jul-Aug;18(4-5):383-99.

34. Favreliere S, Perault MC, Huguet F, et al. DHA-enriched phospholipid diets modulate age-related alterations in rat hippocampus. Neurobiol Aging. 2003 Mar-Apr;24(2):233-43.

35. Yehuda S, Rabinovitz S, Carasso RL, Mostofsky DI. The role of polyunsaturated fatty acids in restoring the aging neuronal membrane. Neurobiol Aging. 2002 Sep-Oct;23(5):843-53.

36. Martin DS, Lonergan PE, Boland B, et al. Apoptotic changes in the aged brain are triggered by interleukin-1beta-induced activation of p38 and reversed by treatment with eicosapentaenoic acid. J Biol Chem. 2002 Sep 13;277(37):34239-46.

37. Marrugat J, Covas MI, Fito M, et al. Effects of differing phenolic content in dietary olive oils on lipids and LDL oxidation—a randomized controlled trial. Eur J Nutr. 2004 Jun;43(3):140-7.

38. Gimeno E, Fito M, Lamuela-Raventos RM, et al. Effect of ingestion of virgin olive oil on human low-density lipoprotein composition. Eur J Clin Nutr. 2002 Feb;56(2):114-20.

39. Weinbrenner T, Fito M, de la Torre R, et al. Olive oils high in phenolic compounds modulate oxidative/antioxidative status in men. J Nutr. 2004 Sep;134(9):2314-21.

40. Fito M, Gimeno E, Covas MI, et al. Postprandial and short-term effects of dietary virgin olive oil on oxidant/antioxidant status. Lipids. 2002 Mar;37(3):245-51.

41. Covas MI, Fito M, Lamuela-Raventos RM, Sebastia N, de la Torre-Boronat C, Marrugat J. Virgin olive oil phenolic compounds: binding to human low density lipoprotein (LDL) and effect on LDL oxidation. Int J Clin Pharmacol Res. 2000;20(3-4):49-54.

42. O'Dowd Y, Driss F, Dang PM, et al. Antioxidant effect of hydroxytyrosol, a polyphenol from olive oil: scavenging of hydrogen peroxide but not superoxide anion produced by human neutrophils. Biochem Pharmacol. 2004 Nov 15;68(10):2003-8.

43. Visioli F, Bogani P, Grande S, Galli C. Mediterranean food and health: building human evidence. J Physiol Pharmacol. 2005 Mar;56 Suppl 1:37-49.

44. Vissers MN, Zock PL, Leenen R, Roodenburg AJ, van Putte KP, Katan MB. Effect of consumption of phenols from olives and extra virgin olive oil on LDL oxidizability in healthy humans. Free Radic Res. 2001 Nov;35(5):619-29.

45. Visioli F, Bellomo G, Galli C. Free radical-scavenging properties of olive oil polyphenols. Biochem Biophys Res Commun. 1998 Jun 9;247(1):60-4.

46. Visioli F, Galli C. Oleuropein protects low density lipoprotein from oxidation. Life Sci. 1994;55(24):1965-71.

47. Masella R, Vari R, D'Archivio M, et al. Extra virgin olive oil biophenols inhibit cell-mediated oxidation of LDL by increasing the mRNA transcription of glutathione-related

enzymes. J Nutr. 2004 Apr;134(4):785-91.

48. Kris-Etherton PM, Hecker KD, Bonanome A, et al. Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer. Am J Med. 2002 Dec 30;113 Suppl 9B:71S-88S.

49. Simopoulos AP. The Mediterranean diets: what is so special about the diet of Greece? The scientific evidence. J Nutr. 2001 Nov;131(11 Suppl):3065S-73S.

50. Romero C, Brenes M, Garcia P, Garrido A. Hydroxytyrosol 4-beta-D-glucoside, an important phenolic compound in olive fruits and derived products. J Agric Food Chem. 2002 Jun 19;50(13):3835-9.

51. Romero C, Brenes M, Garcia P, Garcia A, Garrido A. Polyphenol changes during fermentation of naturally black olives. J Agric Food Chem. 2004 Apr 7;52(7):1973-9.

52. Aviram M. Interaction of oxidized low density lipoprotein with macrophages in atherosclerosis, and the antiatherogenicity of antioxidants. Eur J Clin Chem Clin Biochem. 1996 Aug;34(8):599-608.

53. Mateos R, Dominguez MM, Espartero JL, Cert A. Antioxidant effect of phenolic compounds, alpha-tocopherol, and other minor components in virgin olive oil. J Agric Food Chem. 2003 Nov 19;51(24):7170-5.

54. Masella R, Giovannini C, Vari R, et al. Effects of dietary virgin olive oil phenols on low density lipoprotein oxidation in hyperlipidemic patients. Lipids. 2001 Nov;36(11):1195-202.

55. Vissers MN, Zock PL, Katan MB. Bioavailability and antioxidant effects of olive oil phenols in humans: a review. Eur J Clin Nutr. 2004 Jun;58(6):955-65.

56. Lavelli V. Comparison of the antioxidant activities of extra virgin olive oils. J Agric Food Chem. 2002 Dec 18;50(26):7704-8.

57. de la Puerta R, Martinez-Dominguez E, Ruiz-Gutierrez V. Effect of minor components of virgin olive oil on topical antiinflammatory assays. Z Naturforsch [C]. 2000 Sep-Oct;55(9-10):814-9.

58. de la Puerta R, Martinez Dominguez ME, Ruiz-Gutierrez V, Flavill JA, Hoult JR. Effects of virgin olive oil phenolics on scavenging of reactive nitrogen species and upon nitrergic neurotransmission. Life Sci. 2001 Jul 27;69(10):1213-22.

59. Wiseman SA, Tijburg LB, van de Put FH. Olive oil phenolics protect LDL and spare vitamin E in the hamster. Lipids. 2002 Nov;37(11):1053-7.

60. Owen RW, Giacosa A, Hull WE, Haubner R, Spiegelhalder B, Bartsch H. The antioxidant/anticancer potential of phenolic compounds isolated from olive oil. Eur J Cancer. 2000 Jun;36(10):1235-47.

61. Tuck KL, Freeman MP, Hayball PJ, Stretch GL, Stupans I. The in vivo fate of hydroxytyrosol and tyrosol, antioxidant phenolic constituents of olive oil, after intravenous and oral dosing of labeled compounds to rats. J Nutr. 2001 Jul;131(7):1993-6.

62. Miles EA, Zoubouli P, Calder PC. Differential anti-inflammatory effects of phenolic compounds from extra virgin olive oil identified in human whole blood cultures. Nutrition. 2005

Mar;21(3):389-94.

63 Balaban RS, Nemoto S, Finkel T. Mitochondria, oxidants, and aging. Cell. 2005 Feb 25;120(4):483-95.

64. Inoue M, Sato EF, Nishikawa M, Hiramoto K, Kashiwagi A, Utsumi K. Free radical theory of apoptosis and metamorphosis. Redox Rep. 2004;9(5):237-47.

65. Harman D. The free radical theory of aging. Antioxid Redox Signal. 2003 Oct;5(5):557-61.

66. Donaldson MS. Nutrition and cancer: A review of the evidence for an anti-cancer diet. Nutr J. 2004 Oct 20;3(1):19.

67. Lucas EA, Lightfoot SA, Hammond LJ, et al. Flaxseed reduces plasma cholesterol and atherosclerotic lesion formation in ovariectomized Golden Syrian hamsters. Atherosclerosis. 2004 Apr;173(2):223-9.

68. Jenkins DJ, Kendall CW, Vidgen E, et al. Health aspects of partially defatted flaxseed, including effects on serum lipids, oxidative measures, and ex vivo androgen and progestin activity: a controlled crossover trial. Am J Clin Nutr. 1999 Mar;69(3):395-402.

69. Prasad K. Flaxseed: a source of hypocholesterolemic and antiatherogenic agents. Drug News Perspect. 2000 Mar;13(2):99-104.

70. Prasad K, Mantha SV, Muir AD, Westcott ND. Reduction of hypercholesterolemic atherosclerosis by CDC-flaxseed with very low alpha-linolenic acid. Atherosclerosis. 1998 Feb;136(2):367-75.

71. Dabrosin C, Chen J, Wang L, Thompson LU. Flaxseed inhibits metastasis and decreases extracellular vascular endothelial growth factor in human breast cancer xenografts. Cancer Lett. 2002 Nov 8;185(1):31-7.

72. Platt R. Current concepts in optimum nutrition for cardiovascular disease. Prev Cardiol. 2000 Spring;3(2):83-7.

73. Bierenbaum ML, Reichstein R, Watkins TR. Reducing atherogenic risk in hyperlipemic humans with flax seed supplementation: a preliminary report. J Am Coll Nutr. 1993 Oct;12(5):501-4.

74. Kamal-Eldin A, Pettersson D, Appelqvist LA. Sesamin (a compound from sesame oil) increases tocopherol levels in rats fed ad libitum. Lipids. 1995 Jun;30(6):499-505.

75. Matsumura Y, Kita S, Tanida Y, et al. Antihypertensive effect of sesamin. III. Protection against development and maintenance of hypertension in stroke-prone spontaneously hypertensive rats. Biol Pharm Bull. 1998 May;21(5):469-73.

76. Noguchi T, Ikeda K, Sasaki Y, et al. Effects of vitamin E and sesamin on hypertension and cerebral thrombogenesis in stroke-prone spontaneously hypertensive rats. Hypertens Res. 2001 Nov;24(6):735-42.

77. Utsunomiya T, Shimada M, Rikimaru T, et al. Antioxidant and anti-inflammatory effects of a diet supplemented with sesamin on hepatic ischemia-reperfusion injury in rats. Hepatogastroenterology. 2003 Sep-Oct;50(53):1609-13.

78. McGeer PL, McGeer EG. Inflammation and the degenerative diseases of aging. Ann N Y Acad Sci. 2004 Dec;1035:104-16.

79. Larbi A, Dupuis G, Douziech N, Khalil A, Fulop T Jr. Low-grade inflammation with aging has consequences for T-lymphocyte signaling. Ann N Y Acad Sci. 2004 Dec;1030:125-33.

80. Napoli C, Palinski W. Neurodegenerative diseases: insights into pathogenic mechanisms from atherosclerosis. Neurobiol Aging. 2005 Mar;26(3):293-302.

81. Finch CE. Developmental origins of aging in brain and blood vessels: an overview. Neurobiol Aging. 2005 Mar;26(3):281-91.

82. Schwartsburd PM. Age-promoted creation of a pro-cancer microenvironment by inflammation: pathogenesis of dyscoordinated feedback control. Mech Ageing Dev. 2004 Sep;125(9):581-90.

83. Weinreb O, Mandel S, Amit T, Youdim MB. Neurological mechanisms of green tea polyphenols in Alzheimer's and Parkinson's diseases. J Nutr Biochem. 2004 Sep;15(9):506-16.

84. Nagatsu T, Sawada M. Inflammatory process in Parkinson's disease: role for cytokines. Curr Pharm Des. 2005;11(8):999-1016.

85. Roland I, De Leval X, Evrard B