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Dietary Supplements Attacked by the Media

By William Faloon

The media has launched an assault against healthy lifestyles and some popular dietary supplements. The public has been thrust into a state of confusion by these frenzied media reports that contradict long-established scientific principles.

I am impressed by how quickly Life Extension *members* picked up on the errors contained in the studies used to ridicule those who practice healthy living.

The outrage over these biased reports was not limited to Life Extension members. The front page of the *Wall Street Journal* carried a scathing report about how the *Federal Government* issued misleading press releases that gave the media the green light to discredit alternative approaches to disease treatment. According to the *Wall Street Journal*:

> ***"Design problems in all the trials means the results don't really answer the questions they were supposed to address. And a flawed communications effort led to widespread misinterpretation of the results by the news media and the public."*** [1]

What you are about to read might at first seem unbelievable. Please remember, however, that the studies we describe were conducted by mainstream doctors who know virtually nothing about natural ways to prevent and treat disease.

As you will also find out, many of the doctors who designed and authored these flawed studies received financial compensation from the very pharmaceutical companies that stood to gain the most by deriding low-cost natural approaches to disease prevention.

Media says: Eat all the fat you want

Does eating a low-fat diet reduce the risk of contracting common diseases? The media answered this question by boldly proclaiming that there is no benefit to women eating a low fat diet. According a lead article in the *Washington Post*:

> ***"Low-fat diets do not protect women against heart attacks, strokes, breast cancer or colon cancer."*** [2]

The study that this headline story was based on, however, failed to differentiate between health-promoting fats (such as monounsaturated and omega-3 fats) and lethal *trans* fats.[3-5] It was long ago established that over-consumption of *trans* fats is related to atherosclerosis, cancer, and chronic inflammation.[6-12] Furthermore, there was no attempt to measure the balance of omega-3 and omega-6 fatty acids.

Most Western diets contain an abundance of omega-6 fatty acids (e.g., corn, safflower oils) and completely inadequate levels of omega-3 fatty acids (such as fish oil, flaxseed, and walnut oils).

The "excuse" some researchers gave when confronted with these flaws was that when the low-fat studies were designed, doctors did not know the difference between friendly and deadly fats. The facts are that when these studies were designed, there was an abundance of published scientific data to show that friendly fats like olive oil[13-35], flax oil[36-43], and fish oil[44-57] conferred life-saving benefits while *trans* fats were proven killers.

Researchers also were unable to rigorously monitor whether or not the participants actually followed low-fat diets. Food-intake questionnaires were used, which are notoriously unreliable indicators of what is really eaten.

In what is perhaps the most outrageous defect in these studies, only 1 in 7 women actually achieved the low-fat diet threshold! Specifically, only 14.4% of the "low-fat" group really followed a low-fat diet. Furthermore, the average reduction in total fat intake in the "low-fat group" was only 8.2% (with just a 2.9% decrease in saturated fat intake). Assuming that this paltry 8.2% figure is accurate (i.e., that the food questionnaires were completely accurate), this number does not come close to the percentage of fat-calorie reduction other studies have shown is needed to reduce disease risk.

These flaws rendered this multimillion-dollar low-fat diet study worthless. This did not stop major newspapers, however, from featuring articles on their front pages stating that reduced-fat diets provide no health benefits.

Media says calcium does not protect bones

One of the most controversial media stories dealt with a study that supposedly showed that women who took calcium and vitamin D supplements did not obtain any protection against hip fracture.[58]

We at Life Extension initially thought this negative finding was because the active group was not given magnesium, zinc, manganese, and other nutrients that are essential to maintaining optimal bone density.

When we got our hands on the study itself, we were startled to find that the women in the study who actually *took* their calcium and vitamin D supplements suffered **29%** *fewer* hip fractures.[58] This was contrary to what the headlines said. It turned out that the media believed the government's negative press release and obviously did not read the actual scientific study.

Many study subjects failed to take their calcium-vitamin D supplements

In this study to evaluate the efficacy of calcium and vitamin D compared to placebo, it was startling to learn that many women in the active arm *did not* take their calcium-vitamin D supplements! According to the study report, about 40% of the women assigned to take calcium and vitamin D did not achieve a standard rate of compliance with their supplements!

When the entire study was tallied, the women in each group (active and placebo) officially remained in their respective group, whether or not they actually followed the study protocol. This meant that women in the active group (the one given the calcium-vitamin D supplements) were counted as having taken the calcium-vitamin D, whether they really took the supplement or not. According to the scientists who conducted this study:

> ***"Participants were followed for major outcomes, regardless of their adherence to the study medication…"***[58]

The "study medication" mentioned above is the *calcium-vitamin D* supplement. The fact that a study could be published in a medical journal "regardless" of whether the participants actually took the active ingredient defies logic. The application of common sense would invalidate the findings of this study, regardless of what statisticians might argue.

Placebo group allowed to take calcium and vitamin D

Further confounding the study results were previously unheard-of rules that allowed the placebo group to take multi-vitamin, calcium, and vitamin D supplements on their own if they wanted. It turned out that many in the placebo group were taking calcium and vitamin D. According to the study design, since they were part of the placebo arm, they were officially not taking calcium-vitamin D supplements, even though many of them were indeed taking calcium-vitamin D.

The fact that the placebo group was freely allowed to take multivitamins, calcium and vitamin D meant that many of the placebo participants may have consumed more bone-protecting nutrients (including boron, magnesium, zinc, and manganese) than the active group (who were supposed to be taking only calcium and vitamin D). By failing to separate who was really taking bone-protecting supplements, it was impossible draw a scientific conclusion, yet the media boldly asserted that there was no difference in the hip fracture rate in the group assigned the calcium-vitamin D supplements (many of whom were *not* taking their supplements) as compared to the placebo group (many who *were* consuming calcium, vitamin D, and other bone-protecting supplements).

Bone building hormones and drugs also permitted

Not only was the placebo group allowed to take their own calcium, vitamin D, and other bone-maintenance supplements, but both groups were also allowed to take drugs (bisphosphonates and calcitonin) and hormone therapies that are known to prevent bone loss and restore bone density. In this study that the Federal government spent over $10 million funding, virtually anything was allowed.

Media grossly misleads public

While the study itself was badly flawed, the media distortion of the findings is nothing short of abominable. Front-page news stories declared calcium-vitamin D supplements had been proven worthless, yet the actual study stated:

> ***"Women receiving calcium with vitamin D supplements had greater preservation of total-hip bone mineral density…"***[58]
>
> ***"Among women who were adherent (i.e., those who took at least 80 percent of the study medication), calcium with vitamin D supplementation resulted in a 29 percent reduction in hip fracture…"***[58]
>
> ***"The effect of calcium with vitamin D might require higher doses of vitamin D than were used…"***[58]
>
> ***"It is also plausible that there was a benefit only among the women who adhered to the study treatment."***[58]

As you will read in the June 2006 issue of ***Life Extension*** magazine, there are even more serious flaws in this calcium-vitamin D study than what I just described, but it is safe to state that this may have been one of the most poorly designed studies in the history of modern medicine. This did not stop the media from turning it into one of the main headline news stories of the day.

Millions of American women will discard their calcium and vitamin D supplements based on these false and misleading headlines. This is great news for pharmaceutical companies that sell expensive drugs to treat osteoporosis.

Biased attack on glucosamine

The next victim of the media's witch hunt was glucosamine, which was one of several agents tested as a treatment for osteoarthritis of the knee.

The media's deceptive stories were based on a study of people with mild to severe knee pain who were given a form of glucosamine *not* normally found in dietary supplements. Some participants received this form of glucosamine by itself, while others were given chondroitin sulfate by itself, a combination of glucosamine and chondroitin, or the drug Celebrex®.

The results of this study were encouraging, but the media distorted the findings in a way that made it appear that glucosamine-chondroitin supplements were of little value. A number of media outlets proclaimed that arthritis sufferers were wasting their money by taking glucosamine. While this made compelling headlines, it did not accurately convey what was written in the actual study.

The findings from the actual scientific study made it clear that glucosamine and chondroitin taken together were effective in those with **moderate to severe** arthritis of the knees. [59]

Media may not have read glucosamine study

The media appears to have relied on a biased editorial that accompanied the actual scientific report on glucosamine. For instance, the *New York Times* said the following about this arthritis study:

> ***"No effect was found for glucosamine, chondroitin, or the combination of both."*** [60]

Yet on page 804 of the study (which was published in *New England Journal of Medicine*), the following was stated about patients with moderate to severe arthritis of the knee who took glucosamine-chondroitin therapy:

> ***"…combined treatment was significantly more effective than placebo"*** [59]

The actual study went on to say that in those with moderate to severe arthritis, the combination of glucosamine-chondroitin resulted in a **24.9% to 26.4% improvement** in pain relief. This result exceeded the 20% response to treatment measurement that the scientists themselves stated would prove efficacy.[59]

As far as reversing the structural damage inflicted to the knee by osteoarthritis, the scientists stated:

> ***"Treatment with chondroitin sulfate was associated with a significant decrease in the incidence of joint swelling, effusion, or both."*** [59]

In their concluding remarks, the scientists stated:

> ***"Our finding that the combination of glucosamine and chondroitin sulfate may have some efficacy in patients with moderate-to-severe pain is interesting, but must be confirmed by another trial."*** [59]

As anyone who understands the English language can read, even this different form of glucosamine, when combined with chondroitin sulfate, demonstrated efficacy in patients most in need, i.e., those with moderate-to-severe pain! The media overlooked these clearly written findings in their haste to viciously attack glucosamine and chondroitin dietary supplements.

Better than Celebrex®

One of the arms in this arthritis study was given 200 mg a day of Celebrex®, an FDA-approved arthritis drug.

In patients with moderate to severe knee pain, however, the *only* treatment that showed *significant* benefit was glucosamine-chondroitin.

The media, however, chose to tout the mediocre benefits that Celebrex® showed in this study. For instance, in a widely distributed *Associated Press* story, the following was stated about Celebrex®:

> ***"The drug Celebrex did reduce pain — 70 percent reported improvement — affirming the study's validity."*** [61]

The inclusion of Celebrex, in fact, did not affirm the study's validity considering that 60 percent of the placebo group also reported improvement. The authors of this study stated that compared to placebo, Celebrex® was ***"not significantly better."*** [59]

In the concluding remarks, these scientists stated:

> ***"However, even the effects of celecoxib (Celebrex®) were smaller than those seen in other studies."*** [59]

The media exaggerated the benefits of Celebrex while vilifying glucosamine-chondroitin, carrying on a long tradition of bias against dietary supplements.

The arthritis study's disappointing findings

The data that caused these negative media stories involved study subjects with *mild* knee pain. The scientists noted that in these patients, "***differences between placebo and the various agents were relatively small.***" [59]

Conflicts of Interest

The *New England Journal of Medicine* recently enacted a policy of mandating disclosure of potential financial conflicts of interest amongst the authors of the studies it publishes. The reason for this was past instances of questionable articles supporting the safety-efficacy of drugs authored by doctors who were financially beholden to pharmaceutical companies that made the drugs.

What follows are the potential conflicts of the authors of the negative glucosamine study as reported by the *New England Journal of Medicine*:

"Drs. Bingham, Brandt, Clegg, Hooper, and Schnitzer report having received consulting fees or having served on advisory boards for **McNeil Consumer and Specialty Pharmaceuticals**. Drs. Brandt, Moskowitz, Schnitzer, and Schumacher report having received consulting fees or having served on advisory boards for **Pfizer**. Dr. Brandt reports having equity interests in **Pfizer**. Drs. Moskowitz and Weisman report having received lecture fees from **Pfizer**; Dr. Brandt, lecture fees from McNeil Consumer and Specialty Pharmaceuticals; Drs. Bingham, Clegg, Hooper, Jackson, Molitor, Sawitzke, and Schnitzer, grant support from **Pfizer**; and Dr. Bingham, grant support from **McNeil Consumer and Specialty Pharmaceuticals**. Dr. Brandt reports having received royalties from books related to osteoarthritis. Dr. Moskowitz reports having served as an expert consultant for **Pfizer**." – pp. 807 "Dr. Hochberg reports having received consulting fees from **Pfizer** and **Merck** and speaker's fees from **Merck** and Institut Biochimique."[59]

Arthritis drugs are (or have been) huge money makers for the pharmaceutical companies. These same companies have paid monies to doctors who designed, oversaw, and authored the *New England Journal of Medicine* study and the negative editorial about glucosamine. Readers can make their own determination if this represents frank bias or, at a minimum, a disingenuous approach to scientific research.

As compared to placebo, here were the pain score percentage point improvements for overall groups within this study: [59]

Therapy	Improvement in Primary Pain Score	Improvement in Secondary Pain Score
Glucosamine HCL only (note this is not glucosamine sulfate)	3.9%	3.7%
Chondroitin sulfate only	5.3%	6.6%
Glucosamine HCL plus chondroitin sulfate	6.5%	8.7%
Celebrex®	10%	10.4%

The scientists who conducted this study appropriately noted that only three of the above changes were significant overall. Furthermore, for the primary outcome in the combined glucosamine + chondroitin group, the results were very close to reaching statistical significance. For the secondary outcome, it did reach significance!

The media misinterpreted these findings and used them as ammunition to attack the efficacy of glucosamine and chondroitin supplements.

The encouraging findings from the arthritis trial

As noted earlier, significant benefits were seen in patients with *moderate to severe* arthritis of the knee in the *glucosamine-chondroitin* group. Compared to placebo, the pain score percentage point improvements in the moderate to severe arthritis group were as follows: [59]

Therapy	Improvement in Primary Pain Score	Improvement in Secondary Pain Score
Glucosamine HCL only (note this is not glucosamine sulfate)	11.9%	17.1%
Chondroitin sulfate only	7.1%	10%
Celebrex®	15.1%	18.1%
Glucosamine HCL plus chondroitin sulfate	24.9%	26.4%

In patients with moderate to severe knee pain, Celebrex® provided modest relief, whereas *glucosamine-chondroitin* showed *significant* reductions in pain scores. It is interesting that Celebrex® was not criticized by the media, even though it failed to produce the expected results in this sub-group of patients suffering with moderate to severe pain.

Wrong form of glucosamine used

A troubling flaw in this study is that the wrong form of glucosamine was given to the study subjects. Glucosamine sulfate is the most prevalent form of glucosamine used in dietary supplements. Most of the studies showing significant efficacy used glucosamine sulfate, but the form used in the *New England Journal of Medicine* study was glucosamine hydrochloride.

Since the study subjects received glucosamine hydrochloride, they were not obtaining the joint-protecting benefits conferred by the sulfur found in the "sulfate" part of the glucosamine compound. The anti-arthritis benefits of sulfur are so well documented that many arthritis patients find relief with a low-cost supplement called MSM (methylsulfonylmethane), which is a concentrated source of sulfur. [62-72] The anti-arthritic properties of SAMe (s-adenosyl-methionine) are also thought to be related to its high sulfur content. [73-79]

In this *New England Journal of Medicine* study that made headline news around the world, the subjects taking glucosamine only were getting no supplemental sulfur. Even the group getting the glucosamine and chondroitin was only getting a small amount of sulfur (from the chondroitin sulfate only).

Why the media attacked glucosamine

In an editorial appearing in the same issue of the *New England Journal of Medicine*, glucosamine was harshly criticized. It was obviously a lot easier for the media to echo one doctor's condemnation than to take the time to read the actual study itself.

This one doctor, by the way, receives consulting fees from Pfizer and Merck. In fact, a number of the authors of the glucosamine study published in the *New England Journal of Medicine* receive compensation from big pharma, mostly from Pfizer, which is the maker of Celebrex®. None of the study's authors had an economic interest in glucosamine or chondroitin. Some in alternative medicine have said this is equivalent to having an opposing team's referees dictate the outcome of a sporting event.

What most people don't realize, however, is that it is not the obligation of the media to provide *accurate* reporting. The media is responsible for generating profits for its shareholders, which means they have to grab the public's attention with sensational headlines that sell newspapers, TV viewing time, etc.

Reporting on the positive parts of the *New England Journal of Medicine* study would not have motivated many people to buy a newspaper. After all, there are dozens of studies substantiating the anti-arthritic properties of glucosamine sulfate and chondroitin sulfate. [59, 80-110] One more new study is hardly a newsworthy event.

There are now millions of Americans using glucosamine-based dietary supplements. These are the seventh most popular dietary supplement sold in the United States. There are over 20 million Americans affected by osteoarthritis.[111] So when the largest newspaper in the United States ran the headline, "**Two Arthritis Drugs Found To Be Ineffective,**" they knew it would catch a lot of attention. The fact that glucosamine and chondroitin were labeled as "drugs" is an indication of how little time this newspaper spent evaluating the actual study.

How effective is glucosamine-chondroitin?

In previous issues of ***Life Extension*** magazine, we have discussed the studies indicating a significant benefit to arthritic patients who take glucosamine sulfate and chondroitin sulfate.[112-113] It is because of these successful earlier studies that this latest study published in the *New England Journal of Medicine* was conducted.

While glucosamine-chondroitin have documented efficacy, many arthritis sufferers need to take a broader approach to relieving inflammation, immobility, and chronic pain. Fish oil, for instance, has been shown to help reduce pro-inflammatory *eicosanoids* such as *prostaglandin E2* and *leukotriene B4,* along with pro-inflammatory *cytokines* such as *TNF-alpha* and *IL-1b*.[114-116] These inflammatory factors play a major role in degenerative joint disease. Over the past 10 years, we have published findings showing benefits when combinations of fish oil, borage oil, glucosamine, and other nutrients are taken together.[117]

Sulfur for the Joints

One of the flaws in the *New England Journal of Medicine* study may have been that the form of glucosamine used did not provide any sulfur.

Animal studies have shown that joints affected by osteoarthritis have lower sulfur content,[118] and that arthritic mice given a sulfur-containing nutrient (MSM) experience less joint degeneration.[119] In a double-blind trial in people with osteoarthritis, study participants who received MSM by itself experienced significant pain relief.[120]

In a study published in 2004, the combination of glucosamine with MSM was found to more effective in improving the signs and symptoms of osteoarthritis than either agent alone.[62] After 12 weeks of treatment, the average pain score in the glucosamine-only group dropped from 1.74 to 0.65…a **63%** reduction. In the MSM-only group, it fell from 1.53 to 0.74...a **52%** reduction. However, in the group taking glucosamine and MSM, the average pain score dropped from 1.7 to 0.36…an astounding reduction of **79%**! The researchers also found that the combination therapy had a faster effect on pain and inflammation than either glucosamine or MSM alone.

It is important to point out, however, that some studies have used glucosamine HCL to effectively relieve arthritis pain.

Media tries to bury saw palmetto

More than 20 published studies show that saw palmetto alleviates symptoms associated with *benign* prostate disease such as frequent urination, low urine stream, and a feeling of not completely emptying the bladder.[121-141]

A recent study however, found saw palmetto to be ineffective in men with *moderate-to-severe* benign prostate hypertrophy. As a result of this one study, the media declared saw palmetto useless.

The doctors who conducted this negative saw palmetto study received financial compensation from **Merck** (which makes Proscar®), **GlaxoSmithKline** (which makes Avodart®), and **TAP Pharmaceuticals** (which makes Lupron®). *Proscar* and *Avodart* are drugs that directly compete against saw palmetto, whereas *Lupron* is used mostly by men who develop prostate cancer.

Some in the alternative medical community have cried "foul," in as much as the doctors overseeing this negative saw palmetto study received *financial compensation* from the same pharmaceutical companies that stood to gain the most from discrediting non-prescription herbal therapies such as saw palmetto.

Flaws in saw palmetto study

One of the defects of the negative saw palmetto study is that it evaluated men who had more advanced prostate disease than did most of the participants in the favorable saw palmetto studies. In the numerous European studies that documented saw palmetto's efficacy, most of the men evaluated were considered to have moderate prostate disease. The study used to attack saw palmetto, on the other hand, looked at men with **moderate-to-severe** prostate disease. Researchers long ago determined that men with **moderate-to-severe** benign prostate disease need aggressive therapy to achieve effective relief. This is why recent studies showing positive benefit to herbal prostate remedies have used *saw palmetto* combined with *nettle root*.[142-146] This fact raises questions as to why so much money was spent funding a study of men with significant prostate disease using only saw palmetto, when European doctors prescribe combination herbal therapies to treat benign prostate disease.

Another flaw of this study is that the group assigned the saw palmetto had more pronounced prostate disease than did the placebo group. For instance, the group receiving saw palmetto had a *BPH Impact Score* that was statistically significantly worse than the placebo group at baseline. Whether these baseline differences had an impact on the study's outcome is unknown. By placing men with more severe prostate disease in the saw palmetto group, however, the study was biased against saw palmetto from the beginning.

Why this study is irrelevant to aging men today

European doctors use various combinations of *pygeum, nettle root, beta-sitosterol, saw palmetto,* and other herbs to treat benign prostate disease. Despite numerous scientific studies

The Overlooked Effects of Estrogen on the Prostate

Mainstream medicine remains fixated on the role of *testosterone* and *dihydrotestosterone* in promoting prostate gland overgrowth. Prostate disease, however, does not strike young men with high testosterone levels.

The overlooked fact is that as men grow older, they produce less testosterone and a lot more estrogen. Prostate cells contain estrogen receptor sites, demonstrating that the gland can respond directly to the growth-promoting effects of estrogen. Recent data suggest that estrogens play a role in prostate disease.[147-149]

Aging men, in particular those with the so-called pot belly (abdominal obesity), often have excess levels of the *aromatase* enzyme that converts testosterone into estrogen. The prostate itself expresses *aromatase* that can convert testosterone into estrogen within the gland itself. Two herbal extracts used extensively in Europe (*pygeum* and *nettle root*) have demonstrated aromatase-suppressing effects *in vitro*, especially when they are used together.[150]

indicating that treatment of prostate enlargement should include a combination of herbal extracts, the doctors who designed the one recent negative study choose to test saw palmetto in isolation.

Based on evidence that prostate disease is caused by several different factors, it would appear that the recent study that used only saw palmetto to treat men with moderate-to-severe prostate disease was *designed to fail*. The study therefore has no relevance to men taking combination supplements that provide nettle root (*Urtica dioica*), pygeum, beta-sitosterol, and other plant extracts that have proven efficacy in dozens of published scientific studies.[151-181]

It is important to also note that this is only one study of a relatively small group of men with moderate-to-severe prostate enlargement who were only allowed to use saw palmetto. Ten times as many men with varying degrees of prostate disease have participated in other studies that showed even saw palmetto taken *by itself* to be highly effective.[121-141]

Exposing the Recent Media Attack Against Dietary Supplements

Over the past several months, the media has questioned the efficacy of several popular dietary supplements. In the upcoming June 2006 issue of ***Life Extension*** magazine, we dissect these negative media reports down to the bone to reveal the hard scientific facts.

In doing so, we expose the absurdity of the headline-hungry media making proclamations such as "***another natural remedy bit the dust***" when describing the recent glucosamine study. We also reveal the inappropriateness of conventional doctors, with little knowledge about the proper use of nutrients, but with strong financial ties to the pharmaceutical industry, conducting studies that contain so many flaws that their findings are largely irrelevant.

Members of the ***Life Extension Foundation*** discover the science behind the headlines in order to avoid being victimized by the medical establishment's ominous propaganda machine.

For longer life,

William Faloon

P.S.- At the beginning of this letter, I stated that the front page of the *Wall Street Journal* featured an article stating:

"Design problems in all the trials means the results don't really answer the questions they were supposed to address. And a flawed communications effort led to widespread misinterpretation of the results by the news media and the public." [1]

It is important to note that like other media outlets, the *Wall Street Journal* (in other articles) regurgitated the same negative reports about dietary supplements as did the *New York Times*, *Washington Post*, *Associated Press*, et al.

REFERENCES

Dietary Supplements Attacked by the Media

1. What's Next for Arthritis Sufferers: Doctors Hold Out Hope for Supplements. *The Wall Street Journal*; Feb 28, 2006; D.1 Available at: www.wsj.com Accessed February 2006
2. Available at: http://www.washingtonpost.com/wp-dyn/content/article/2006/02/07/AR2006020701681.html Accessed February 2006
3. Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006 Feb 8;295(6):655-66.
4. Beresford SA, Johnson KC, Ritenbaugh C, et al. Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006 Feb 8;295(6):643-54.
5 Prentice RL, Caan B, Chlebowski RT, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006 Feb 8;295(6):629-42.
6. Available at: www.healthy.net/asp/templates/news.asp?Id=5713 Accessed March 2006
7. de Roos NM, Bots ML, Katan MB. Replacement of dietary saturated fatty acids by trans fatty acids lowers serum HDL cholesterol and impairs endothelial function in healthy men and women. *Arterioscler Thromb Vasc Biol*. 2001 Jul;21(7):1233-7.
8. Oomen CM, Ocke MC, Feskens EJ, van Erp-Baart MA, Kok FJ, Kromhout D. Association between trans fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study. *Lancet*. 2001 Mar 10;357(9258):746-51.
9. 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.
10. Mensink RP, Zock PL, Katan MB, Hornstra G. Effect of dietary cis and trans fatty acids on serum lipoprotein[a] levels in humans. *J Lipid Res*. 1992 Oct;33(10):1493-501.
11. Katan MB, Mensink R, Van Tol A, Zock PL. Dietary trans fatty acids and their impact on plasma lipoproteins. *Can J Cardiol*. 1995 Oct;11 Suppl G:36G-38G.
12. 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.
13. Visalia F, Bogani P, Grande S, Galli C. Mediterranean food and health: building human evidence. *J Physiol Pharmacol*. 2005 Mar;56 Suppl 1:37-49.
14. Trichopoulou A, Bania C, Trichopoulou D. Mediterranean diet and survival among patients with coronary heart disease in Greece. *Arch Intern Med*. 2005 Apr 25;165(8):929-35.
15. 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.
16. Mori TA, Beilin LJ. Omega-3 fatty acids and inflammation. *Curr Atheroscler Rep*. 2004 Nov;6(6):461-7.
17. 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.
18. 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.
19. 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.
20. Roland I, De Leval X, Evrard B, Pirotte B, Dogne JM, Delattre L. Modulation of the arachidonic cascade with omega3 fatty acids or analogues: potential therapeutic benefits. *Mini Rev Med Chem*. 2004 Aug;4(6):659-68.
21. 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.
22. 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.
23. Lavelli V. Comparison of the antioxidant activities of extra virgin olive oils. *J Agric Food Chem*. 2002 Dec 18;50(26):7704-8.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.
30. 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.
31. 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.
32. 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.

33. 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.
34. 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.
35. 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.
36. 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.
37. 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.
38. Platt R. Current concepts in optimum nutrition for cardiovascular disease. *Prev Cardiol*. 2000 Spring;3(2):83-7.
39. Prasad K. Flaxseed: a source of hypocholesterolemic and antiatherogenic agents. *Drug News Perspect*. 2000 Mar;13(2):99-104.
40. 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.
41. 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.
42. Arterial compliance in obese subjects is improved with dietary plant n-3 fatty acid from flaxseed oil despite increased LDL oxidizability. *Arterioscler Thromb Vasc Biol*. 1997 Jun;17(6): 1163-70.
43. 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.
44. AHRQ Evidence Reports Confirm that Fish Oil Helps Fight Heart Disease. Press Release, April 22, 2004. Agency for Healthcare Research and Quality, Rockville, MD. Available at: http://www.ahrq.gov/news/press/pr2004/omega3pr.htm Accessed March 2006
45. Calder, PC. N-3 polyunsaturated fatty acids and inflammation: from molecular biology to the clinic. *Lipids*. 2003 Apr;38(4):343-52.
46. Mayer, K, Merfels, M, Muhly-Reinholz, M, et al. Omega-3 fatty acids suppress monocyte adhesion to human endothelial cells: role of endothelial PAF generation. *Am J Physiol Heart Circ Physiol*. 2002 Aug;283(2):H811-8.
47. Terry P, Lichtenstein P, Feychting M, Ahlbom A, Wolk A. Fatty fish consumption and risk of prostate cancer. *Lancet*. 2001 Jun 2;357(9270):1764-66.
48. Aronson WJ, Glaspy JA, Reddy ST, Reese D, Heber D, Bagga D. Modulation of omega-3/omega-6 polyunsaturated ratios with dietary fish oils in men with prostate cancer. *Urology*. 2001 Aug;58(2):283-8.
49. Curtis CL, Hughes CE, Flannery CR, Little CB, Harwood JL, Caterson B. n-3 fatty acids specifically modulate catabolic factors involved in articular cartilage degradation. *J Biol Chem*. 2000 Jan 14;275(2):721-4.
50. Andrioli G, Carletto A, Guarini P, et al. Differential effects of dietary supplementation with fish oil or soy lecithin on human platelet adhesion. *Thromb Haemost*. 1999 Nov;82(5):1522-7.
51. Caughey GE, Mantzioris E, Gibson RA, Cleland LG, James MJ. The effect on human tumor necrosis factor alpha and interleukin 1 beta production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. *Am J Clin Nutr.* 1996 Jan;63(1):116-22.
52. Mori TA, Vandongen R, Beilin LJ, Burke V, Morris J, Ritchie J. Effects of varying dietary fat, fish, and fish oils on blood lipids in a randomized controlled trial in men at risk of heart disease. *Am J Clin Nutr*. 1994 May;59(5):1060-8.
53. Bartram HP, Gostner A, Scheppach W. Effects of fish oil on rectal cell proliferation, mucosal fatty acids, and prostaglandin E2 release in healthy subjects. *Gastroenterology* 1993 Nov;105(5):1317-22.
54. Espersen GT, Grunnet N, Lervang HH et al. Decreased interleukin-1 beta levels in plasma from rheumatoid arthritis patients after dietary supplementation with n-3 polyunsaturated fatty acids. *Clin Rheumatol.* 1992 Sep;11(3):393-5.
55 Li XL, Steiner M. Dose response of dietary fish oil supplementations on platelet adhesion. *Arterioscler Thromb*. 1991 Jan-Feb;11(1):39-46.
56. Sperling RI, Weinblatt M, Robin JL, et al. Effects of dietary supplementation with marine fish oil on leukocyte lipid mediator generation and function in rheumatoid arthritis. *Arthritis Rheum* 1987 Sep;30(9):988-97.
57. Jolly, CA, Muthukumar, A, Avula, CP, et al. Lifespan is prolonged in food-restricted auto-immune-prone [NZ-NZW] F[1] mice fed a diet enriched with [n-3] fatty acids. Available at: http://www.nutrition.org/cgi/content/abstract/131/10/2753 Accessed March 2006.
58. Rebecca D. Jackson, M.D., Andrea Z. LaCroix, Ph.D., Margery Gass, M.D, et al. Calcium plus Vitamin D Supplementation and the Risk of Fractures. *N Engl J Med*. 2006 Feb 16;
354(7):669-83.
59. Daniel O. Clegg, M.D., Domenic J. Reda, Ph.D., Crystal L. Harris, Pharm.D., et al. Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis. *N Engl J Med*. 2006 Feb 23;354(8):795-808.
60. Kolata G. "2 Arthritis Drugs Are Found to Be Ineffective." NY Times article. 2006 Feb 23.
61. Available at: http://abcnews.go.com/Health/wireStory?id=1651917&CMP=OTC-RSSFeeds0312 Accessed March 2006.
62. Usha PR, Naidu MU. Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis. *Clin Drug Invest*. 2004 Jun;24(6):353-63.
63. Ekmekcioglu C, Strauss-Blasche G, Holzer F, Marktl W. Effect of sulfur baths on antioxidative defense systems, peroxide concentrations and lipid levels in patients with degenerative osteoarthritis. *Forsch Komplementarmed Klass Naturheilkd*. 2002 Aug;9(4):216-20.
64. Parcell S. Sulfur in human nutrition and applications in medicine. *Altern Med Rev*. 2002 Feb;7(1):22-44.
65. Elkayam O, Ophir J, Brener S, Paran D, Wigler I, Efron D, Even-Paz Z, Politi Y, Yaron M. Immediate and delayed effects of treatment at the Dead Sea in patients with psoriatic arthritis. *Rheumatol Int*. 2000 19(3):77-82.
66. Jacob SW, Lawrence RM, Zucker M. The Miracle of MSM. New York: Berkley Books, 1999.
67. Sukenik S, Flusser D, Codish S, Abu-Shakra M. Balneotherapy at the Dead Sea area for knee osteoarthritis. *Isr Med Assoc J*. 1999 Oct;1(2):83-5.
68. Prater, G. MSM: the multi-purpose compound. *Life Extension Magazine* 1999 Sep;5(9):71-2. Ft. Lauderdale, FL: Life Extension Foundation.
69. Lawrence RM. Methylsulfonylmethane (MSM): a double-blind study of its use in degenerative arthritis. *Int J Anti-Aging Med*. 1998 1:50.
70. Bradley H, Gough A, Sokhi RS, Hassell A, Waring R, Emery P. Sulfate metabolism is abnormal in patients with rheumatoid arthritis. Confirmation by in vivo biochemical findings. *J Rheumatol*. 1994 Jul;21(7):1192-6.

71. Emery P, Bradley H, Gough A, Arthur V, Jubb R, Waring R. Increased prevalence of poor sulphoxidation in patients with rheumatoid arthritis: effect of changes in the acute phase response and second line drug treatment. *Ann Rheum Dis*. 1992 Mar;51(3):318-20.
72. Herschler RJ. Dietary and Pharmaceutical Uses of Methylsulfonylmethane and Compositions Comprising It. 1985 December 17;U.S. Patent 4,559,329.
73. Hardy ML, Coulter I, Morton SC, et al. S-Adenosylmethionine for treatment of depression, osteoarthritis and liver disease. *Evid Rep Technol Assess (Summ)*. 2003 Aug;(64):1-3.Available at: http://www.ahrq.gov/clinic/epcsums/samesum.htm Accessed March 2006.
74. Parcell S. Sulfur in human nutrition and applications in medicine. *Altern Med Rev.* 2002 Feb;7(1):22-44.
75. Konig B. A long-term (two years) clinical trial with S-adenosylmethionine for the treatment of osteoarthritis. *Am J Med.* 1987 Nov 20;83(5A):89-94.
76. Maccagno A, Di Giorgio E, Caston O, Sagasta C. Double-blind controlled clinical trial of oral S-adenosylmethionine versus piroxicam in knee osteoarthritis. *Am J Med*. 1987 Nov 20;83(5A):72-7.
77. Vetter G. Double-blind comparative clinical trial with S-adenosylmethionine and indomethacin in the treatment of osteoarthritis. *Am J Med*. 1987 Nov 20;83(5A):78-80.
78. Muller-Fassbender H. Double-blind clinical trial of S-adenosylmethionine versus ibuprofen in the treatment of osteoarthritis. *Am J Med*. 1987 Nov 20;83(5A):81-3.
79. Polli E, Cortellaro M, Parrini L, Tessari L, Cherie Ligniere G. Pharmacological and clinical aspects of S-adenosylmethionine (SAMe) in primary degenerative arthropathy (osteoarthrosis). *Minerva Med*. 1975 Dec 5;66(83):4443-59.
80. Glucosamine long-term treatment and the progression of knee osteoarthritis: systematic review of randomized controlled trials. *Ann Pharmacother*. 2005 Jun;39(6):1080-7.
81. Blakeley JA & Iberia VEO. Glucosamine & Osteoarthritis. *Am J Nurs*. 2004 Feb;104(2):54-9; quiz 68-9.
82. Richy F, Bruyere O, Ethgen O, Cucherat M, Henrotin Y, Reginster JY. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis. A comprehensive meta-analysis. *Arch Intern Med*. 2003 Jul 14;163(13):1514-22.
83. Miller DC, Richardson J, Roberts RW. Does glucosamine relieve arthritis joint pain? *J Fam Pract*. 2003 52:645-7.
84. Bruyere O, Honore A, Ethgen O, et al. Correlation between radiographic severity of knee osteoarthritis and future disease progression. Results from a 3 year prospective, placebo-controlled study evaluating the effect of glucosamine sulfate. *Osteoarthritis & Cartilage*. 2003 Jan;11(1):1-5.
85. Miller G, Rejeski W, Williamson J, et al. The Arthritis, Diet and Activity Promotion Trial (ADAPT): design, rationale, and baseline results. *Control Clin Trials*. 2003 Aug;24(4):462-80.
86. Braham R, Dawson B, Goodman C. The effect of glucosamine supplementation on people experiencing regular knee pain. *Br J Sports Med*. 2003 Feb;37(1):45-9.
87. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati L. 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.
88. Reginster J, Deroisy R, Rovati L, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet*. 2001 357:251-6.
89. Chard J, Dieppe P. Glucosamine for osteoarthritis: magic, hype, or confusion? *BMJ*. 2001 June 16;322(7300):1439–1440.
90. Nahin RL, Straus SE. Research into complementary and alternative medicine: problems and potential. *BJM*. 2001 Jan 20;322(7279):161-4.
91. Mazieres B, Combe B, Phan Van A, Tondut J, Grynfeltt M. Chondroitin sulfate in osteoarthritis of the knee: a prospective, double-blind, placebo controlled multicenter clinical study. *J Rheumatol*. 2001 Jan;28(1):173-81.
92. Debi R, Robinson D, Agar G, Halperin N. GAG for osteoarthritis of the knee - a prospective study. *Harefuah*. 2000 Mar 15;138(6):451-3, 518.
93. McAlindon TE, La valley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis. *JAMA*. 2000 Mar 15;283(11):1469-75.
94. Leeb BF, Schweitzer H, Montag K, Smolen JS. A Metaanalysis of Chondroitin Sulfate in the Treatment of OA. *J Rheumatol*. 2000 Jan;27(1):205-11.
95. Leffler CT. Philippi AF, Leffler SG, Mosure JC, Kim PD. Glucosamine, chondroitin and manganese ascorbate for degenerative joint disease of the knee or low back : a randomized, double-blind, placebo-controlled pilot study. *Mil Med*. 1999 Feb;164(2):85-91.
96. Conn DL, Arnold WJ, Hollister JR. Alternative Treatments and Rheumatic Disease. *Bull Rheum Dis.* 1999 48(7):1-3.
97. da Camara CC, Dowless GV. Glucosamine Sulfate for Osteoarthritis. *Ann Pharmacother.* 1998 May;32(5):580-7.
98. Qiu GX, Gao SN, Giacovelli G, Rovati L, Setnikar I. Efficacy and safety of glucosamine sulfate versus ibuprofen in patients with knee osteoarthritis. *Arzneimit-telforschung*. 1998 May;48(5):469-74.
99. McAlindon T, Felson D. Nutrition: risk factors for osteoarthritis. *Ann Rheum Dis*. 1997 56:397-402.
100. Muller-Fasbender, H, et al.; Glucosamine sulfate compared to ibuprofen in osteoarthritis of the knee. *Osteoarthritis Cartilage*. 1997 Jul;56(7):397-400.
101. Morreale P, Manopulo R, Galati M, Boccanera L, Saponati G, Bocchi L. Comparison of the antiinflammatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis. *J Rheumatol*. 1996 Aug 23;(8):1385-91.
102. Bucsi L, Poor G. Efficacy and tolerability of oral chondroitin sulfate as a symptomatic slow-acting drug for osteoarthritis (SYSADOA) in the treatment of knee osteoarthritis. *Osteoarthritis Cartilage.* 1998 May;6 Suppl A:31-6.
103. Miller DC, Richardson J. Does glucosamine relieve arthritis joint pain? *J Fam Pract*. 2003 52:645-7.
104. Deal C, Moskowitz R. Nutraceuticals as therapeutic agents in osteoarthritis. The role of glucosamine, chondroitin sulfate, and collagen hydrolysate. *Rheum Dis Clin North Am*. 1999 25:379-95.
105. Uebelhart D, Thonar E, Delmas PD, et al. Chondroitin 4 and 6 sulfate: A symptomatic slow-acting drug for osteoarthritis does also have structural modifying properties. *Osteoarthritis & Cartilage*. 1997 5:70.
106. Verbruggen G, Goemaere S, Veys EM. Chondroitin sulfate S/DMOAD (Structure/Disease Modifying Osteoarthritis (OA) Drug) in the treatment of OA of the finger joints. *Osteoarthritis & Cartilage*. 1997 5:70.
107. D'Ambrosia E, Casa B, Bompani R, Scali G, Scali M. Glucosamine sulfate: a controlled clinical investigation in arthrosis. *Pharmatherapeutica*. 1981;2(8):504-8.
108. Crolle G, D'Este.. Glucosamine sulfate for the management of arthrosis. *Curr Med Res Opin*. 1980 7:104-9.

109. Vajaradul Y. Double-blind clinical evaluation of intra-articular glucosamine in outpatients with gonarthrosis. *Clin Ther*. 1981;3(5):336-43.
110. Pujalte JM, Llavore EP, Ylescupidez FR. Double-blind clinical evaluation of oral glucosamine sulphate in the basic treatment of osteoarthrosis. *Curr Med Res Opin*. 1980;7(2):110-14.
111. Singh G, Miller JD, Lee FH, Pettitt D, Russell MW. Prevalence of cardiovascular disease risk factors among U.S. adults with self-reported osteoarthritis: data from the Third National Health and Nutrition Examination Survey. *Am J Manag Care*. 2002 Oct;8(15 Suppl):S383-91.
112. Available at: http://www.lef.org/magazine/mag99/oct99-cover.html Accessed March 2006
113. Available at: http://www.lef.org/magazine/mag2001/jan2001_report_cox2_1.html Accessed March 2006
114. Hendler SS, Rorvik D. PDR for Nutritional Supplements, 1st Ed. Montvale, NJ: Medical Economics Co; 2001:149.
115. Mayatepek E, Paul K, Leichsenring M, et al. Influence of dietary (n-3)-polyunsaturated fatty acids on leukotriene B4 and prostaglandin E2 synthesis and course of experimental tuberculosis in guinea pigs. *Infection*. 1994 Mar;22(2):106-12.
116. Ferretti A, Flanagan VP, Reeves VB. Occurrence of prostaglandin E3 in human urine as a result of marine oil ingestion: gas chromatographic-mass spectrometric evidence. *Biochim Biophys Acta*. 1988 Apr 15;959(3):262-8.
117. Available at: http://www.lef.org/magazine/mag2004/jun2004_ch_01.htm Accessed March 2006
118. Rizzo R, Grandolfo M, Godeas C, Jones KW, Vittur F. Calcium, sulfur, and zinc distribution in normal and arthritic articular equine cartilage: a synchrotron radiation-induced X-ray emission (SRIXE) study. *J Exp Zool*. 1995 Sep 1;273(1):82-6.
119. Murav'ev I, Venikova MS, Pleskovskaia GN, Riazantseva TA, Sigidin I. Effect of dimethyl sulfoxide and dimethyl sulfone on a destructive process in the joints of mice with spontaneous arthritis. *Patol Fiziol Eksp Ter*. 1991 Mar-Apr;(2):37-9.
120. Lawrence RM. Methylsulfonylmethane (MSM): a double-blind study of its use in degenerative arthritis. *Int J Anti-Aging Med*. 1998 1:50.
121. Buck AC. Is there a scientific basis for the therapeutic effects of serenoa repens in benign prostatic hyperplasia? Mechanisms of action. *J Urol*. 2004 Nov;172(5 Pt 1):1792-9.
122. Gong EM, Gerber GS. Saw palmetto and benign prostatic hyperplasia. *Am J Chin Med*. 2004 32(3):331-8.
123. Gerber GS, Fitzpatrick JM. The role of a lipido-sterolic extract of Serenoa repens in the management of lower urinary tract symptoms associated with benign prostatic hyperplasia. *BJU Int*. 2004 Aug;94(3):338-44.
124. Boyle P, Robertson C, Lowe F, Roehrborn C. Updated meta-analysis of clinical trials of Serenoa repens extract in the treatment of symptomatic benign prostatic hyperplasia. *BJU Int*. 2004 Apr;93(6):751-6.
125. Wilt TJ, Ishani A, Rutks I, MacDonald R. Phytotherapy for benign prostatic hyperplasia. *Public Health Nutr*. 2000 Dec;3(4A):459-72.
126. Gerber G. Saw Palmetto For The Treatment Of Men With Lower Urinary Tract Symptoms. *J Urol* 2000 May;163(5):1408-12 (Review)
127. Al-Shukri SH, Deschaseaux P, Kuzmin IV, Amdiy RR. Early urodynamic effects of the lipido-sterolic extract of Serenoa repens (Permixon(R)) in patients with lower urinary tract symptoms due to benign prostatic hyperplasia. *Prostate Cancer Prostatic Dis*. 2000 Nov;3(3):195-199.
128. Goepel M, Hecker U, Krege S, Rubben H, Michel MC. Saw palmetto extracts potently and noncompetitively inhibit human alpha1-adrenoceptors in vitro. *Prostate*. 1999 Feb 15;38(3):208-15.
129. Debruyne F, Koch G, Boyle P, et al. [Comparison of a phytotherapeutic agent (Permixon) with an alpha-blocker (Tamsulosin) in the treatment of benign prostatic hyperplasia: a 1-year randomized international study]. *Prog Urol*. 2002 Jun;12(3):384-92; discussion 394-4. French.
130. Marks LS, Partin AW, Epstein JI, et al. Effects of a saw palmetto herbal blend in men with symptomatic benign prostatic hyperplasia. *J Urol*. 2000 May;163(5):1451-6.
131. Carraro JC, Raynaud JP, Koch G, et al. Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia: a randomized international study of 1,098 patients. *Prostate*. 1996 Oct;29(4):231-40.
132. Vela Navarrete R, Garcia Cardoso JV, Barat A, Manzarbeitia F, Lopez Farre A. BPH and inflammation: pharmacological effects of Permixon on histological and molecular inflammatory markers. Results of a double blind pilot clinical assay. *Eur Urol*. 2003 Nov;44(5):549-55.
133. Veltri RW, Marks LS, Miller MC, Et Al. Saw palmetto alters nuclear measurements reflecting DNA content in men with symptomatic BPH: evidence for a possible molecular mechanism. *Urology*. 2002 Oct;60(4):617-22.
134. Giannakopoulos X, Baltogiannis D, Giannakis D, Et al. The lipidosterolic extract of Serenoa repens in the treatment of benign prostatic hyperplasia: a comparison of two dosage regimens. *Adv Ther*. 2002 Nov-Dec;19(6):285-96.
135. Oki T, Suzuki M, Nishioka Y, Yasuda A, Umegaki K, Yamada S. Effects of saw palmetto extract on micturition reflex of rats and its autonomic receptor binding activity. *J Urol*. 2005 Apr;173(4):1395-9.
136. Pytel' IuA, Lopatkin NA, Gorilovskii LM, Vinarov AZ, Sivkov AV, Medvedev AA. [The results of long-term permixon treatment in patients with symptoms of lower urinary tracts dysfunction due to benign prostatic hyperplasia]. *Urologiia*. 2004 Mar-Apr;(2):3-7.
137. Aliaev IuG, Vinarov AZ, Lokshin KL, Spivak LG. [Five-year experience in treating patients with prostatic hyperplasia patients with permixone (Serenoa repens "Pierre Fabre Medicament)]. *Urologiia*. 2002 Jan-Feb;(1):23-5.
138. Stepanov VN, Siniakova LA, Sarrazin B, Raynaud JP. Efficacy and tolerability of the lipidosterolic extract of Serenoa repens (Permixon) in benign prostatic hyperplasia: a double-blind comparison of two dosage regimens. *Adv Ther*. 1999 Sep-Oct;16(5):231-41.
139. Wilt TJ, Ishani A, Stark G, MacDonald R, Lau J, Mulrow C. Saw palmetto extracts for treatment of benign prostatic hyperplasia: a systematic review. *JAMA*. 1998 Nov 11;280(18):1604-9.
140. Plosker GL, Brogden RN. Serenoa repens (Permixon). A review of its pharmacology and therapeutic efficacy in benign prostatic hyperplasia. *Drugs Aging*. 1996 Nov;9(5):379-95.
141. Gerber G, Kuznetsov D, Johnson B, Burstein, J. Randomized, Double-Blind, Placebo-Controlled Trial Of Saw Palmetto In Men With Lower Urinary Tract Symptoms. *Urology*. 2001 58**:**960–965.
142. Popa G, Hagele-Kaddour H, Walther C. [Efficacy of a combined Sabal-urtica preparation in the symptomatic treatment of benign prostatic hyperplasia. Results of a placebo-controlled double-blind study]. *MMW Fortschr Med*. 2005 Oct 6;147 Suppl 3:103-8.
143. Sokeland J. Combined sabal and urtica extract compared with finasteride in men with benign prostatic hyperplasia: analysis of prostate volume and therapeutic outcome. *BJU Int*. 2000 Sep;86(4):439-42.
144. Odenthal KP. Phytotherapy of benign prostatic hyperplasia (BPH) with Cucurbita, Hypoxis, Pygeum, Urtica and Sabal serrulata (Serenoa repens). *Phytotherapy Research*. 1996 10/SUPPL. 1(S141-S143)

145. Lopatkin N, Sivkov A, Walther C. Long-term efficacy and safety of a combination of sabal and urtica extract for lower urinary tract symptoms—a placebo-controlled, double-blind, multicenter trial. World J Urol. 2005 Jun;23(2):139-46.
146. Preventing diseases of the prostate in the elderly using hormones and nutriceuticals. *Aging Male*. 2004 Jun;7(2):155-69.
147. Ellem SJ, Risbridger GP. Aromatase and prostate cancer. *Minerva Endocrinol*. 2006 Mar;31(1):1-12.
148. Harkonen PL, Makela SI. Role of estrogens in development of prostate cancer. *J Steroid Biochem Mol Biol*. 2004 Nov;92(4):297-305.
149. Risbridger GP, Bianco JJ, Ellem SJ, McPherson SJ. Oestrogens and prostate cancer. *Endocr Relat Cancer*. 2003 Jun;10(2):187-91.
150. Krzeski T, Kazon M, Borkowski A, Witeska A, Kuczera J. Combined extracts of Urtica dioica and Pygeum africanum in the treatment of benign prostatic hyperplasia: double-blind comparison of two doses. *Clin Ther*. 1993 Nov-Dec;15(6):1011-20.
151. Vahlensieck W Jr, Fabricius PG, Hell U. [Drug therapy of benign prostatic hyperplasia]. *Fortschr Med*. 1996 Nov 10;114(31):407-11.
152. Katz AE. Flavonoid and botanical approaches to prostate health. *J Altern Complement Med*. 2002 Dec;8(6):813-21.
153. Wilt TJ, Ishani A, Rutks I, MacDonald R. Phytotherapy for benign prostatic hyperplasia. *Public Health Nutr*. 2000 Dec;3(4A):459-72.
154. Sokeland J, Albrecht J. [Combination of Sabal and Urtica extract vs. finasteride in benign prostatic hyperplasia (Aiken stages I to II). Comparison of therapeutic effectiveness in a one year double-blind study]. Urologe A. 1997 Jul;36(4):327-33.
155. Schneider HJ, Honold E, Masuhr T. [Treatment of benign prostatic hyperplasia. Results of a treatment study with the phytogenic combination of Sabal extract WS 1473 and Urtica extract WS 1031 in urologic specialty practices]. Fortschr Med. 1995 Jan 30;113(3):37-40.
156. Vahlensieck W Jr, Fabricius PG, Hell U. [Drug therapy of benign prostatic hyperplasia]. *Fortschr Med*. 1996 Nov 10;114(31):407-11.
157. Preuss HG, Marcusen C, Regan J, Klimberg IW, Welebir TA, Jones WA. Randomized trial of a combination of natural products (cernitin, saw palmetto, B-sitosterol, vitamin E) on symptoms of benign prostatic hyperplasia (BPH). *Int Urol Nephrol*. 2001 33(2):217-25.
158. Breza J, Dzurny O, Borowka A, et al. Efficacy and acceptability of tadenan (Pygeum africanum extract) in the treatment of benign prostatic hyperplasia (BPH): a multicentre trial in central Europe. *Curr Med Res Opin.* 1998 14(3):127-39.
159. Wilt TJ, Ishani A, Mac Donald R, Rutks I, Stark G. Pygeum africanum for benign prostatic hyperplasia (Cochrane Review). The Cochrane Library. Vol Issue 3. Chichester, UK: John Wiley & Sons, Ltd.; 2004.
160. Santa Maria M, Paciucci B, Reventos P, Morote R, Thomson O. Antimitogenic effect of Pygeum africanum extracts on human prostatic cancer cell lines and explants from benign prostatic hyperplasia. *Arch Esp Urol*. 2003 May;56(4):369-78.
161. Konrad L, Muller HH, Lenz C, Laubinger H, Aumuller G, Lichius JJ.Antiproliferative effect on human prostate cancer cells by a stinging nettle root (Urtica dioica) extract. *Planta Med*. 2000 Feb;66(1):44-7.
162. Riehemann K, Behnke B, Schulze-Osthoff K. Plant extracts from stinging nettle (Urtica dioica), an antirheumatic remedy, inhibit the proinflammatory transcription factor NF-kappaB. *FEBS Lett*. 1999 Jan 8;442(1):89-94.
163. Lichius JJ, Muth C. The inhibiting effects of Urtica dioica root extracts on experimentally induced prostatic hyperplasia in the mouse. *Planta Med*. 1997 Aug;63(4):307-10.
164. Yablonsky F, Nicolas V, Riffaud JP, Bellamy F. Antiproliferative effect of Pygeum africanum extract on rat prostatic fibroblasts. *J Urol* 1997 Jun;157(6):2381-7.
165. Berges RR, Kassen A, Senge T. Treatment of symptomatic benign prostatic hyperplasia with beta-sitosterol: an 18-month follow-up. BJU Int. 2000 May;85(7):842-6. PMID 10792163
166. Berges RR, Windeler J, Trampisch HJ, Senge T. Randomised, placebo-controlled, double-blind clinical trial of beta-sitosterol in patients with benign prostatic hyperplasia. Beta-sitosterol Study Group. Lancet. 1995 Jun 17;345(8964):1529-32. PMID 7540705
167. Klippel KF, Hiltl DM, Schipp B. A multicentric, placebo-controlled, double-blind clinical trial of beta-sitosterol (phytosterol) for the treatment of benign prostatic hyperplasia. German BPH-Phyto Study group. Br J Urol. 1997 Sep;80(3):427-32. PMID 9313662
168. Wilt TJ, MacDonald R, Ishani A. beta-sitosterol for the treatment of benign prostatic hyperplasia: a systematic review. BJU Int. 1999 Jun;83(9):976-83. PMID 10368239
169. Wilt T, Ishani A, MacDonald R, Stark G, Mulrow C, Lau J. Beta-sitosterols for benign prostatic hyperplasia. Cochrane Database Syst Rev. 2000;(2):CD001043. PMID 10796740
170. von Holtz RL, Fink CS, Awad AB. Beta-Sitosterol activates the sphingomyelin cycle and induces apoptosis in LNCaP human prostate cancer cells. Nutr Cancer. 1998;32(1):8-12. PMID 9824850
171. Awad AB, Fink CS, Williams H, Kim U. In vitro and in vivo (SCID mice) effects of phytosterols on the growth and dissemination of human prostate cancer PC-3 cells. Eur J Cancer Prev. 2001 Dec;10(6):507-13. PMID 11916349
172. Awad AB, Gan Y, Fink CS. Effect of beta-sitosterol, a plant sterol, on growth, protein phosphatase 2A, and phospholipase D in LNCaP cells. Nutr Cancer. 2000;36(1):74-8. PMID 10798219
173. Nakase S, Takenaka K, Hamanaka T, Kimura M. Effects of Cernilton pollen-extract on urethral smooth muscle and diaphragmatic neuromuscular specimen. Folio Pharmacol Jpn. 1988;91:385-92.
174. Ito R, Ishii M, S. Y, et al. Antiprostatic hypertrophic action of Cernilton pollen-extract. Pharmacometrics. 1986;31:1-11.
175. Kimura M, Kimura I, Nakase K, Sonobe T, Mori N. Micturition activity of pollen extract: contractile effects on bladder and inhibitory effects on urethral smooth muscle of mouse and pig. Planta Med. 1986 Apr;(2):148-51.
176. Loschen G, Ebeling L. Inhibition of arachidonic acid cascade by extract of rye pollen. Arzneimittelforschung. 1991 Feb;41(2):162-7.
177. Tunn S, Krieg M. Hormone metabolism in the human prostate. In: Vahlensieck W, Rutishauser G, eds. Benign Prostate Diseases. New York, NY: Thieme Medical Publishers, Inc.; 1992:17-21.
178. Dutkiewicz S. Usefulness of Cernilton in the treatment of benign prostatic hyperplasia. Int Urol Nephrol. 1996;28(1):49-53.
179. Yasumoto R, Kawanishi H, Tsujino T, et al. Clinical evaluation of long-term treatment using cernitin pollen extract in patients with benign prostatic hyperplasia. Clin Ther. 1995 Jan-Feb;17(1):82-7.
180. Buck AC, Cox R, Rees RW, Ebeling L, John A. Treatment of outflow tract obstruction due to benign prostatic hyperplasia with the pollen extract, cernilton. A double-blind, placebo-controlled study. Br J Urol. 1990 Oct;66(4):398-404.
181. Habib FK, Ross M, Buck AC, Ebeling L, Lewenstein A. In vitro evaluation of the pollen extract, cernitin T-60, in the regulation of prostate cell growth. Br J Urol. 1990 Oct;66(4):393-7.