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REPORT

Anti-Inflammatory Properties of Tart Cherry

By Michael Downey

On October 17, 2005, the **FDA** sent out warning letters to cherry growers insisting that they cease making substantiated health claims that specific chemicals found in cherries could reduce pain and inflammation.[1,2]

The FDA wanted cherry growers to stop citing published scientific studies showing that **cherries** are packed with unique *anthocyanins* and other compounds that naturally mediate the inflammatory process.[3-6] These compounds deliver comparable anti-inflammatory activity to *ibuprofen* (Advil®) and *naproxen* (Aleve®)[7]—*but without the significant side effects!*

Standard treatment for muscle pain and inflammation has been with *nonsteroidal anti-inflammatory drugs*. With over **111 million** prescriptions and accounting for around **60%** of over-the-counter pain reliever sales in the USA alone, these are some of the most commonly used types of medications.[8] But because they can have *deadly* side effects, including gastric bleeding, heart attack, and kidney failure, the search for natural agents that could prove more beneficial and safer has gained increased attention.[9,10]

The compounds found in cherries modulate numerous pathways to protect against other conditions associated with ***inflammation***—including cancer, cardiovascular disease, metabolic syndrome, and Alzheimer's disease.[11-14] For example, **tart cherry** constituents can switch critical genes off and on;[15,16] modulate cell-signaling molecules like tumor necrosis factor;[17] and target multiple cardiovascular factors—producing, in one study model, ***an astounding 65% reduction in early mortality!***[18]

In this article, you will learn of the multiple benefits found in cherries that the FDA did not want to be publicized.

Broad-Spectrum Tart Cherry Compounds

One of nature's most potent classes of flavonoids is **anthocyanins**. These powerhouse nutrients are responsible for the deep colors in some berries, fruits, and vegetables. Naturally, like other anthocyanin-rich foods, tart cherries deliver substantial antioxidant and anti-inflammatory activity.[3-6]

But tart cherries are superior because they provide high levels of some novel anthocyanins that are absent from a number of other anthocyanin-rich foods, such as blueberries or bilberries![7]

Also, the unique composition of tart cherries goes far beyond anthocyanins.

In fact, *tart* cherries were shown to contain much higher amounts of total phenolics than even their nutritious cousins, *sweet* cherries.[19] Aside from a greater abundance of anthocyanins, tart cherries also deliver a cast of supporting compounds.

Tart cherries were ranked 14th among the top 50 foods for highest **antioxidant** content per serving—surpassing such well-known antioxidant sources as red wine and dark chocolate.[20]

This complex profile prompted researchers to investigate what turned out to be numerous biochemical pathways modulated by tart cherry compounds.[3-7,12,21-26]

The range of activity was breathtaking. Here's a partial sampling: bioactive compounds found in tart cherries beneficially inhibit certain enzymes[5,7] while boosting others,[12,21,22] switch-on cancer defenses,[23,24] down-regulate glucose,[25] and enhance primary antioxidants.[26] We'll examine this multi-potent network of underlying mechanisms later.

But first, let's learn about their resulting impact on degenerative conditions—starting with muscle inflammation.

Muscle Protection

High-intensity or prolonged physical activity of any kind typically causes **muscle damage**, resulting in oxidative stress, inflammation, and pain.[27-29]

As people age, muscle mass and strength tend to decrease, in a process called *sarcopenia*.[30] Although exercise can help overcome this process, post-exercise pain and loss of strength tend to last much longer.

The observed anti-inflammatory benefits of tart cherries prompted researchers to investigate whether they could be used to protect muscles, lower pain, and accelerate muscle repair.

Research demonstrated that orally administered anthocyanins from tart cherries significantly lowered inflammation-induced pain in rats in a dose-dependent manner[3] and that tart cherry juice blend lowered indicators of exercise-induced muscle damage in horses.[31]

Then researchers turned to controlled human trials, first testing the impact of tart cherries on the degree of pain following intense exercise.

The effects of tart cherry juice consumption were tested in a double-blind, randomized trial of runners participating in a 24-hour relay race. Runners drank **two 355 milliliter** beverages containing either tart cherry juice or a placebo beverage daily for one week prior to the race and during the race. (Two **355 mL** bottles of tart cherry juice daily provides at least **80 mg** anthocyanins which is the equivalent of 90 to 100 cherries.)[32]

Both groups reported pain after the race. But the runners who drank tart cherry juice experienced a substantially **smaller pain increase** after the race.[32] This natural protection against acute muscle soreness suggested that tart cherries must be providing some defense against muscle damage.

To confirm this, scientists conducted a controlled trial on indices of muscle recovery. Participants were given either tart cherry juice or a control drink for five days before, on the day of, and for two days after a marathon race.

Runners in the tart cherry group had significantly lower inflammation biomarkers (*Interleukin-6* and *C-reactive protein*) compared to the placebo group. The tart cherry group also recovered isometric strength faster than the control runners, demonstrating an **accelerated recovery** following strenuous exercise.[33]

To further assess the potential decrease in muscleinjury and strength loss, another research team gave 14 male college students who never exercised **12 ounces** of either a tart cherry juice blend or a placebo **twice daily** for eight consecutive days. Then participants performed a type of repeated arm exercise (*elbow flexion eccentric exercise*) that typically induces muscle damage. Isometric elbow flexion strength, pain, and muscle soreness were measured before, and for four days after, the protocol.

After 24 hours, the control group's arm strength was decreased by **30%**—while the tart cherry group's arm strength was diminished by only **12%**. After **four days**, the control group's arm strength was still down by over **10%** while, remarkably, the tart cherry group's arm strength had **increased** by **6%**![34]

The research team concluded that tart cherry significantly reduced the typical pain and loss of strength induced by exercise—and produced marked preservation of muscle function.[34]

The most recent trial on muscle injury and recovery included ten males, half of whom drank **one ounce** of a tart cherry beverage **twice daily** for ten days, while the other half drank the same amount of a placebo beverage during this period. All subjects completed two sets of an intensive, unilateral leg exercise—first, one set with one leg before the ten-day beverage consumption period, and then another set with the other leg after the beverage period.

Faster recovery of the knee extension (maximum voluntary contraction force) was observed with the tart cherry juice protocol versus control. The researchers concluded that the improved muscle recovery time may have been due to attenuation of oxidative damage.[35]

The study author suggested that tart cherry components produce a significant myoprotective—or muscle-protecting—benefit.[35]

WHAT YOU NEED TO KNOW

Guard Against Degenerative Disease and Inflammation with Tart Cherries

- Physical exercise can induce **muscle damage** that generates inflammation and with it, burning, stiffness, and pain. The effect worsens with age.
- Standard treatment with nonsteroidal anti-inflammatory drugs such as *ibuprofen* (Advil®) involves potentially deadly adverse effects, such as stroke.
- Evidence shows that the weave of complex anthocyanins and phenols in **tart cherries** provides superior protection against muscle injury—by safely inhibiting the pain and inflammatory effects.
- The potent components in tart cherries have been demonstrated to deliver high-level protection against inflammatory and degenerative diseases, including cardiovascular disease, metabolic syndrome, and neurodegenerative diseases such as Alzheimer's.

Joint Defense

Experts estimate that one out of every two Americans will develop symptomatic **osteoarthritis** at some point in their lifetime.[36] Osteoarthritis is a chronic condition characterized by a breakdown of joint cartilage that leads to pain and injury.[37]

The Arthritis Foundation reports that the risk of developing osteoarthritis is greater among those of increased age, those who are athletic or regularly engage in repetitive-motion work, and those who are obese.[38]

Osteoarthritis has a strong inflammatory component.[39] *Acetaminophen* is the most commonly used osteoarthritis pain medication.[40] However, this pain-reliever does *not* help lower inflammation,[40] and its side effects can include kidney or liver damage.[41]

In a 2007 pilot study, researchers at Baylor Research Institute gave **tart cherries** in pill form to patients with osteoarthritis of the knee. They documented that, after 8 weeks, more than half the subjects experienced a significant **improvement in pain and function**.[42]

Then, in 2012, a double-blind, randomized, placebo-controlled trial was presented at the annual meeting of the American College of Sports Medicine, ahead of publication. Scientists measured the impacts of tart cherry on serum inflammatory biomarkers among **inflammatory osteoarthritis** patients. (Patients with *inflammatory* or *erosive* osteoarthritis are those who suffer from *sudden* signs of inflammation, such as redness, pain, and swelling.)

The trial included 20 female participants between 40 and 70 years old who experienced at least moderate pain from osteoarthritis. The participants consumed **two 10.5-ounce** bottles of either tart cherry juice or a control beverage for 3 weeks.

Among those patients consuming the tart cherry juice, there was a statistically significant ***decrease*** in **inflammation**, indicated by reduced levels of *C-reactive protein* (CRP). The impact was greatest for those women who had shown the highest inflammation levels at the start of the investigation.[43]

This research demonstrates that tart cherry juice provides osteoarthritis patients with anti-inflammatory activity without the adverse effects and risks of traditional arthritis medications.

Gout is another type of inflammatory arthritis, and it is associated with higher risks of cardiovascular disease and mortality.[44] High blood concentration of **uric acid** is considered its main pathway.[45]

Typically, drugs such as *allopurinol* and *probenecid* are used to help lower uric acid levels. But the side effects of these drugs can include difficulty breathing, unusual bleeding, vomiting, nausea, or severe skin rash.[46,47] They may even interfere with other medications.[48,49]

Fortunately, research has spotlighted a safe alternative. For decades, gout sufferers have consumed tart cherry juice for symptomatic relief, on the basis of anecdotal evidence. Now, rigid science has begun to support this tradition.

A study conducted by scientists at Boston University found that intake of cherry extract reduced the risk of gout attacks in those who suffered recurrent gout attacks by **45%**.[50] Additionally, the researchers discovered that when cherry intake was combined with allopurinol use, the risk for gout attacks was reduced by **75%** versus no intervention. What's more, these results persisted even across subgroups stratified for sex, obesity status, purine intake, and alcohol use.[50] Tart cherries appear to be a natural—and safe—way to inhibit the key gout pathway.

Quelling the Chronic Inflammation of Obesity

Chronic **inflammation** significantly boosts the risk of a number of conditions, including cancer and heart disease.[51] But few people realize that **obesity** can be both a cause—and a consequence—of chronic low-level inflammation.[52,53]

Adipose cells are not simply fat stores—they are chemically active cells.[52] In obese individuals, belly fat deposits generate a torrent of pro-inflammatory cell-signaling molecules known as ***cytokines***.[54] Left unchecked, these cytokines trigger a cascade of destruction that can lead to a number of degenerative diseases.[55,56]

Researchers demonstrated that obese or overweight human adults who consumed **8 ounces daily** of tart cherry juice for4 weeks exhibited significantly **lowered inflammation**. This was evidenced by marked decreases in *erythrocyte sedimentation* rate, *tumor necrosis factor* levels, and *monocyte chemotactic protein*—all key indicators of inflammation.[44]

Tart cherries are clearly a potent tool for inhibiting the chronic, often obesity-related, low-level inflammation that can lead to many disorders—and they could even inhibit obesity itself!

Cardiovascular Disease Prevention

Elevated readings of low-density lipoprotein (LDL) cholesterol are a factor in the onset of atherosclerosis and other **cardiovascular diseases**.[57]

To help decrease low-density lipoprotein to a safer range, the standard medical approach is to prescribe *statins* or *fibrates* to decrease blood lipid levels.[58] However, some patients encounter **side effects** with these drugs that range from muscle pain (*myalgia*) to very serious complications such as liver dysfunction and *rhabdomyolysis*, a condition in which damaged skeletal muscle is broken down, sometimes resulting in kidney failure.[59,60]

A series of studies on rats concluded that diets enriched with tart cherries improved multiple cardiovascular risk factors. These included a reduction in cholesterol, body fat, weight, and abdominal fat. Tart cherries also calmed inflammation at sites—such as the belly and heart—*specifically* linked to heart disease risk.[61-63]

Then, in 2011, scientists reported a **26**% **decrease in cholesterol** in mice given tart cherry powder, as well as a **65**% **reduction in early death**. This lower mortality was believed to be due to improved cardiovascular health.[62]

Turning their attention to *humans*, researchers investigated the impact of tart cherry juice on serum **triglycerides**. They reported in 2011 that consuming **8-ounce-daily** of tart cherry juice lowered triglycerides levels by over **17%** on average![44]

Together, these studies suggest that tart cherries promote cardiovascular health by safely lowering levels of cholesterol and triglycerides, as well as other risk factors.

Anti-Cancer Mechanisms

Studies have shown that berry anthocyanins—found in tart cherries—can **switch off genes** involved in the multiple pathways of **cancer**.

These include genes for ***cell proliferation*** and inflammation, and for ***angiogenesis*** (the growth of new blood vessels that feed a tumor).[14,64,65]

Anthocyanins can also trigger ***apoptosis***, the programmed cell death that causes pre-cancerous cells to self-destruct.[64,66]

These studies establish that anthocyanins work through a **network** of mechanisms to promote a broad spectrum of natural anticancer protection. And because there is a unique **synergy** among the anthocyanins and phenolic acids in tart cherries, scientists have been investigating them for their anticancer benefits.[7]

In mice, a diet of tart cherries inhibited both the incidence and size of *adenomas* (benign tumors) of the *cecum*, an area at the beginning of the large intestine that is a common site for colon cancer. In the same study, the growth of **human** colon cancer cell lines was shown to be reduced by tart cherry anthocyanins.[67]

Finally, in 2011, a review of past studies concluded that cherries exert a variety of anti-carcinogenic effects.[11]

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SWEET OR TART: WHICH TYPE OF CHERRY PACKS THE ***MOST POWERFUL*** PHENOL PUNCH?

Not all cherries contain the same type—let alone the same amounts—of potent compounds.

The two cultivated varieties of cherry are the sweet cherry *(Prunus avium L.)*, sometimes known as the wild cherry, and the tart cherry *(Prunus cerasus L.)*, sometimes known as sour cherry or pie cherry.

All cherries provide substantial quantities of antioxidants and other nutrients. But **tart cherries** deliver a much greater content of various anthocyanins than sweet cherries, as well as higher amounts of other phenolic compounds and other nutrients.[19]

But keep in mind that tart cherries are not the cherries you are likely to see at the grocery store, which will almost certainly be sweet cherries. The potent but less common tart cherries are chiefly used for baking and so usually come frozen, canned, dried, or juiced. Tart cherries may occasionally be located at a farmer's market. Fortunately, standardized extracts of tart cherries are available.

Superior Results

An impressive study released in 2013 reported that after 28 days of consumption, ***sweet*** cherries were found to selectively and significantly reduce a number of biomarkers associated with inflammatory diseases. Among other decreased inflammation indicators, blood levels of *C-reactive protein* were reduced by over **20%** and blood levels of *plasminogen activator inhibitor-1* were reduced by **19.9%**. And newly identified ligand for *advanced glycation end products* was slashed by a full **29%**![75]

The take-away message? If sweet cherries provide this degree of anti-inflammatory impact, try to imagine the powerful wallop you get from tart cherries—which pack twice the phenol content![19]

And tart cherries don't contain the sugar and calories found in sweet cherries.

What Cherry Suppliers Can't Tell You

A series of studies reporting on the compelling anti-inflammatory activity of ***sweet*** cherries—and especially **tart** cherries—has many scientists excited.

But not the Food and Drug Administration.

The agency has taken draconian steps to suppress this information. It may seem difficult to believe, but on October 17, 2005, the Food and Drug Administration issued an edict that precludes cherry companies from posting scientific data about cherries on their websites.[1,2] Letters from the agency went out to 29 companies warning them that if they continue to inform consumers about these scientific studies, ***criminal*** prosecutions will ensue.[1,2]

What can't cherry suppliers tell you? Simply this: tart cherries may well be the ultimate super food. Due to their superior phenolic matrix, tart cherry compounds help reduce the risk of osteoarthritis, gout, obesity, cardiovascular disease, metabolic syndrome, diabetes, and neurodegenerative diseases such as Parkinson's and Alzheimer's.

And **Life Extension**® will ***continue*** to report the latest scientific findings about tart cherries and their potent health benefits!

Optimal Metabolic Support

Metabolic syndrome—which often precedes the development of type II diabetes—is comprised of a spectrum of *phenotypes* (observable physical or biochemical characteristics), often associated with a high-fat diet.

A number of these metabolic syndrome phenotypes became significantly reduced—*after just 90 days*—in obesity-prone rats fed a diet comprised partly of whole tart cherry powder. These included a reduction in **fat** mass, **weight** around the abdomen, **hyperlipidemia** (elevated fats in the blood), and expression of **inflammation** markers, and *tumor necrosis factor*, along with other beneficial metabolic changes.[17]

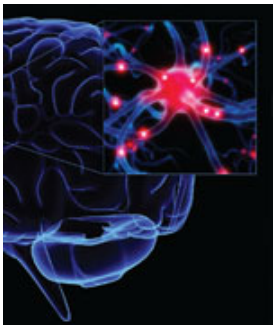
The research team concluded that, "Tart cherries may reduce the degree or trajectory of metabolic syndrome, thereby reducing risk for the development of type II diabetes."[17]

A 2005 investigation extracted phenols from both tart and sweet cherries for further analysis and reported that tart cherries have substantially higher concentrations of total **phenolics** than sweet cherries due to a much greater content of anthocyanins.[19]

Neurodegenerative Disease Defense

The combination of aging and oxidative stress can cause some neurons (nerve cells) in certain regions of the brain to die, contributing to **neurodegenerative disorders**[68] such as Alzheimer's,[69] Parkinson's,[69] and Huntington's[70] diseases, as well as amyotrophic lateral sclerosis (known as ALS or Lou Gehrig's Disease) and general cognitive decline.[68]

As the population ages, there is growing interest in the neuroprotective benefits of antioxidants,[71] and one scientific report concluded that rich sources of **polyphenolic** compounds, such as tart cherries, can play a role.[68]



Both sweet and tart cherries are known to contain a matrix of bioactive constituents that are characterized as beneficial against multiple degenerative diseases.[11,19]

But studies have now shown that ***tart cherries***, more than sweet cherries, act in a dose-dependent manner to **protect neurons** from cell-damaging oxidative stress.[19]

Tart cherries' richer content of phenolics, including anthocyanins, was shown to be responsible for this neuron defense—which the researchers described as "strong anti-neurodegenerative activity."[19]

Underlying Mechanisms of Action

To understand how tart cherries can target so many disease origins, it's important to appreciate their many underlying biochemical pathways. Extensive evidence demonstrates that these versatile components naturally:

- Inhibit ***cyclooxygenase-1*** and ***cyclooxygenase-2*** (COX-1 and COX-2) enzymes that help make inflammatory ***prostaglandins***.[7]
- Suppress ***nuclear factor-kappaB*** activation (linked to autoimmune reactions) in monocytes (a type of white blood cell)[17] and calm inflammatory factors in the body.[3-7,43,44]
- Switch off pivotal genes involved in cancer and inflammation[14-16,64,65] and switch on ***apoptosis***, the programmed death of potentially pre-cancerous cells.[64,66]
- Prevent lipoprotein peroxidation that leads to ***endothelial*** damage that causes white blood cells to cling to blood vessel walls.[72]
- Target cholesterol and triglycerides and improve some high-risk metabolic ***phenotypes***.[61-63]
- Aid in controlling blood glucose levels and interfere with glucose synthesis and release.[19,25,73,74]
- Boost detoxifying enzymes[12,21,22] and the natural body antioxidants ***glutathione peroxidase*** and ***superoxide dismutase***.[12,26]
- Lower blood levels of ***uric acid***.[44]
- Exert an analgesic activity,[32,34] inhibit oxidative stress,[68] ***neurodegeneration***,[19] and ***tumorigenesis***.[67]

Summary

Prolonged physical exertion, especially with advancing age, causes the inflammation, pain, redness, and swelling that indicate **muscle damage**.

Emerging data demonstrate that the anthocyanins, phenols, flavanols, and other constituents in **tart cherries** provide protection against muscle injury, inhibiting inflammation.

In fact, while nonsteroidal anti-inflammatory drugs such as *ibuprofen* (Advil®) and *naproxen* (Aleve®) involve potentially deadly side effects such as kidney failure, the molecules in tart cherries deliver anti-inflammatory impact safely.

The same potent effects that tart cherry compounds deliver to muscles similarly protect the entire body against an array of inflammation-associated pathologies. Unique compounds in tart cherries have been shown to substantially decrease the risk of osteoarthritis, cardiovascular disease, cancer, metabolic syndrome, and neurodegenerative diseases.

Tart cherry standardized anthocyanin extract has now been added to some multi-nutrient formulas and is also available as a standalone dietary supplement.

If you have any questions on the scientific content of this article, please call a Life Extension® Health Advisor at 1-866-864-3027.

References

1. Available at: http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/ComplianceEnforcement/ucm081724.htm (http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/%20ComplianceEnforcement/ucm081724.htm). Accessed February 27, 2013.
2. Available at: http://usatoday30.usatoday.com/news/health/2006-03-19-cherry-warnings_x.htm (http://usatoday30.usatoday.com/news/health/2006-03-19-cherry-warnings_x.htm). Accessed February 27, 2013.
3. Tall JM, Seeram NP, Zhao C, Nair MG, Meyer RA, Raja SN. Tart cherry anthocyanins suppress inflammation-induced pain behavior in rat. *Behav Brain Res*. 2004 Aug 12;153(1):181-8.
4. Seeram NP, Bourquin LD, Nair MG. Degradation products of cyanidin glycosides from tart cherries and their bioactivities. *J Agric Food Chem.* 2001;49:4924-9.
5. Wang H, Nair MG, Strasburg GM, et al. Antioxidant and anti-inflammatory activities of anthocyanins and their aglycon, cyanidin, from tart cherries. *J Nat Prod*. 1999;62:294-6.
6. Blando F, Gerardi C, Nicoletti I. Sour cherry *(Prunus cerasus L.)* anthocyanins as ingredients for functional foods. *J Biomed Biotechnol.* 2004;5:253-8.
7. Seeram NP, Momin RA, Nair MG, Bourquin LD. Cyclooxygenase inhibitory and antioxidant cyanidin glycosides in cherries and berries. *Phytomedicine.* 2001 Sep;8(5):362-9.
8. Conaghan PG. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. *Rheumatol Int.* 2012 Jun;32(6):1491-502.
9. Labianca R, Sarzi-Puttini P, Zuccaro SM, Cherubino P, Vellucci R, Fornasari D. Adverse effects associated with non-opioid and opioid treatment in patients with chronic pain. *Clin Drug Investig.* 2012 Feb;32 Suppl 1:53-63.
0. Gosslau A, Shiming L, Ho CT, Chen KY, Rawson NE. The importance of natural product characterization in studies of their anti-inflammatory activity. *Mol Nutr Food Res*. 2010;55:74-82.
11. McCune LM, Kubota C, Stendell-Hollis NR, Thomson CA. Cherries and health: a review. *Crit Rev Food Sci Nutr.* 2011 Jan;51(1):1-12.
2. Ferretti G, Bacchetti T, Belleggia A, Neri D. Cherry antioxidants: from farm to table. *Molecules*. 2010 Oct 12;15(10):6993-7005.
3. Mulabagal V, Lang GA, DeWitt DL, Dalavoy SS, Nair MG. Anthocyanin content, lipid peroxidation and cyclooxygenase enzyme inhibitory activities of sweet and sour cherries. *J Agric Food Chem.* 2009 Feb 25;57(4):1239-46.
4. Hou DX. Potential mechanisms of cancer chemoprevention by anthocyanins. *Curr Mole Med.* March 2003;3(2):149-59.
5. Seymour EM, Lewis A, Kirakosyan A, Bolling S. The effect of tart cherry-enriched diets on abdominal fat gene expression in rats. *J Am Diet Assoc*. 2008;108(9):A14-14E.
6. Seymour EM, Singer AA, Kirakosyan A, Urcuyo-Llanes DE, Kaufman PB, Bolling SF. Altered hyperlipidemia, hepatic steatosis, and hepatic peroxisome proliferator-activated receptors in rats with intake of tart cherry. *J Med Food.*2008 Jun;11(2):252-9.
7. Seymour EM, Lewis SK, Urcuyo-Llanes DE, Tanone II, Kirakosyan A, Kaufman PB, Bolling SF. Regular tart cherry intake alters abdominal adiposity, adipose gene transcription, and inflammation in obesity-prone rats fed a high fat diet. *J Med Food.* 2009 Oct;12(5):935-42.
8. Seymour EM, Kondoleon MG, Huang MG, Kirakosyan A, Kaufman PB, Bolling SF. Tart cherry-enriched diets reduce atherosclerosis and mortality in mice. *FASEB J.* Apr 2011;25(Meeting Abstract Supplement):980.10.
9. Kim DO, Heo HJ, Kim YJ, Yang HS, Lee CY. Sweet and sour cherry phenolics and their protective effects on neuronal cells. *J Agric Food Chem*. 2005;53:9921-7.
20. Halvorsen BL, Carlsen MH, Phillips KM, Bohn SK, Holte K, Jacobs DR, Blomhoff R. Content of redox-active compounds (i.e., antioxidants) in foods consumed in the United States. *Am J Clin Nutr.* 2006;84:95-135.
21. Shih PH, Yeh CT, Yen GC. Anthocyanins induce activation of phase II enzymes through the antioxidant response element pathway against oxidative stress-induced apoptosis. *J Agric Food Chem.* 2007;55:9427-35.
22. Nguyen T, Sherratt PJ, Pickett CB. Regulatory mechanisms controlling gene expression mediated by the antioxidant response element. *Annu Rev Pharmacol Toxicol.* 2003;43:233-60.

23. Kang SY, Seeram NP, Nair MG, Bourquin LD. Tart cherry anthocyanins inhibit tumor development in Apc(Min) mice and reduce proliferation of human colon cancer cells. *Cancer Lett*. 2003 May 8;194(1):13-9.
24. Thomasset S, Teller N, Cai H, et al. Do anthocyanins and anthocyanidins, cancer chemopreventive pigments in the diet, merit development as potential drugs? *Cancer Chemoth Pharm.* 2009 June;64(1):201-11.
25. Lachin T, Reza H. Anti diabetic effect of cherries in alloxan induced diabetic rats. *Recent Pat Endocr Metab Immune Drug Discov.* 2012 Jan;6(1):67-72.
26. Sarić A, Sobocanec S, Balog T, et al. Improved antioxidant and anti-inflammatory potential in mice consuming sour cherry juice (Prunus Cerasus cv. Maraska). *Plant Foods Hum Nutr.* 2009 Dec;64(4):231-7.
27. Neme Ide B, Alessandro Soares Nunes L, Brenzikofer R, Macedo DV. Time course of muscle damage and inflammatory responses to resistance training with eccentric overload in trained individuals. *Mediators Inflamm.* 2013;2013:204942. Epub 2013 Jan 22.
28. Howatson G, Van Someren KA: The prevention and treatment of exercise-induced muscle damage. *Sports Med*. 2008;38:483-503.
29. Morton JP, Kayani AC, McArdle A, Drust B. The exercise-induced stress response of skeletal muscle, with specific emphasis on humans. *Sports Med.* 2009;39(8):643-62.
30. Morley JE, Baumgartner RN, Roubenoff R, Mayer J, Nair KS. Sarcopenia. *J Lab Clin Med.* 2001 Apr;137(4):231-43.
31. Ducharme NG, Fortier LA, Kraus MS, et al. Effect of a tart cherry juice blend on exercise-induced muscle damage in horses. *Am J Vet Res.* 2009 Jun;70(6):758-63.
32. Kuehl KS, Perrier ET, Elliot DL, Chesnutt JC. Efficacy of tart cherry juice in reducing muscle pain during running: a randomized controlled trial. *Journal Int Soc Sports.* 2010;7:17.
33. Howatson G, McHugh MP, Hill JA, et al. Influence of tart cherry juice on indices of recovery following marathon running. *Scand J Med Sci Sports.* 2010;20:843-52.
34. Connolly DAJ, McHugh MP, Padilla-Zakour OI. Efficacy of a tart cherry juice blend in preventing the symptoms of muscle damage. *Br J Sports Med*. 2006;40:679-83.
35. Bowtell JL, Sumners DP, Dyer A, Fox P, Mileva KN. Montmorency cherry juice reduces muscle damage caused by intensive strength exercise. *Med Sci Sports Exerc.* 2011;43:1544-51.
36. Available at: http://www.cdc.gov/arthritis/data_statistics/arthritis_related_stats.htm#2 (http://www.cdc.gov/arthritis/data_statistics/arthritis_related_stats.htm#2). Accessed March 1, 2013.
37. Available at: http://www.nlm.nih.gov/medlineplus/osteoarthritis.html (http://www.nlm.nih.gov/medlineplus/osteoarthritis.html). Accessed March 1, 2013.
38. Available at: http://www.arthritis.org/conditions-treatments/disease-center/osteoarthritis/ (http://www.arthritis.org/conditions-treatments/disease-center/osteoarthritis/). Accessed March 1, 2013.
39. Available at: http://med.stanford.edu/ism/2011/november/osteoarthritis.html (http://med.stanford.edu/ism/2011/november/osteoarthritis.html). Accessed March 1, 2013.
40. Available at: http://www.arthritistoday.org/conditions/osteoarthritis/treatment/oa-medications.php (http://www.arthritistoday.org/conditions/osteoarthritis/treatment/oa-medications.php). Accessed March 1, 2013.
41. Zhao YL, Zhou GD, Yang HB, et al. Rhein protects against acetaminophen-induced hepatic and renal toxicity. *Food Chem Toxicol*. 2011 Aug;49(8):1705-10.
42. Available at: http://media.baylorhealth.com/releases/Can-Cherries-Relieve-the-Pain-of-Osteoarthritis (http://media.baylorhealth.com/releases/Can-Cherries-Relieve-the-Pain-of-Osteoarthritis). Accessed March 1, 2013.
43. Kuehl KS, Elliot DL, Sleigh A, Smith J. Efficacy of tart cherry juice to reduce inflammation biomarkers among women with inflammatory osteoarthritis. *J Food Stud.* 2012;1:14-25.
44. Martin KR, Bopp J, Burrell L, Hook G. The effect of 100% tart cherry juice on serum uric acid levels, biomarkers of inflammation and cardiovascular disease risk factors. *FASEB J*. April 2011;25 (Meeting Abstract Supplement):339.2.
45. Available at: http://www.niams.nih.gov/health_info/Gout/gout_ff.asp (http://www.niams.nih.gov/health_info/Gout/gout_ff.asp). Accessed March 1, 2013.
46. Available at: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682673.html#side-effects (http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682673.html#side-effects). Accessed March 1, 2013.
47. Available at: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682395.html#side-effects

(http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682395.html#side-effects). Accessed March 1, 2013.
48. Available at: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682395.html#precautions (http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682395.html#precautions). Accessed March 1, 2013.
49. Available at: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682673.html#precautions (http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682673.html#precautions). Accessed March 1, 2013.
50. Zhang Y, Neogi T, Chen C, Chaisson C, Hunter DJ, Choi HK. Cherry consumption and decreased risk of recurrent gout attacks. *Arthritis Rheum*. 2012 Dec;64(12):4004-11. doi: 10.1002/art.34677.
51. McDade TW. Early environments and the ecology of inflammation. Proc Natl Acad Sci USA. 2012 Oct 16;109 Suppl 2:17281-8.
52. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab.* 2004;89(6):2548-56.
53. Calder PC, Ahluwalia N, Brouns F, et al. Dietary factors and low-grade inflammation in relation to overweight and obesity. *Br J Nutr.* 2011 Dec;106 Suppl 3:S5-78.
54. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes.* 2007;56:1010-3.
55. Bachstetter AD, Norris CM, Sompol P, et al. Early stage drug treatment that normalizes proinflammatory cytokine production attenuates synaptic dysfunction in a mouse model that exhibits age-dependent progression of Alzheimer's disease-related pathology. *J Neurosci.* 2012 Jul 25;32(30):10201-10.
56. Bulló M, García-Lorda P, Megias I, Salas-Salvadó J. Systemic inflammation, adipose tissue tumor necrosis factor, and leptin expression. *Obes Res.* 2003 Apr;11(4):525-31.
57. Ference BA, Mahajan N. The role of early LDL lowering to prevent the onset of atherosclerotic disease. *Curr Atheroscler Rep.* 2013 Apr;15(4):312.
58. Ginsberg HN, Bonds DE, Lovato LC, et al. Evolution of the lipid trial protocol of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Am J Cardiol.* 2007 Jun 18;99(12A):56i-67i. Epub 2007 Apr 12.
59. Hippisley-Cox, J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ*. 2010 May 20;340:c2197.
60. Golomb BA, Evans MA. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. *Am J Cardiovasc Drugs.* 2008;8(6):373-418.
61. Seymour EM, Urcuyo-Llanes D, Bolling SF, Bennink MR. Tart cherry intake reduces plasma and tissue inflammation in obesity-prone rats. *FASEB J.* 2010 April;24(Meeting Abstract Supplement):335.1.
62. Seymour EM, Kondoleon MG, Huang MG, Kirakosyan A, Kaufman PB, Bolling SF. Tart cherry-enriched diets reduce atherosclerosis and mortality in mice. *FASEB J.* 2011 March;25(Meeting Abstract Supplement):980.10.
63. Seymour EM, Urcuyo-Llanes D, Kirakosyan A, Kaufman PB, Bolling SF. Comparative impact of tart cherry-enriched diets on metabolic syndrome and inflammation in rats fed high versus low carbohydrate diets. *FASEB J.* 2008 March;22(Meeting Abstract Supplement):702.7.
64. Wang LS, Stoner GD. Anthocyanins and their role in cancer prevention *Cancer Lett*. 2008 Oct 8;269(2):281-90.
65. Bagchi D, Sen CK, Bagchi M, Atalay M. Anti-angiogenic, antioxidant, and anti-carcinogenic properties of a novel anthocyanin-rich berry extract formula. *Biochemistry (Mosc).* 2004 Jan;69(1):75-80, 1 p preceding 75.
66. Hou DX, Ose T, Lin S, et al. Anthocyanidins induce apoptosis in human promyelocytic leukemia cells: structure-activity relationship and mechanisms involved. *Int J Oncol*. 2003 Sep;23(3):705-12.
67. Kang SY, Seeram NP, Nair MG, Bourquin LD. Tart cherry anthocyanins inhibit tumor development in Apc(Min) mice and reduce proliferation of human colon cancer cells. *Cancer Lett*. 2003 May 8;194(1):13-9.
68. Schroeter H, Spencer JPE, Rice-Evans C, Williams RJ. Flavonoids protect neurons from oxidized low-density-lipoprotein-induced apoptosis involving c-Jun N-terminal kinase (JNK), c-Jun and caspase-3. *Biochem. J.* 2001;358:547-57.
69. Halliwell B. Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment. *Drugs Aging.*2001;18(9):685-716.
70. Alexi T, Borlongan CV, Faull RLF, et al. Neuroprotective strategies for basal ganglia degeneration: Parkinson's and Huntington's diseases. *Progr. Neurobiol.* 2000;60:409-70.
71. Cantutui-Castelvetri I, Shukitt-Hale B, Joseph JA. Neurobehavioral aspects of antioxidants in aging. *Int. J. Dev.*

Neurosci. 2000;18:367-81.
12. Wang H, Nair MG, Strasburg GM, Booren AM, Gray JI. Antioxidant polyphenols from tart cherries (Prunus cerasus). *J Agric Food Chem.* 1999 Mar;47(3):840-4.
13. Johnston KL, Clifford MN, Morgan LM. Coffee acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans: glycemic effects of chlorogenic acid and caffeine. *Am J Clin Nutr.* 2003 Oct;78(4):728-33.
14. Hemmerle H, Burger HJ, Below P, et al. Chlorogenic acid and synthetic chlorogenic acid derivatives: novel inhibitors of hepatic glucose-6-phosphate translocase. *J Med Chem.* 1997 Jan 17;40(2):137-45.
15. Kelley DS, Adkins Y, Reddy A, Woodhouse LR, Mackey BE, Erickson KL. Sweet Bing cherries lower circulating concentrations of markers for chronic inflammatory diseases in healthy humans. *J Nutr.* 2013;143:340-4.