

Ibuprofen and Running

Negative effects and novel nutritional substitutes.

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The 100-mile Western States Endurance Run (WSER) is an arduous mountain race in California reserved for the top tier of ultramarathon athletes. The trail racecourse starts at Squaw Valley, ascends 2,500 feet to Emigrant Pass (8,800 feet, the highest point) within the first four miles, and then passes through remote and rugged territory to Auburn. The total altitude gain and loss during the race are 18,000 feet and 23,000 feet, respectively. The race starts at 5:00 A.M., and most runners take about 26 to 27 hours to finish the race.

About a decade ago, I was contacted by Dr. Bob Lind, the medical director of the WSER. During more than 30 years of service to the athletes competing in this grueling mountain race, he had noticed that more than an expected number of the older runners were being diagnosed with cancer. After discussing this issue with the WSER medical board, Dr. Lind invited my research team to conduct a series of studies to investigate whether the physiologic and immunologic demands of competing in the WSER were beyond the limits of what the human body could tolerate.

Over a span of five years, my research team collected data and blood samples from 350 WSER endurance runners. We published multiple papers showing that the WSER was stressful to the immune system, with 25 percent of WSER athletes developing upper respiratory tract infections (URTI) during the two-week period following the summer race (for review, see Nieman 2009). The killing capacity of neutrophils fell by 50 percent during the race, limiting the immune system's upfront ability to kill foreign pathogens (Henson et al. 2008). The immune changes we measured in WSER ultramarathoners were comparable to those measured in marathon runners after running 42.2-kilometer marathon races, but the long duration of the WSER meant that the physiologic and immune stressors were sustained five to 10 times longer.

Some WSER athletes have competed in more than 100 ultramarathon races, and although the long-term effect on health and disease remains to be determined, every indication is that the repeated physiologic and immunologic insult is an unhealthy stressor. I have run 58 marathons and ultramarathons, including the 72-mile race around Lake Tahoe in California, so I understand the satisfaction of training and competing in long-distance races as well as the pain and potential health sacrifice of pushing a good thing (such as exercise) too far.

During and following the race, WSER runners developed significant muscle damage and soreness leading to unusually high inflammation (Nieman et al. 2003, 2005, 2006a, 2006b, 2007a). For example, serum C-reactive protein, an inflammatory protein from the liver, climbed to 32 mg/L, one of the highest values ever reported after exercise. To cope with the pain and inflammation, 70 percent of WSER athletes used ibuprofen (Nieman et al. 2006a).

An unexpected finding was that ibuprofen use was ineffective and potentially harmful. We showed that ibuprofen users (600 mg and 1,200 mg ibuprofen the day before and during the race, respectively) compared with nonusers experienced the same degree of muscle damage and soreness. Moreover, ibuprofen use caused a small leakage of colon bacteria into the circulation that promoted even more inflammation (25 percent to 88 percent, depending on the biomarker) and oxidative stress, with a side effect of mild kidney dysfunction (McAnulty et al. 2007a, 2007b; Nieman et al. 2006a). We were unable to measure any benefit of using ibuprofen by WSER athletes, only harm (Nieman et al. 2005, 2006a). Every indication from our research showed that ibuprofen amplified inflammation and oxidative stress while providing no relief from exercise effort or muscle damage and soreness.



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▲ Ibuprofen is commonly used by endurance athletes but has no proven efficacy. The best evidence shows that ibuprofen amplifies inflammation and oxidative stress and impairs kidney function in long-distance runners.

A majority of other investigators have also reported no beneficial effect of ibuprofen in alleviating muscle soreness and damage after exercise-induced muscle injury (Pizza et al. 1999; Trappe et al. 2002). Thus the high prevalence of ibuprofen use by ultramarathon athletes appears to have few if any physiological or performance benefits (Nieman et al. 2005, 2006a).

Plant extracts as ibuprofen substitutes

I presented the research findings to the WSER athletes in two medical symposiums. Feedback from the athletes made it clear to me that the runners strongly believed ibuprofen helped them, despite my findings, and that only a better substitute would make them stop its use. My research group has spent much time and effort working on an ibuprofen substitute, and we are closing in on a flavonoid-based product that appears efficacious.

Flavonoids provide many of the colors in fruits and vegetables where they serve as defenders against invading microbes, radiation from the sun, and other environmental insults (Lila 2007). Whether flavonoids have similar functions in humans is a hot topic among scientists, but there is growing support for multiple health and fitness benefits. Flavonoids are the major subgroup of phytochemicals—or put more simply, plant chemicals. The latest count lists more than 6,000 flavonoids, and the US Department of Agriculture (USDA) sorts them into six subgroups (USDA 2011).

Most people consume between 50 and 800 mg of flavonoids a day, depending on their intake of fruits, vegetables, and tea (Chun et al. 2010). A medium Gala apple has 24 mg total flavonoids, banana 15 mg, cup of orange juice 35 mg, half cup of blueberries 150 mg, and cup of black tea 280 mg (USDA 2007). If you like green tea, one cup provides a hefty 320 mg of flavonoids, with much of this from epigallocatechin 3-gallate, or EGCG. Americans take in only about 210 mg flavonoids per day, well below the 313 mg/day in Spain (Chun et al. 2010). For both Americans and Europeans, the most important flavonoid sources are tea, citrus fruits and juices, beers and ales, wines, melons and berries, apples, onions, and bananas.

Most flavonoids when studied in the lab in purified form operate as strong anti-inflammatory and antioxidative agents. Interestingly, a big dose of just one type of flavonoid is not nearly as beneficial as a mixture of many different flavonoids (Lila 2007). There is a growing realization that the healthful effects of single types of flavonoids are potentiated when mixed with other flavonoids. Flavonoids ingested together improve absorption and overall anti-inflammatory and antioxidative effects in the body. The plant uses a matrix of flavonoids for protection, and in similar fashion, a flavonoid “cocktail” provides a multifaceted defensive strategy for humans.

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▲ Extracts from blueberries and other fruits are being investigated as ibuprofen substitutes. Studies show that cocktails of fruit and vegetable extracts mitigate exercise-induced inflammation and oxidative stress.

Flavonoid-rich plant extracts are being tested by an increasing number of investigative teams as performance aids and countermeasures to exercise-induced inflammation, delayed onset of muscle soreness (DOMS), and oxidative stress (Nieman et al. 2010). Examples include freeze-dried or condensed formulations of blueberries, black currants, tart cherries, blended juices, green tea, and flavonoid cocktails. Most studies have focused on whether flavonoid-rich teas and fruit extracts can counter oxidative stress and inflammation after exercise, and a growing number of investigators report positive results (Hurst et al. 2010; Lyall et al. 2009; McAnulty et al. 2011). The dosing regimen is still under scientific scrutiny, but most studies support one to three weeks of supplementation with an extract or flavonoid cocktail before beneficial changes can be measured. In other words, flavonoid-rich extracts need a loading period prior to heavy exertion and cannot be taken immediately before and during race events like ibuprofen can.

More exercise-related research has been conducted with quercetin than with any other flavonoid (Nieman 2010). Quercetin is found in apple skins, onions, berries, peppers, and many other fruits and vegetables. In one of the earliest studies with exercise-stressed cyclists, my research group showed that supplementation with pure quercetin (1,000 mg/day) over a five-week period reduced illness rates but did not counter postexercise inflammation, oxidative stress, or immune dysfunction

(Nieman et al. 2007b). In a follow-up study using a similar design, two weeks of quercetin supplementation combined with green tea extract, isoquercetin, and fish oil caused a sizeable reduction in exercise-induced inflammation and oxidative stress (McAnulty et al. 2011; Nieman et al. 2009). In other words, this quercetin-based cocktail functioned as an excellent ibuprofen substitute.

At the very least, I recommend a flavonoid-rich diet with a variety of fruits and vegetables for all individuals seeking health but especially for those who experience the physiologic stress of a heavy exercise schedule. Before and during heavy training periods, the use of flavonoid-rich products such as blueberry, tart cherry, and black currant extracts, or quercetin mixed with green tea extract and fish oil for one or two weeks, should lessen inflammation and oxidative stress. More and more of these types of products will become available soon and should help lower the use of ibuprofen by long-distance runners. What is interesting to me as a researcher is how entrenched ibuprofen use is in the running community despite the lack of supportive research evidence and mounting data indicating potential harm. If I am missing something, let me know (niemandc@appstate.edu). Meanwhile, I will continue my mission of finding a healthy, plant-based alternative to ibuprofen.

References

- Chun, O. K., A. Floegel, S. J. Chung, C. E. Chung, W. O. Song, and S. I. Koo. 2010. Estimation of antioxidant intakes from diet and supplements in U.S. adults. *Journal of Nutrition* 140(2):317-324.
- Henson, D. A., D. C. Nieman, J. M. Davis, C. L. Dumke, S. J. Gross, E. A. Murphy, M. D. Carmichael, D. P. Jenkins, J. C. Quindry, S. R. McAnulty, L. S. McAnulty, A. C. Utter, and E. P. Mayer. 2008. Post-160-km race illness rates and decreases in granulocyte respiratory burst and salivary IgA output are not countered by quercetin ingestion. *International Journal of Sports Medicine*. 29(10):856-863.
- Hurst, R. D., R. W. Wells, S. M. Hurst, T. K. McGhie, J. M. Cooney, and D. J. Jensen. 2010. Blueberry fruit polyphenolics suppress oxidative stress-induced skeletal muscle cell damage in vitro. *Molecular Nutrition & Food Research* 54(3):353-363.
- Lila, M. A. 2007. From beans to berries and beyond: teamwork between plant chemicals for protection of optimal human health. *Annals of the New York Academy of Sciences* 1114:372-380.
- Lyall, K. A., S. M. Hurst, J. Cooney, D. Jensen, K. Lo, R. D. Hurst, and L. M. Stevenson. 2009. Short-term blackcurrant extract consumption modulates exercise-induced oxidative stress and lipopolysaccharide-stimulated inflammatory responses. *American Journal of Physiology—Regulatory, Integrative and Comparative Physiology* 297(1):R70-R81.
- McAnulty, S. R., L. S. McAnulty, D. C. Nieman, J. D. Morrow, C. L. Dumke, and D. A. Henson. 2007a. Effect of NSAID on muscle injury and oxidative stress. *International Journal of Sports Medicine* 28(11):909-915.
- McAnulty, S.R., D. C. Nieman, L. S. McAnulty, W. S. Lynch, F. Jin, and D. A. Henson. 2011. Effect of mixed flavonoids, n-3 fatty acids, and vitamin C on oxidative stress

and antioxidant capacity before and after intense cycling. *International Journal of Sport Nutrition and Exercise Metabolism* 21(4):328-337.

- McAnulty, S. R., J. T. Owens, L. S. McAnulty, D. C. Nieman, J. D. Morrow, C. L. Dumke, and G. L. Milne. 2007b. Ibuprofen use during extreme exercise: effects on oxidative stress and PGE2. *Medicine & Science in Sports & Exercise* 39(7):1075-1079.
- Nieman, D. C. 2009. Immune function responses to ultramarathon race competition. *Medicina Sportiva* 13(4):189-196.
- Nieman, D. C. 2010. Quercetin's bioactive effects in human athletes. *Current Topics in Nutraceutical Research* 8(1):33-44.
- Nieman, D. C., C. L. Dumke, D. A. Henson, S. R. McAnulty, S. J. Gross, and R. H. Lind. 2005. Muscle damage is linked to cytokine changes following a 160-km race. *Brain, Behavior, and Immunity* 19(5):398-403.
- Nieman, D. C., C. L. Dumke, D. A. Henson, S. R. McAnulty, L. S. McAnulty, R. H. Lind, and J. D. Morrow. 2003. Immune and oxidative changes during and following the Western States Endurance Run. *International Journal of Sports Medicine* 24(7):541-547.
- Nieman, D. C., D. A. Henson, J. M. Davis, C. L. Dumke, S. J. Gross, D. P. Jenkins, E. A. Murphy, M. D. Carmichael, J. C. Quindry, S. R. McAnulty, L. S. McAnulty, A. C. Utter, and E. P. Mayer. 2007a. Quercetin ingestion does not alter cytokine changes in athletes competing in the Western States Endurance Run. *Journal of Interferon & Cytokine Research* 27(12):1003-1012.
- Nieman, D. C., D. A. Henson, C. L. Dumke, K. Oley, S. R. McAnulty, J. M. Davis, E. A. Murphy, A. C. Utter, R. H. Lind, L. S. McAnulty, and J. D. Morrow. 2006a. Ibuprofen use, endotoxemia, inflammation, and plasma cytokines during ultramarathon competition. *Brain, Behavior, and Immunity* 20(6):578-584.
- Nieman, D. C., D. A. Henson, C. L. Dumke, R. H. Lind, L. R. Shooter, and S. J. Gross. 2006b. Relationship between salivary IgA secretion and upper respiratory tract infection following a 160-km race. *The Journal of Sports Medicine and Physical Fitness* 46(1):158-162.
- Nieman, D. C., D. A. Henson, S. J. Gross, D. P. Jenkins, J. M. Davis, E. A. Murphy, M. D. Carmichael, C. L. Dumke, A. C. Utter, S. R. McAnulty, L. S. McAnulty, and E. P. Mayer. 2007b. Quercetin reduces illness but not immune perturbations after intensive exercise. *Medicine & Science in Sports & Exercise* 39(9):1561-1569.
- Nieman, D. C., D. A. Henson, K. R. Maxwell, A. Williams, S. R. McAnulty, F. Jin, R. A. Shanely, and T. C. Lines. 2009. Effects of quercetin and EGCG on mitochondrial biogenesis and immunity. *Medicine & Science in Sports & Exercise* 41(7):1467-1475.
- Nieman, D. C., S. J. Stear, L. M. Castell, and L. M. Burke. 2010. A-Z of nutritional supplements: dietary supplements, sports nutrition foods and ergogenic aids for health and performance: part 15, flavonoids. *British Journal of Sports Medicine* 44(16):1202-1205.
- Pizza, F. X., D. Cavender, A. Stockard, H. Baylies, and A. Beighle. 1999. Anti-inflammatory doses of ibuprofen: effect on neutrophils and exercise-induced muscle injury. *International Journal of Sports Medicine* 20(2):98-102.
- Trappe, T. A., F. White, C. P. Lambert, D. Cesar, M. Hellerstein, and W. J. Evans. 2002. Effect of ibuprofen and acetaminophen on postexercise muscle protein synthesis. *American Journal of Physiology—Endocrinology and Metabolism* 282(3):E551-E556.
- US Department of Agriculture, Agricultural Research Service. 2011. USDA Database for the Flavonoid Content of Selected Foods, Release 3.0. Nutrient Data Laboratory Home Page: <http://www.ars.usda.gov/nutrientdata/flav>.

