**Berries and Their effects on Oxidative Stress and Inflammation**

**Introduction**

**The purpose for this article is to review the effects that berries have blood biomarkers of oxidative stress and on inflammation in the body and to see if consuming berries in the diet leads to lower cellular inflammation in participants in randomized clinical control trials.** These studies claim to be the first studies that review the effects that berries have on specific blood levels that correspond with oxidative stress and inflammation. These studies specifically look at the relationship between HbA1c, hs-CRP, Serum IL-6, IL-1β, MMP-3, 8-OHdG, plasma GR, GPx, serum SOD, Serum OxLDL, COX-2, IFN-γ, inducible nitric oxide synthase, and levels of MDA (an oxidative stress markers, and LDL cholesterol levels. Furthermore, lower blood lipid levels of Inflammatory biomarkers may be due to daily berry consumption and decrease oxidative stress and cellular inflammation.

**Review of Articles**

 **In the article “Strawberries Improve Pain and Inflammation in Obese Adults with Radiographic Evidence of Knee Osteoarthritis,” 17 participants were randomized into two different groups, one received a 50 g drink of freeze-dried strawberry powder reconstituted in water, and the other received a 50 g control (placebo) drink composed of a powder that was created to mimic the sensory properties of the freeze-dried strawberry powder in caloric value and nutrient composition. Participants were required to consume their respected drinks twice a day over the course of 12 weeks, followed by a 2- week washout phase. They then had a cross-over trial switching the two groups for another 12 weeks. The overall duration of the study was 26 weeks, during which Researchers measured the differences in blood serum tests, assessments of pain, and quality of life indicators. 1** Researchers conducted a randomized, double- blind cross-over trial over the duration of 26 weeks’ total where they assessed whether the selected biomarkers on inflammation and cartilage degradation, as well as knee pain scores, were different between the strawberry and the placebo phases at 12 vs. 26 weeks of the crossover study. The purpose of conducting the study was to examine the effects of freeze-dried strawberries on pain symptoms and on circulating biomarkers of inflammation and cartilage degradation in obese adults with knee OA. For eligibility into this study, participants were required to be obese adults with radiographic evidence of knee Osteoarthritis (OA) but without fractures or dislocations. Individuals were not approved to participate in the study if they have had previous knee surgeries, rheumatoid arthritis, a metabolic disorder, liver or kidney failure, are pregnant or are lactating, have used corticosteroids or intra-articular injections during the preceding 3 months, use of fish oils and glucosamine, participated in a weight loss program in the preceding 6 months, and recent changes in physical activity levels, smoke regularly, or have an allergy to strawberries. Measurements for assessing blood tests pain levels of the individuals, and quality of life were used with the Visual Analog Scale for Pain (VAS Pain), Measures of Intermittent and Constant Osteoarthritis Pain (ICOAP), and Health Assessment Questionnaire- Disability Index (HAQ-DI) questionnaires, which were completed at weeks 12, 14, and 26 of the study. In regards to inflammation, participants were tested for serum glucose, lipid profiles, HbA1c, and high-sensitivity C-reactive protein (hs-CRP) in their blood samples by using an automated clinical analyzer. Serum IL-6, IL-1β, and MMP-3 and 8 were measured using ELISA kits. Researchers found that Serum IL-6 and IL-1β, were significantly lower in the strawberry vs. control phase at week 12. They concluded that there was a significant decrease in IL-6, IL-1β, and MMP-3 in obese participants with knee OA, consistent with anti-inflammatory effects of dietary berries in OA management. Therefore, the confirmed that strawberry bioactive compounds can improve pain and inflammation in obese adults with OA.

**I am rating this article as neutral.** The researchers were very strong with including a randomized, controlled cross-over study design, they included double- blinding in their study, and they controlled the confounding variables in their study. **However, the reason why I am rating this article as neutral is that, even though the article had all the makings of being a strong article in detail and in content, the sample size of the participants was 17 which is way too low in order to completely validate the findings of the study. They also failed to provide a non-OA control group for the study.**

**The second article reviewed, “Effects of daily blueberry consumption on circulating biomarkers of oxidative stress, inflammation, and antioxidant defense in postmenopausal women with pre- and stage 1-hypertension: a randomized controlled trial,” had 40 postmenopausal women with pre-and stage 1-hypertension randomized into two different groups, one received 22g of freeze-dried highbush blueberry powder per day, while the other group received 22g of a placebo powder (the Control) per day for a duration of 8 weeks regarding the effects that freeze-dried highbush blueberry powder has on oxidative stress and inflammation in the participants.2** Researchers composed a randomized, parallel-arm, double-blind, placebo controlled clinical trial evaluating the blood biomarker of oxidative DNA damage, 8-hydroxyl-21- deoxyguanosine (8-OHdG), and oxidative stress, inflammation, and antioxidant defense. Tests were analyzed at a baseline of 4 and 8 weeks during the study. The participants were randomized to their respected groups by using a computer pre-generated randomization list provided by the statistician and performed by the study coordinator. The participants were advised not to alter their habitual diet and exercise regime during the course of the study. The results of the study were that at 4 weeks’ plasma 8-OHdG concentrations were significantly lower in the group that consumed the blueberry powder drink compared to the control group. However, at 8 weeks there was no statistically significant difference between the plasma 8-OHdG concentrations between the two groups. The Serum TNF-α concentrations were significantly reduced at both 4 and 8 weeks in both the group that consumed the blueberry powder drink and the control group. The plasma GR, GPx, and serum SOD were significantly increased at both 4 and 8 weeks in both groups. Serum OxLDL concentrations were significantly reduced at 4 weeks but not 8 weeks in both groups. And finally, 8-isoprostane levels were significantly reduced in the group that consumed the blueberry powder drink at 8 weeks. Overall, the results of this study concluded that there is no statistically significant difference over an extended amount of time between blood biomarkers of oxidative stress, inflammation, and antioxidant defense between the group that consumed the blueberry powder drink and the control group. However, over the course of 4 weeks, there was a statistically significant difference between the blood biomarkers of oxidative stress, inflammation, and antioxidant defense between the two groups. Because the improvements in oxidative DNA damage and inflammation was not sustainable at 8 weeks, blueberry consumption over 8 weeks cannot be confirmed in successfully improving inflammation over a long period of time according to this specific study. However, at 4 weeks, daily consumptions of blueberries provide modest protection against oxidative DNA damage and inflammation.

**I am rating this article as positive because it is an exceptionally strong article.** This article was very thorough in the details and procedures of the study. The authors included all aspects of an exceptional article as well as listing their limitations, strengths, and explaining their findings.

**The third article reviewed, “Preventive and therapeutic effects of blueberry (*Vaccinium corymbosum*) extract against DSS- induced ulcerative colitis by regulation of antioxidant and inflammatory mediators,” had a total of 42 seven-week-old female mice weighing between 20 and 22g randomized into six different groups, each group consisting of 7 mice. The groups that the mice were put into were a control group and recieved an untreated drinking water for 14 days; the DSS group received 3% DSS in drinking water for 7 days, followed by regular tap water for 7 days; the BE group received 50 mg/kg body weight BE (84 mg/kg fresh weight equivalent of blueberry) for 14 days; the BE prevention group received 50 mg/kg body weight BE (84 mg/kg fresh weight equivalent of blueberry) for 14 days and 3% DSS in drinking water for the last 7 days of BE administration; the BE treatment group received 3% DSS in drinking water for 7 days and 50 mg/kg body weight BE for 7 days after DSS administration; and the sulfasalazine group received 50 mg/kg body weight sulfasalazine orally for 7 days and after 7 days of 3% DSS administration. Researchers used this study to observe the effects that blueberry extract (BE) has on inflammatory diseases, such as ulcerative colitis, in rats.3** All rats in the study were controlled in an artificial environment, where researchers controlled, what they ate and drank, their exercise, and their environmental conditions. CAT and SOD activities in serum sample were measured using kits from the Cayman Chemical Company. Enzyme activity was expressed as nmol/min/mg/tissue. Results after oral administration of DSS showed significant bowel wall thickening, inflammation, and ulcers in both the BE prevention and BE treatment groups in comparison to the DSS group. In the DSS treated group, Inflammation was present through the mucosa, muscularis mucosae, and submucosa of the colonic tissue of the specimen. After dietary treatment with BE, histological analysis showed a reduction in overall cell damage, and a decrease in cellular inflammation. Evidence showed that positive staining for IL-1β was significantly higher in the epithelial cells of the damaged colon with cellular inflammation in the DSS treated group of mice. The effects of BE on messenger RNA expression of proinflammatory cytokines was also assessed and resulted in significantly higher levels of proinflammatory cytokines COX-2, IFN-γ, inducible nitric oxide synthase, and IL-1β of colon tissues compared to the control group. The researchers of this study concluded that levels of MDA (an oxidative stress marker) was significantly higher in the DSS group than in all the other groups. BE was found to significantly downregulate COX-2 and IL-1β expression in the colon of the specimen. They noted that BE activates certain antioxidant functions and suppresses oxidative stress and inflammation in the colon.

The overall content and procedures of this article were exemplary and very thorough, so thorough that it was hard to understand what the information was stating because there was too much information for the reader to process. **I am rating this article as neutral because although they had an extensive amount of information and followed procedure correctly for their study, the information and the way they presented it was no clear enough for the reader to understand, they also failed to list the limitations of their study, which would have been beneficial information for the reader.**

**The fourth article reviewed, “Aronia berry polyphenol consumption reduces plasma total and low-density lipoprotein cholesterol in former smokers without lowering biomarkers of inflammation and oxidative stress: a randomized controlled trial,” had 49 healthy adults who were previous smokers randomized into two groups, one who received 500 mg or aronia extract in capsule form or a placebo capsule composed of rice powder for 12 weeks to determine if aronia polyphenols could significantly reduce plasma lipids and biomarkers of oxidative stress and inflammation in former somkers.4** The eligibility of the participants of the subjects was determined by screening of past pertinent medical history and a questionnaire including an average number of cigarettes smoked per day before smoking cessation, determining BMI, waist circumference, blood pressure, and a fasting blood sample for blood glucose and TC levels of the prospected participants. Participants were asked to complete a 3-day dietary record before the test commenced. Both, before and after the study was completed, participants’ fasting and baseline blood and urine samples were collected, in addition to collecting their anthropometric measurements. In regards to inflammation, biomarkers which were measured in plasma samples by enzyme-linked immunosorbent assay. In regards to oxidative stress, biomarkers that were measured from both plasma and urine tests. From the study, researchers found that aronia polyphenol consumption reduced TC by 8% at 12 weeks, while the placebo group had no significant change, and the aronia group also had 7% and 11% less LDL cholesterol at both 6 and 12 weeks, while the placebo group continued to have no significant changes. Researchers of the study concluded that the consumption of 500mg of aronia berry extract for 12 weeks improved lipid profile of former smokers by reducing plasma TC and LDL cholesterol. However, the consumption of aronia berry extract for 12 weeks did not change biomarkers of chronic inflammation and oxidative stress in former smokers.

Overall, the content of this article was very detailed and thorough. The authors stated their limitations, and followed proper protocol for their systematic review article. Even though there was a lot of information collected for the study, the way that it was presented to the reader was clear, concise, and comprehensible. **However, I am rating this article as neutral because over half of the references that the authors used in order to write their systematic review article was out dated for their findings to be valid.**

**The final article reviewed, “Postprandial Inflammatory Responses and Free Fatty Acids in Plasma of Adults Who Consumed a Moderately High-Fat Breakfast with and without Blueberry Powder in a Randomized Placebo-Controlled Trail,” had 42 participants randomly assigned into two different groups, one group received the blueberry powder with their moderately high-fat breakfast, the other group received a placebo powder with their moderately high-fat breakfast over the course of 3 weeks to assess the effects that blueberry powder has on inflammation in adults.5** Researchers followed a placebo-controlled crossover study design with a wash out period of 2 weeks. instructed the participants were instructed to strictly follow highly specified diets, 3 days before each test. The time the participants were allotted to consume their breakfast was controlled to 20 minutes. IL-6, IL-β, TNF-α, and INF-γ were determined by using the Human Pro Inflammatory II 4-plex ultra-sensitive kit from Meso Scale Discovery. The significance of blueberry powder on inflammation was tested with a Turkey-Kramer’s test which was used for a post hoc analysis. The purpose of this study was to determine whether changes in blood lipid levels induced by a single moderately high-fat breakfast could decrease cellular inflammation in adults. The study showed that levels of IL-6, IL-8, and TNF-α were significantly lower than in fasting plasma levels. IL-β was below the level of detection in the plasma samples. They found that there was no substantial effect of blueberry powder on plasma cytokine concentrations. The researchers concluded that overall blueberry intake suppressed IL-β and IL-6 production in participants who consumed the blueberry powder, as compared to those who did not. They stated that there may be a relationship between blueberry powder consumption and lowering cellular inflammation, but it is not significant according to their findings.

**I am rating this article as weak because it was very confusing to read and asses the data and information given.** Although it was through in explaining their procedures they failed to specify exactly what the time frame of the study was. They also failed to collect information that was up to date, therefore, compromising the findings of their study and eliminating the validity of their study. This article did, however, explain the limitations of their study and follow proper protocol for conducting their study.

**Summary and Conclusion**

Most of the studies reviewed in this paper were detailed and through in explaining their findings and how they conducted their respected studies. Most of the articles were easy to read and decipher what the information and data meant, however some were confusing and lacked basic information that was pertinent to the conclusion of their study. Most of the studies reviewed in this article had a big enough sample size to deduce cause and effect in regards to berry consumption and its effects on inflammation and oxidative stress. **I grade this research II- Fair.**

 **Out of the five articles, three were neutral, one was positive (strong), and one was negative (weak).** Four out of the five articles reviewed showed some type of relationship between berry consumption and it effects of lowering cellular inflammation and oxidative stress in the body. However, the articles that obtained their sources from outdated references tended to have results that weren’t as strong as the articles that hade up to date references. That being said, the articles that had references that were out of date, could not be completely valid in their findings that berries either did not have an effect on inflammation or had little effect on inflammation in the body, because they were working with information that is out of date and has been re-evaluated for newer and more accurate results. From these studies it can be concluded that there may be a statistically significant relationship between berry consumption and their effects on lowering inflammation and oxidative stress in the body. More up to date research needs to be done in order to generalize the findings of this study to a broader spectrum of the population. Most subjects were adult in the studies. Overall, the studies were well put together and contained enough information to understand the results of the studies.

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