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Diets Rich in Stearidonic Acid Impact on Joint Inflammation in a Murine Model of Rheumatoid Arthritis

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INTRODUCTION: Chronic inflammation is the hallmark of inflammatory diseases, including rheumatoid arthritis (RA). While the etiology of RA remains unclear, several cell types promote the inflammatory stage of the disease by producing inflammatory lipid mediators and cytokines. Omega-3 polyunsaturated fatty acids (PUFA) from fish oil are precursors of immunoregulatory lipids and their consumption has been shown to moderate inflammation in RA patients. However, the sustainability of fish oils has been questioned due to depleting ocean resources. Plant-derived oils rich in stearidonic acid (SDA, 18:4 *n*-3) such as *Buglossoides arvensis* oil may be alternative, sustainable and effective sources of dietary omega-3 PUFA.

OBJECTIVE: The aim of this study is to evaluate the effects of dietary *Buglossoides arvensis* oil on disease severity in a mouse model of induced RA.

METHODS: We compared the effects of a control diet (based on the typical western human diet) with diets enriched with a low dose (3% of kcal) or a high dose of Buglossoides oil (10% kcal) on the (K/BxN) murine model of RA. C57B6 mice (n = 25-31 per group) consumed experimental diets for 3 weeks. RA was then induced by the intraperitoneal injection of 150 µl of serum from K/BxN mice and disease progression was followed for 9 days. Liver fatty acid profiles were measured on day 9 to determine the impact of diet on tissue lipids. Disease-associated inflammation was measured daily over 9 days by clinical index score and ankle thickness, and by inflammatory cell infiltration into joints measured histologically following H&E staining at day 9. Since energy metabolism is impacted in RA and by omega-3 PUFA consumption, mitochondrial oxidative capacity was also measured in soleus muscles on day 9. All studies were approved by the institutional review board protocol (Université de Moncton). Guidelines of the Canadian Council on Animal Care were followed in a protocol approved by the Animal Welfare Committee at Université de Moncton.

RESULTS: Liver fatty acid profiles were significantly different between all groups. Specifically, omega-3 PUFA content, including SDA, EPA and DPA significantly increased (2-way ANOVA, $p < 0.05$) with the dose of dietary Buglossoides oil. DHA was significantly increased in both Buglossoides groups compared to control mice. Mice consuming high dose Buglossoides diets showed significantly elevated inflammation scores (2-way repeated measures ANOVA, $p < 0.05$) compared to control diets, whereas low dose Buglossoides diets showed significantly decreased inflammation scores ($p < 0.05$) compared to the control group. Mitochondrial oxidative capacity was significantly decreased in animals consuming the high dose Buglossoides diet compared to the other two groups (1-way ANOVA, $p < 0.05$).

CONCLUSION: These findings suggest that consumption of diets containing moderate quantities of SDA-rich oil (a human equivalent dose of 6.6 g of oil (1.3 g SDA) per day based on percent calories) can alleviate inflammation associated with RA. Conversely, consumption of a daily human equivalent dose of 22 g of SDA-rich oil exacerbates inflammation in this murine model of RA. Lipidomic and cytokine analysis of inflamed paws may provide mechanistic explanations of these dietary effects.

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