Abstract

Obesity is one of the most significant global health problems associated with the development of metabolic disorders such as insulin resistance, type 2 diabetes, and cardiovascular diseases. Excessive adipose tissue accumulation leads to chronic inflammation and metabolic dysfunctions, particularly glucose metabolism disturbances. In light of the growing number of individuals with overweight and obesity, which is projected to increase in the coming years, there is an urgent need to identify effective methods for the prevention and treatment of this condition. A safe therapeutic strategy may involve the use of natural bioactive compounds that can interfere with hyperplastic and hypertrophic growth of adipose tissue by modulating signaling pathways related to adipogenesis, lipogenesis, lipolysis, production of adipokines, inflammatory mediators, and insulin sensitivity.

This study aimed to evaluate the bioactivity of extracts from elderberry (*Sambucus nigra* L.) and blackcurrant (*Ribes nigrum* L.) fruits in the context of preventing and treating obesity and its related metabolic disorders. The study was conducted *in vitro*, using cell models, including preadipocytes differentiating into fat cells, mature insulin-sensitive adipocytes, and hypertrophic adipocytes with induced insulin resistance and inflammation. Furthermore, a model of macrophages activated to the inflammatory response was applied in the experiments to analyze the anti-inflammatory properties.

The results of the study demonstrated that elderberry and blackcurrant extracts inhibited the differentiation of preadipocytes into mature adipocytes by reducing the expression of transcription factors *Pparγ*, *C/ebpα*, and *Srebp1*, which control adipogenesis. The suppression of adipogenesis regulators resulted in reduced expression of genes *Fabp4/aP2*, *Lpl*, and *Fas* involved in lipogenesis, leading to a significant decrease in lipid accumulation in adipocytes. Elderberry extract also reduced the expression of *Hsl* and *Plin1* genes involved in lipolysis. An important finding of the study was the observed decrease in reactive oxygen species (ROS) levels in adipocytes following treatment with the extracts. This effect was attributed to inhibiting of NADPH oxidase (NOX4) mRNA expression. Moreover, it was found that the elderberry extract enhanced the expression of superoxide dismutase (*SOD2*) and glutathione peroxidase (*GPx*).

One of the key aspects of the study was evaluating the effect of elderberry and blackcurrant extracts on glucose uptake in insulin-sensitive and insulin-resistant adipocytes. The results showed that the extracts improved glucose uptake in adipocytes, regardless of insulin sensitivity. The increased glucose uptake by insulin-resistant cells in the case of elderberry extract was associated with enhanced mRNA expression of the glucose transporter gene *Glut-4*. In turn, blackcurrant extract demonstrated the ability to modulate the gene expression of apelin and SFRP5 and SOCS3

proteins, suggesting its potential role in improving insulin signaling and cellular insulin sensitivity. The study also demonstrated that the extracts could reduce carbohydrate and fat absorption by inhibiting the activity of digestive enzymes, including α-amylase, α-glucosidase, and pancreatic lipase.

The research also investigated the ability of elderberry and blackcurrant extracts to mitigate the inflammatory process, which contributes to the development of insulin resistance and other metabolic disorders associated with obesity. The results indicated that the analyzed extracts could modulate the inflammatory response by reducing the expression and/or secretion of pro-inflammatory cytokines and mediators (IL-6, TNF-α, *Ptgs2*, *iNos*) in activated RAW 264.7 macrophages. The inhibition of *Ptgs2* and *iNos* expression led to reduced production of prostaglandin PGE2 and nitric oxide in the cells. Furthermore, blackcurrant extract effectively reduced the expression of IL-1β and MCP-1 cytokines, as well as the transcription factor NFκB. Inhibition of NFκB expression by this extract resulted in the suppression of pro-inflammatory signaling pathways in macrophages. Moreover, blackcurrant extract exhibited strong anti-inflammatory potential in the TNF-α-induced hypertrophic 3T3-L1 adipocyte model. The extract inhibited mRNA expression of key pro-inflammatory cytokines, including IL-1β, TNF-α, IL-6, MCP-1, and the transcription factor NFκB.

The results of the experiments provided valuable data on the biological potential of elderberry and blackcurrant extracts, indicating that the extracts may represent a valuable dietary component for preventing and treating obesity and its related metabolic disorders. However, it should be emphasized that further in-depth *in vitro* studies, *in vivo* model studies, and clinical trials are needed to fully understand the mechanisms of action of the extracts, confirm their therapeutic efficacy, and establish appropriate doses for potential human use.

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