

Title: *Searching for natural compounds in the treatment of inflammatory-based diseases*

According to the World Health Organization (WHO) reports from 2023, non-communicable diseases (NCDs) such as cardiovascular diseases, cancer, type II diabetes, autoimmune diseases, and neurodegenerative disorders account for 7 out of 10 deaths, corresponding to 41 million cases annually (including 17 million premature deaths - before the age of 70). Additionally, a significant issue is the increasing percentage of patients (including children and adolescents) experiencing risk factors for NCDs development, such as hypertension, dyslipidemia, hyperglycemia, obesity, and insulin resistance, collectively referred to as the Metabolic Syndrome (MetS or Syndrome X).

The development of systemic, subclinical inflammation, termed "meta-inflammation", is attributed to playing a fundamental role in NCDs. This condition is originally associated with obesity resulting from an unbalanced, highly processed diet, low in plant-derived products, limited physical activity, and the dynamic development of the industry, leading to multifaceted immunological interactions, including the stimulation of inflammatory signaling pathways and the oxidative stress development.

The increasing demand for healthcare resources and the ongoing aging of populations create a constant need for effective preventive measures to reduce the growing incidence of NCDs. Consequently, in recent years, much attention has been devoted to the correlation between lifestyle hygiene and a well-balanced diet rich in plant-derived products, coupled with rational supplementation.

Due to the pleiotropic mechanisms of action of natural substances arising from their structural diversity and the formation of numerous metabolites with significant biological activity, plant resources have become valuable sources of substances introduced into medicine or used as a basis for creating new compounds with therapeutic potential. 80% of the population of developing countries rely on traditional medicine for their primary health care needs. This correlates with the fact that 40% of pharmaceutical preparations come from natural products, which emphasizes the importance of substances of plant origin.

Despite the long-term use of some plant substances in traditional medicine, the credibility of their application is undermined by insufficient preclinical and clinical research and the lack of standardization for the content of active ingredients. Furthermore, many local sources of raw materials remain untapped due to a lack of knowledge about their phytochemical composition and therapeutic potential.

The aim of the study was a comprehensive phytochemical analysis of the leaves of four species from the Oleaceae family, leading to the isolation of dominant compounds, as well as the assessment of the mechanisms of anti-inflammatory activity of extracts and individual structures.

During the LC-MS analysis, the composition of extracts prepared from the leaves of four Oleaceae family species, including three *Forsythia* species collected at two different vegetation periods and the leaves of common ash, was analyzed. Three plant species with

significant levels of polyphenolic compounds were identified, allowing for the isolation of compounds from the groups of lignans, phenylethanoids, and secoiridoids.

In vitro studies were conducted using a model of LPS-stimulated PBMC monocyte/macrophage cells and TDM macrophages, differentiated from the THP-1 monocytic cell line. The work assessed, the cytotoxicity of individual plant extracts and single compounds, as well as their impact on the secretion of pro-inflammatory (TNF- α , IL-6, IL-1 β , MPC-1) and anti-inflammatory mediators (IL-10, IL-10R, TGF- β) using ELISA immunoassays and flow cytometry. Due to promising results, obtained for a wide range of lignan compounds (19 structures) and their widespread presence in food products and many natural raw materials, their impact on Mitogen-Activated Protein Kinase (MAPK) and NF- κ B signaling pathways was determined using the western blot method. Furthermore, the influence of the two most active structures (arctiin and arctigenin) on the modulation of signal transduction through TLR receptors in LPS-stimulated macrophages was assessed using real-time PCR. Additionally, I assessed the impact of 7 lignans on the processes of cholesterol accumulation in macrophages by evaluating the expression of CD36 and ABCA1 proteins, along with associated pathways.

Obtained results demonstrate the high value of formulations prepared from the leaves of *Forsythia* species (collected in spring) and ash leaves, in the context of potential prevention of inflammatory-based diseases. The presented results may serve as a basis for further analyses regarding the introduction of *Forsythia* leaves into phytotherapy and the utilization of lignans as components of functional food or dietary supplements.

Keywords: Noncommunicable diseases, macrophages, Oleaceae, lignans, phenylethanoids, inflammation, cholesterol, atherosclerosis