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THERAPEUTIC POTENTIAL AND PREVENTIVE EFFECTS OF MAJOR TRITERPENIC SECONDARY METABOLITES FROM LAVANDULA ANGUSTIFOLIA

POTENȚIALUL TERAPEUTIC ȘI EFECTE PREVENTIVE ALE METABOLITELOR TRITERPENICE SECUNDARE MAJORITARE DIN LAVANDULA ANGUSTIFOLIA

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Rezumat. Acizii ursolic și oleanolic se găsesc pe scară largă în diverse plante sunt triterpenoide pentaciclice naturale eficiente cu rol profilactic și terapeutic în diferite boli, precum scleroza multiplă, tulburări metabolice, diabet și diferite tipuri de cancer.

Acest reviu al literaturii prezintă cele mai recente rapoarte privind impoactul acizilor ursolic și oleanolic și mecanismul biologic al activităților lor. Astfel reviul prezintă date care propun că acizii ursolic și oleanolic sunt o alternativă potențială și complementară pentru tratamentul și managementul mai multor maladii.

Cuvinte cheie: *Lavandula angustifolia*, polifenoli, acid ursolic, acid oleanolic.

Summary. Ursolic and oleanolic acids are widely found in diverse plants and are natural effective pentacyclic triterpenoids with prophylactic and therapeutic roles in various diseases suuch as multiple sclerosis, metabolic disorders, diabetes and different cancers.

This review presents the latest reports on the impacts of ursolic and oleanolic acids and the biological mechanism of their activities. Thus, this review presents data proposing that ursolic and oleanolic acids are potential alternative and complementary therapies for the tratment and management of several diseases.

Keywords: *Lavandula angustifolia*, polyphenols, ursolic acid, oleanolic acid.

INTRODUCTION

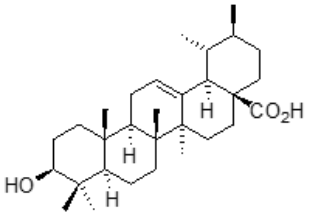
Medicinal plants play a major role in medicine as a prime material for perfume industry, cosmetics, or phytotherapy. Herbs contain many active compounds that exhibit multidirectional phytotherapeutic activity and are used in the treatment and prevention of cardiovascular, respiratory, gastrointestinal diseases, urinary infections, as well as in chronic diseases of children and elderly people.

Considerable attention has been paid to the bioactive compounds in herbs and spices in an effort to reveal their potential contribution to health and the preservation of food quality. Several previous studies have suggested that polyphenols from natural sources could be a potential alternative to the use of synthetic antioxidants. Natural antioxidants from various botanical sources have been regularly reviewed by focusing on a single species, genus, origin, popularity, applications, bioactivities, selected phytochemical groups of antioxidants [1].

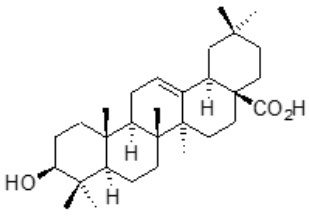
Lavender (*Lavandula angustifolia* Mill, family Lamiaceae) is a plant with a number of beneficial properties for the human body. Besides its application in herbal treatment, lavender is widely used in the cosmetic, perfume, food, and aromatherapeutic industries. Plant contains essential oil, polyphenols, ursolic and oleanolic acids, anthocyanins, phytosterols, coumarin and tannins [2,3].

Polyphenols are a large group of natural compounds that are widely distributed in the plant kingdom, as constituents of medicinal herbs and are integral part of the human diet. Within the last few years extensive research has revealed that including of certain fruits and vegetables rich in polyphenols in a diet can reduce the risk of acquiring specific cancers [4]. Polyphenolic extracts are attractive ingredients for pharmaceutical and cosmetic industry due to their beneficial biological properties. These compounds may reduce the risk of the development of several diseases due to a complex effect but many authors claim that some of their properties may be related both to their antioxidant capacity and other biological activities [5].

Ursolic (**1**) and oleanolic (**2**) acids are secondary plant metabolites that are known to be involved in the plant defence system against water loss and pathogens. Nowadays these triterpenoids are also regarded as potential pharmaceutical compounds and there is mounting experimental data that either purified compounds or triterpenoid-enriched plant extracts exert various beneficial effects, on model systems of both human or animal origin. Some of those effects have been linked to the ability of ursolic and oleanolic acids to modulate intracellular antioxidant systems and also inflammation and cell death-related pathways. Ursolic and oleanolic acids are common phytochemicals naturally found in various plants, the wax-like coatings of fruits and many medicinal herbs – lavender, rosemary, oregano in the form of free acids or aglycones for triterpenoid saponins. For a long time, these compounds were considered to be biolog



1 (Ursolic acid)



2 (Oleanolic acid)

ically inactive, but in recent years they have attracted the interest of medical scientists because of their pharmacological effects combined with low toxicity.

Herb mixtures are widely used in traditional medicine of many cultures and their clinical potential is well established. Many of them contain ursolic, oleanolic acids and their derivatives [6].

Ursolic acid (**1**) and its isomer oleanolic acid (**2**) share many pharmacological effects, including neuroprotection, antimicrobial, antifungal, antiulcer, antiparasitic, anticancer, sedation, hepatoprotection, anti-inflammation, anti-oxidation and regulating blood glucose [7,8].

The aim of this work was bibliographic evaluation of pharmaceutical properties and therapeutic potential of ursolic (**1**) and oleanolic (**2**) acids in context of the pharmaceutical revaluation of dried waste of *Lavandula angustifolia* cultivated in Republic of Moldova.

MATERIALS AND METHODS

Generalization and analysis of bibliographic data, selected from international databases: PubMed, Medline, Environmental Issues & Policy Index, Google Scholar, etc., about chemical composition of *Lavandula angustifolia* Mill species, important role of phenolic compounds, inclusive of ursolic and oleanolic acids, active principles with therapeutic potential and pharmacological activities.

RESULTS AND DISCUSSION

Anticancer potential. Ursolic acid was examined for its ability to inhibit the breast cancer cells by modulating different signaling cascades such as PI3K/Akt/mTOR-, ERK- and EGFR-related signaling cascades. UA also arrests BC cells by inhibiting tumor growth, metastasis and angiogenesis, induces apoptosis, arrest cell cycle thereby reducing the tumor size [9].

Prof. Sen A. *et al.* [10] evaluated anti-cancer effects of oleanolic acid. The molecular mechanisms of this substance are diverse, such as inhibiting the proliferation of cancer cells, preventing cancer cell migration and invasion, restraining angiogenesis, and inducing autophagy and apoptosis. Although a very large number of *in vitro* studies have been carried out showing the inhibition of carcinogenesis, only a few *in vivo* studies have confirmed that oleanolic acid is promising anti-cancer agent.

Another research on anti-cancer effects of oleanolic acid was evaluated. Prof. Ziberna *et al.* [11] studied oleanolic acid inducing both extrinsic and intrinsic apoptosis in human lung cancer cells by multiple signaling pathways. Oleanolic acid activated intrinsic apoptosis, as observed by the up-regulation of caspase-3 and caspase-9, poly (ADP-ribose) polymerase (PARP) cleavage, release of cytochrome c, as well as increase in Bax/Bcl-2 expression ratio.

Anti-inflammatory potential. Prof. Kashyap *et al.* [2] have determined the anti-inflammatory therapeutic potential of ursolic and oleanolic acids.

The administration of oleanolic acid enhanced the development of serum antibody immunoglobulin G in mice and showed the marked inhibition of the hemolytic activity of the total complement by the classical pathway in guinea pigs. In integration, the similar passive cutaneous anaphylaxis in mice or rats and the degranulation of mast cells of calvarial periosteum in rats was significantly obviated by oleanolic acid along with the reduction in capillary permeability and type I allergic reaction. In a similar way, the anti-inflammatory activity of ursolic acid was analyzed by utilizing different *in vitro/in vivo* inflammatory models like croton oil-induced oedema in albino swiss mice.

Prof. Tsao *et al.* [12] evaluated the anti-inflammatory effect of oleanolic acid on bronchial epithelial cells.

Cigarette smoke or particulate matter could stimulate the release of hydrogen peroxide in airway epithelial cells, which contributes to apoptotic, oxidative, and inflammatory stress in those cells. In present study, pretreatment with oleanolic acid markedly protected two human bronchial epithelial cell lines (16HBE and BEAS-2B cells) against hydrogen peroxide induced oxidative and inflammatory injury, which in turn enhanced cell survival. In addition, it was found that this compound was able to mediate protein expression of NADPH oxidase, COX-2, NF-κB, and MAPK in these bronchial epithelial cells. Furthermore, this triterpenic acid treatments alone, without hydrogen peroxide, did not affect the growth of these test cells. These findings implied that oleanolic acid might be safe and benefit respiratory epithelium stability and functions.

*Antidiabetic potential.*The triterpenoic acids were examined for protective effects in diabetes type 2 by Portuguese scientists [13]. The results of the experiment show that ursolic and oleanolic acids reduce the absorption and uptake of glucose, lower endogenous glucose production, increase insulin biosynthesis, secretion, and sensitivity, and protect against diabetic complications. These protective effects occur without noticeable hepatotoxicity, at the dose used in the experimental studies, as indicated by the decreased values of aspartate aminotransferase and alanine aminotransferase measured. This relevant fact is contrary to most currently used antidiabetic drugs, including sulfonylureas, α-glucosidase inhibitors, biguanides, and thiazolidinediones, which can cause liver toxicity.

Antihypertensive potential. The anti-hypertensive effects of oleanolic and ursolic acids may be mainly attributed to their potent anti-hyperlipidemic and antioxidant effects, combined with diuretic, natriuretic, and saluretic effects, mostly due to the inhibition of Na+ and K+ reabsorption in the early portion of the distal tubule. However, it was also reported that the anti-hypertensive and antiatherogenic properties of these compounds may also result from their effects on endothelium-dependent

vasorelaxation. Impaired endothelial function, due to decreased bioavailability of NO (nitric oxide), is a hallmark of atherosclerosis. In contrast, an increase in NO induces vasorelaxation, preventing the development of atherosclerosis. In this context, ursolic acid displayed vasorelaxing properties, mediated by an increase of NO release and relaxation by activation of endothelial nitric oxide synthase [7].

Neuroprotective potential. Mild to severe defects in the nervous system typically result due to oxidative stress and excitotoxicity. An imbalance in cellular homeostasis may permanently reduce cognitive function and cause brain damage, resulting in various brain diseases. Ursolic acid inhibits oxidative stress and excitotoxicity, suggesting that it may play a protective role in various brain diseases induced by oxidative stress and excitotoxicity. In addition, suppresses apoptotic signaling and exerts anti-inflammatory effects in the brain. Ursolic acid significantly reduces free radical levels in rat neuronal cultures. In addition, it attenuates reactive oxygen species (ROS) levels in the brain. It was found that UA increases the levels of antioxidant components, such as glutathione (GSH)/oxidized glutathione (GSSH) ratio, catalase (CAT) activity, and superoxide dismutase (SOD) activity in a rat model of subarachnoid hemorrhage [14].

Despite the fact that triterpenoic acids have applications in medicine and research, the obtaining and synthesis of these compounds still remains a growing need. The study of waste of *Lavandula angustifolia* can be a solution. Therefore, after obtaining the essential oil from *Lavandula angustifolia* aerial parts, the waste may contain an amount of some unknown compounds not studied yet. In this context the study of the extracts obtained from dried waste of *Lavandula angustifolia* especially for content of ursolic acid and oleanolic acid is substantial for the production of new pharmaceutical preparations.

CONCLUSIONS

Being natural triterpene compounds existing in a variety of plants, ursolic (**1**) and oleanolic (**2**) acids exhibit widespread pharmacological activities and can be included in the treatment of some severe diseases – some types of cancer, neurodegenerative, cardiovascular, diabetes.

Studies performed on the *Lavandula angustifolia* extracts have determined the content of polyphenols, flavonoids, triterpenoic acids, which shows that these compounds can be found in dry waste after oil extracting. The valuation of *Lavandula angustifolia* dried waste containing ursolic acid (**1**) and oleanolic acid (**2**) also denotes an economic potential in production of new pharmaceutical preparations.

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