JAP&T
TPA-Timişoara

Available online at http://journal-of-agroalimentary.ro

Journal of Agroalimentary Processes and Technologies 2021, *27* (1), 46-51

Journal of Agroalimentary Processes and Technologies

Olive leaf extracts and bioactive phenolic compounds related to population health

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Abstract

The data and evidence that directly associate diet and health are countless and are based on studies of many foods (e.g. fruits, vegetables, aromatic and medicinal herbs) rich in compounds with antioxidant properties and multiple benefits for human health. The present study aims to analyse the existing evidence related to the beneficial capacity of olive leaf extracts and its polyphenolic compounds, with emphasis on preclinical studies, clinical trials and epidemiological studies available in the literature. The chemical composition of olive leaf extract, based mainly on phenolic compounds, is responsible for the antioxidant, antidiabetic and cardioprotective effects proven by clinical studies. Preclinical studies based on the evaluation of the biological effects of the compounds in olive leaves are innumerable and highlight mainly their antitumor, antiviral and antimicrobial potential. Taken together, olive leaf extract is a viable alternative with an important role in preventing certain diseases and maintaining health.

Keywords: oleuropein, preclinical studies, clinical trials, human health

1. Introduction

Aromatic and medicinal plants have been used since ancient times to treat certain diseases (being the first known form of medical care) and are the basis for the development of the drug industry but also for prevention having an important role in public health. A medicinal plant abounds in bioactive components which exerts a number of pharmacological effects, when consumed in its natural form or after special preparation, in a form of therapeutic administration for the approach certain diseases [1]. Different studies have analysed the beneficial biological activity of plants, and the antioxidant, anti-inflammatory, anti-diabetic, and antitumor effects were among the most frequently noted [2]. Moreover, more than half of the drugs approved for human use are of plant origin [3]. The beneficial therapeutic effects of plants are based on the chemical composition that most often abounds in phenolic compounds, terpenes, alkaloids, flavonoids, and others. Data presented by the World Health Organization showed that almost 80% of the world's population still uses traditional herbal medicine [4]. Currently, increasing life expectancy, the link between diet and health, a healthy climate and stress reduction are terms that relate to health policies focused on quality of life. The proper functioning of the human body involves maintaining homeostasis which is directly related to nutrition, through a balanced diet, fundamental in these processes [5]. A balanced and healthy diet involves a mandatory consumption of fresh fruits and vegetables, due to the high content of fiber and phenolic compounds. A number of epidemiological studies have shown that these molecules exert beneficial immunomodulatory effects, have important antioxidant activity and have significant anti-inflammatory and antitumor potential [6]. Dysbiosis, the imbalance of the intestinal microbiota, can contribute to the appearance of cardiovascular diseases, inflammatory bowel diseases, mental health disorders, etc. Modulation of the intestinal microbiota is a key point in studies aimed at alternatives to current synthetic treatments and plant extracts are the most viable solution [7].

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Olive has been used for various actions related to human health since ancient times [8]. Following the consumption of different parts of the plant, it has been observed that it manifests beneficial biological activity against diabetes, inflammation, hypertension, infections, intestinal diseases, asthma, rheumatism, etc. [9]. Consumption of olive oil has been shown to be beneficial to human health, being highly valued in the Mediterranean diet, recognized for the prevention of cardiovascular disease, certain cancers or type 2 diabetes (chronic non-communicable diseases) [10]. Olive leaves have a varied chemical composition that includes: iridoid monoterpenes (predominate oleuropein), triterpenes, flavonoids, chalcones, phenolic acids and coumarins [11]. This paper aims to evaluate the transition from preclinical studies to clinical evaluations of plant extract and the importance of olive leaf extract in public health.

2. Biochemical composition of olive leaf

Plant molecules responsible for biological activity are not easy to identify and quantify. Therefore, various studies have treated and are still studying the optimal way to extract medically valuable components. Depending on main factors such as the type of solvent and the applied methods, the final composition in biologically active compounds is quite varied. The most used methods of separation of bioactive compounds in the form of plant extract are: maceration, infusion, digestion, decoction, percolation, Soxhlet extraction, microwave-assisted extraction, ultrasound-assisted extraction and supercritical fluid extraction [12,13]. Regarding olive leaf extracts, alcoholic samples contain a large proportion of oleuropein and other secoiridoids (e.g. secologanoside, oleoside, comselogoside, etc.), triterpenoids (ursolic, oleanolic acids), flavonoids (e.g. apigenin-7-O-rutinoside, luteolin-7-O-glucoside, rutin, diosmetin etc.) [14,15]. The aqueous extracts contain mainly oleoside, oleuroside and oleacein, while the ethyl acetate extract showed the presence of oleuricines A and B and the chloroform-soluble fraction also contains oleoside and ligstroside [16,17]. Finally, hexane extract contains a number of compounds from different classes, such as: terpenic alcohols, esters, tocopherols, hydrocarbons, triglycerides etc. [18]. Some of the major chemical compounds identified in the olive leaf extract, responsible for its therapeutic benefits, are shown in Figure 1.

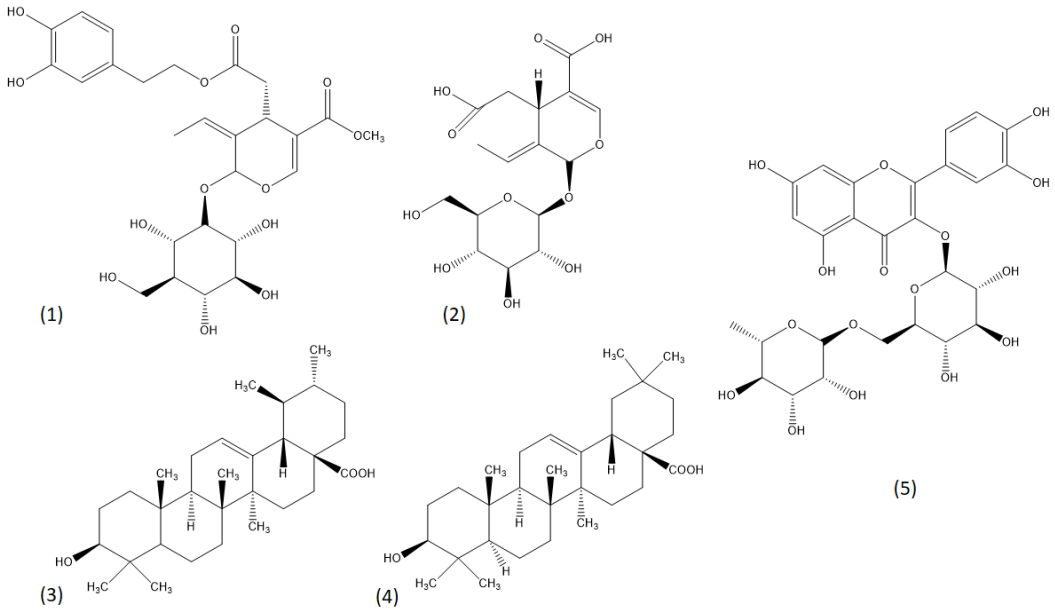

Figure 1. Chemical structures of main compounds found in olive leaf extracts: (1) oleuropein, (2) oleoside, (3) ursolic acid, (4) oleanolic acid, (5) rutin

3. Biological activity exerted by olive leaf extract

Olive leaves have been used since antiquity and a first mention of them is related to the use of antimicrobial oils obtained from them, in Egyptian mummification processes [19,20]. Prevention or treatment of various ailments often involves the use of olive leaves. The traditional uses of the past are still preserved today in certain regions: in Asian countries olive leaves are administered orally for stomach and intestinal diseases, in Greece hot aqueous extract of olive leaves is administered orally to combat hypertension, in Italy, leaf tincture (olive leaf extract) is used as an antipyretic and in different countries olive leaf extract has been shown to be effective in fighting malaria [9]. Studies demonstrated that oleuropein is the most potent bioactive compound found in olive leaf extract and certain polyphenols such as apigenin, rutin, verbascoside, etc. they are also present in significant quantities and prove a pharmacological action synergistic with oleuropein increasing the natural activity of the extract [21].

Oleuropein, an important representative of the olive leaf extracts, was reported to be involved in gene expression and activation of protein signalling pathways that are implicated in proliferation and apoptosis, eliciting a high capacity in oncology field [22]. The anticancer activity of oleuropein is dose-dependent being active against various tumoral cell lines such as: (i) breast cancer – tested at doses between 6.25-370 µM (SKBR3/HER2, MCF-7, MDA-MB-231 cells), (ii) colon cancer – tested at doses between 10-800 µM (HT29, SW620 cells), (iii) liver cancer – at doses between 20-80 µM (HCC, HepG2, Huh7 cells), (iv) prostate, pancreatic, thyroid cancer, (v) osteosarcoma etc. [22].

Regarding the metabolism of biologically active compounds predominant in olive leaf extract, data from the literature show the presence of conjugated metabolites in biological fluids *in vivo*. The study directions of interest for both present and future focus on the bioactivity of major metabolites which in some cases is superior to parent compounds (e.g. hydroxytyrosol glucuronate is a free radical scavenger five times stronger than hydroxytyrosol) [23]. The presumed *in vivo* pathways of the major metabolites of oleuropein are shown in Figure 2.

The mechanisms involved in the biological activity exerted by the olive leaf extract are not fully understood. Regarding the antioxidant activity, the problems that arise are related to the selection of reactive oxygen species responsible for oxidative stress but taking into account the fact that the association of reactive oxygen species with the progressive development of systemic diseases is not entirely true if are taken into account the essential need for the presence of superoxides for normal metabolome and physiological function [24].

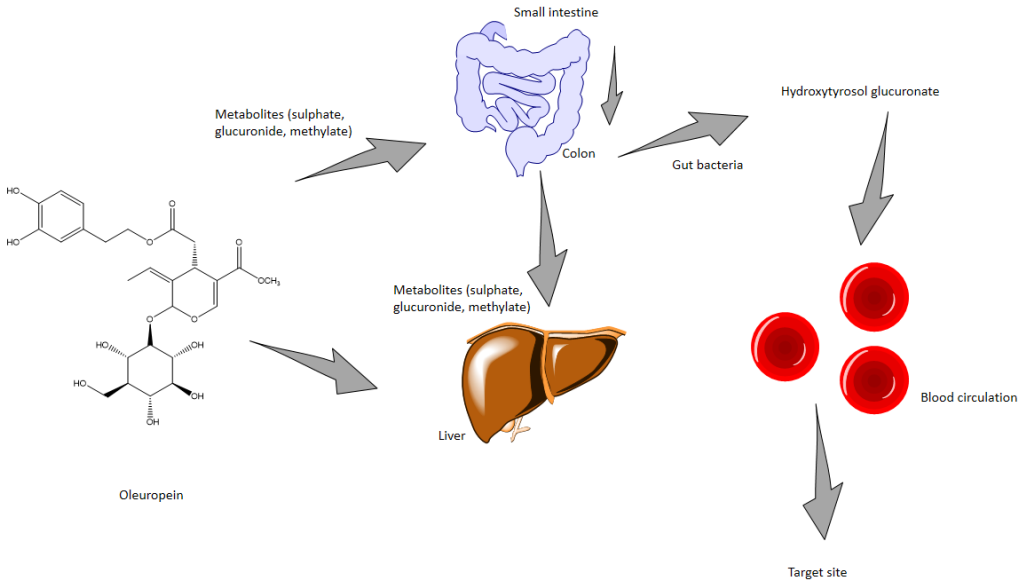

Figure 2. The presumed *in vivo* pathways of the major metabolites of oleuropein

4. Clinical studies based on olive leaf extract

The steps required to obtain a finite form that reflects clinical activity are complex and the transition from *in vitro* studies to clinical evaluation is based on complex resources, both human and material. *In vitro* studies, which predominate in the literature, despite the variety of methods used, provide only a small part of the information on possible beneficial effects obtained with *in vivo* administration. As research on these effects progresses to *in vivo* studies, the results in the literature are considerably reduced and, in the end, clinical trials provide a limited amount of information. The sulphate and glucuronide (conjugate) metabolites of hydroxytyrosol appear to be the main metabolites of oleuropein that are found in biological fluids (plasma, urine) after administration of olive leaf extract. Among the main factors influencing the absorption and metabolism of biologically active compounds in the extract are the type of preparation administered (solid, liquid, syrup, capsules, etc.), the method of release or the frequency of administration [23]. Some of the clinical trials based on olive leaf extract are presented in Table 1.

Metabolic syndrome is currently a major public health concern due to its involvement in increasing the risk of developing diabetes and cardiovascular disease. The role of olive leaf extract and implicitly oleuropein in the complications associated with diabetes (obesity, hypertension, dyslipidemia) is a potentially beneficial one supported by *in vivo* studies on animal models but also by clinical studies [25]. To date, olive leaf extract has proven its clinical efficacy in certain diseases associated with the cardiovascular system but also in pathologies of the upper tract or those associated with diabetes (Figure 3), being a product of interest that contributes to public health.

Table 1. Olive leaf extract found in clinical trials (based on the data from clinicaltrials.gov)

Code / Status	Title	Conditions	Administration protocol	Observations
NCT02421835 / completed	Olive Leaf Extract as Part of a Healthy Lifestyle in the Reduction of Blood Pressure	Pre Hypertension	132 mg of oleuropein per day suspended in olive leaf extract 700 mg	Interventional study (clinical trial)
NCT01427998 / completed	Effect of Olive Leaves as Hypoglycemic Agents in Diabetic Subjects	Diabetes	Olive leaf extract	Interventional study (clinical trial) Phase III
NCT01479699 / completed	Absorption and Metabolism of Olive Leaf Extract and Its Effect on Vascular Reactivity and Cytokine Concentrations	Absorption and metabolism	Olive leaf extract capsules	Interventional study (clinical trial)
NCT01796561 / completed	The Effect of Olive Leaf Extract on Blood Pressure in Overweight Prehypertensives	Hypertension	Olive leaf extract liquid	Interventional (Clinical Trial)
NCT02990637 / completed	The Effect of Olive Leaf Extract Administration on Cardiovascular Health	Overweight and Obesity Elevated Cholesterol	Olive leaf extract	Interventional (Clinical Trial)
NCT04440020 / active, not recruiting	Management of Dementia With Olive Oil Leaves - GOLDEN	Prevention	Beverage of Olive Oil Leaves	Interventional (Clinical Trial)

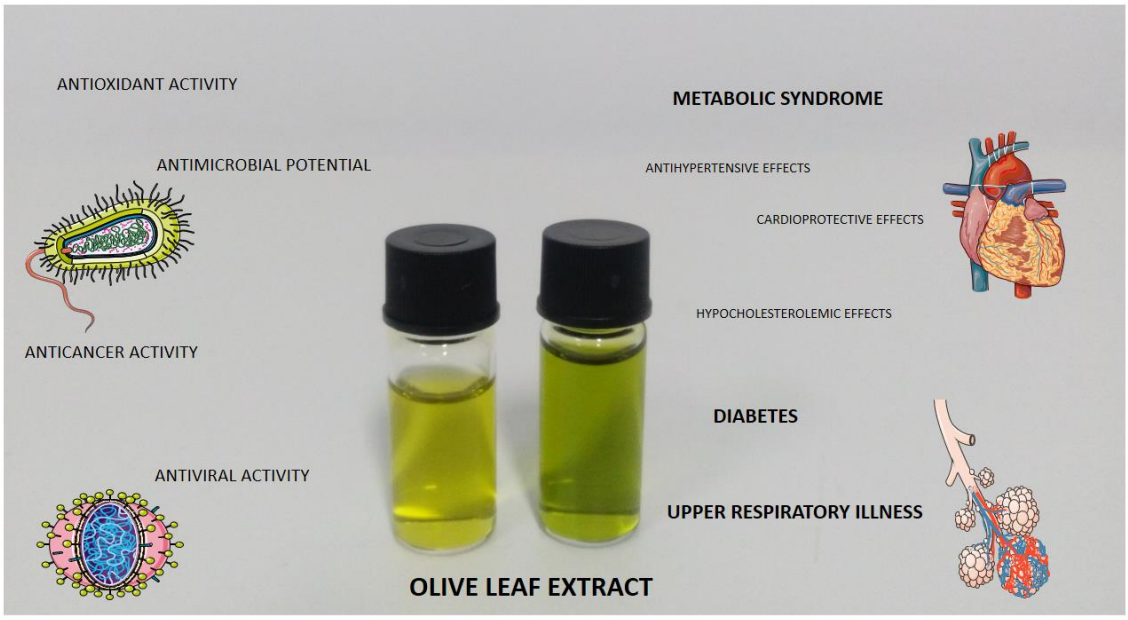

Figure 3. Schematic representation of the connection between olive leaf extract and human health

The biological activities (antioxidant, anti-inflammatory and anticancer) exerted by oleuropein are transposed into epidemiological studies that associate a diet rich in this compound with the prevention of non-communicable diseases, one of the leading causes of morbidity and mortality in the world.

5. Conclusion

The individual phenolic compounds in the olive leaf extract are known for their strong biological activities tested by *in vitro* methods. However, most reports highlight the benefits of using extracts due to combinations of classes of biologically active compounds that based on synergistic effects have antioxidant and antimicrobial activities at least similar to those of individual compounds but often superior to them. Natural compounds derived from olive leaf extract are considered a valuable source of models as the basis of new chemopreventive or therapeutic agents for various human diseases. Despite the fact that, a significant number of phytocompounds are effective in preclinical studies (*in vitro* or *in vivo* on an animal model) the therapeutic efficacy is considerably reduced when they reach clinical trials. Finding the optimal formulations for capitalizing on the therapeutic efficacy of olive leaf extract remains a challenge for researchers involved primarily in preclinical studies and selecting patients for clinical trials based on current population health issues remains a challenge for medical staff.

Compliance with Ethics Requirements. Authors declare that they respect the journal's ethics requirements. Authors declare that they have no conflict of interest.

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