



ANTIFUNGAL POTENTIAL OF OLIVE OIL: A COMPREHENSIVE REVIEW OF PHYTOCHEMICAL MECHANISMS AND CLINICAL EVIDENCE

¹Seyed Mahdi Rezayat Sorkhabadi^{1*}, Seyyedeh Elaheh Mousavi², Bakhtiar Zahedi Lomar³

¹Professor, Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

²Associate Professor, Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

³PhD Candidate in Pharmacology, Islamic Azad University, Tehran Pharmaceutical Sciences Branch, Tehran, Iran

Corresponding Author: Seyed Mahdi Rezayat Sorkhabadi

ABSTRACT

Skin fungal infections are among the most common diseases worldwide, and their treatment, especially in drug-resistant cases, is challenging. Recently, there has been heightened interest in the incorporation of natural chemicals in topical preparations. One of the most widely used herbal compounds is olive oil, which has shown antifungal, antibacterial, and anti-inflammatory properties due to its active compounds, such as oleic acid, polyphenols, and squalene. The aim of this article is to provide a comprehensive review of laboratory and clinical studies conducted on the antifungal effects of olive oil and to investigate its potential in topical formulations such as creams, ointments, and medicinal gels. The results of the studies indicate that olive oil is particularly effective against species of *Candida* and *Aspergillus* and can be considered as a complementary or alternative agent in the topical treatment of fungal infections. However, limitations such as formulation stability and differences in extract quality require further investigation, especially in human clinical trials. Finally, future research should focus on optimizing the formulation structure and investigating the synergistic effect of olive oil with common antifungal drugs.

Keywords: Olive Oil, Antifungal Properties, Oleuropein and Hydroxytyrosol, Fungal Infections, Natural Therapies.

1. INTRODUCTION

Preface Superficial fungal infections, including cutaneous candidiasis, dermatophytosis, and

pityriasis versicolor, are prevalent skin disorders that significantly impact patients' overall health and quality of life(Hay, 2018). These infections predominantly occur in warm and humid surroundings, exacerbated by factors such as inadequate hygiene, compromised immune systems, excessive antibiotic usage, and underlying conditions like diabetes(Shields et al., 2019). Standard therapies for these conditions encompass chemical antifungal agents, including azoles (e.g., ketoconazole, clotrimazole) and allylamines (e.g., terbinafine), which, while notably efficacious, may occasionally lead to adverse effects, localized irritation, drug resistance, and constraints on prolonged administration(von Lilienfeld-Toal, Wagener, Einsele, Cornely, & Kurzai, 2019). Consequently, the pursuit of natural alternative molecules exhibiting satisfactory efficacy and reduced side effects has emerged as a prominent research domain(Segal & Elad, 2018). Olive oil, a natural product historically utilized in folk medicine, has garnered the interest of researchers in alternative therapies in recent years owing to its bioactive compounds, including polyphenols (such as oleuropein and Hydroxytyrosol), unsaturated fatty acids, and squalene(Tuck & Hayball, 2002). Numerous research have investigated the antifungal characteristics of this oil and its active constituents, demonstrating potential efficacy against harmful fungus(Ciafardini & Zullo, 2018). These substances can impede the growth and multiplication of fungi by processes including the disruption of the fungal cell membrane, inhibition of essential enzymes, and creation of oxidative stress(Korukluoglu, Sahan, & Yigit, 2008). The antioxidant and anti-inflammatory properties of olive oil can significantly mitigate the inflammatory symptoms associated with fungal infections(Al-Waili, 2004). In light of the increasing prevalence of drug resistance in pathogenic fungi, novel strategies have been focused on utilizing natural substances with diverse functionalities, such as olive oil and its derivatives(Augello et al., 2024). The topical application of pure olive oil or pharmaceutical formulations can significantly exert antifungal effects, while also expediting the healing process by enhancing the skin's defensive barrier and diminishing inflammation(Markakis et al., 2021). A thorough examination of the scientific evidence regarding the antifungal effects of olive oil and its associated mechanisms may pave the way for the advancement of natural and safer therapies for fungal skin disorders.

2. CHEMICAL AND PHARMACOLOGICAL COMPONENTS OF OLIVE OIL

Olive oil, derived from the fruit of the *Olea europaea* tree, is a premier source of advantageous compounds included in vegetable oils, and its intricate chemical composition imparts numerous health benefits, particularly in dermatological applications(Markakis et al., 2021). This oil comprises two primary categories of components: saponifiable components, predominantly consisting of fatty acids with varying chain lengths, and unsaponifiable components, which encompass phenolic compounds, tocopherols, squalene, terpenoids, and plant sterols. Examining the structure and function of these molecules from a pharmacological standpoint would enhance the understanding of the potential processes underlying the antifungal properties of olive oil. Olive oil predominantly consists of fatty acids, accounting for about 95% of its total weight. Oleic acid (C18:1), the predominant fatty acid and a representative of monounsaturated acids, significantly influences the biological qualities of the oil. This chemical effectively preserves the structural integrity of the stratum corneum, diminishes fungal permeability by altering membrane lipid dynamics, and suppresses fungal proliferation. Laboratory studies indicate that elevated concentrations of oleic acid can induce cell lysis in pathogenic fungus, including *Candida albicans* and *Aspergillus Niger*, likely due to the loss of plasma membrane integrity. Alongside oleic acid, olive oil contains linoleic acid (C18:2), a polyunsaturated fatty acid recognized for its anti-inflammatory qualities. Despite its lesser percentage contribution compared to oils like sunflower or sesame, this acid has a crucial function in modulating skin immune responses and mitigating chronic inflammation induced by fungal infections. This oil contains saturated fatty acids, including palmitic and stearic acids, which, while lacking direct antifungal properties, contribute to the stabilization of cream

structures and the formulation of appropriate textures in topical applications. The unsaponifiable fraction of olive oil contains significant phenolic and antioxidant components, including oleuropein, Hydroxytyrosol, and tyrosol, particularly in cold-extracted samples (extra virgin). Oleuropein, a significant phenolic glycoside, can inhibit critical enzymes that assist fungi in constructing their cell walls. This chemical induces programmed cell death in fungi by generating oxidative stress at the cellular level. In vitro investigations have shown that oleuropein inhibits a variety of harmful fungus, including species of *Trichophyton* and *Candida*. Hydroxytyrosol, derived from oleuropein, is an exceptional natural antioxidant for preventing skin infections due to its uncomplicated structure and ability to permeate skin tissue effectively. This chemical not only mitigates oxidative stress induced by fungal inflammation but also directly inhibits fungal proliferation in laboratory models. Moreover, research investigating the interplay between Hydroxytyrosol and prevalent antifungal agents reveals a notable synergistic effect between these two classes of chemicals. Squalene, an unsaturated triterpenoid present in olive oil at roughly one percent of its weight, is highly effective in delivering beneficial ingredients to deeper skin tissues due to its emollient, hydrating, and high permeability characteristics. Squalene does not directly combat fungi; instead, it enhances the efficacy of phenolic compounds in dermatological treatments by facilitating their absorption through the skin. The inclusion of tocopherols (vitamin E) and phytosterols in olive oil augments its antioxidant properties and mitigates additional damage to skin tissue during fungal infections. The interplay of fatty acids, phenolic chemicals, antioxidants, and squalene renders olive oil a multifaceted agent with significant antifungal efficacy in topical applications. A comprehensive understanding of the mechanisms by which these compounds operate and their interactions with the skin and pathogenic microorganisms is crucial for the formulation of plant-derived pharmaceuticals and can also aid in devising novel techniques to address treatment resistance in superficial fungal infections.

3. PHENOLIC COMPOUNDS AND POLYPHENOLS: FOCUS ON OLEUROPEIN AND HYDROXYTYROSOL

Among the unsaponifiable components of olive oil, polyphenols have a special place and play a fundamental role in explaining the medicinal properties of this oil. Phenolic compounds of olive oil are mainly found in virgin and unprocessed olives and have a wide range of biological activities, including antioxidant, anti-inflammatory, antibacterial, and especially antifungal effects. Among them, oleuropein and Hydroxytyrosol are known as the key compounds responsible for many of the biological effects of olive oil.

3.1. Oleuropein:

Oleuropein, which is found in large amounts in olive leaves and skin, is a type of phenolic glycoside that has a special structure and is present in high levels when olives are still developing. This compound, with its hydrophilic and lipophilic parts, has a high permeability to biological membranes, which makes it an important factor in inhibiting the growth of microorganisms. In the field of antifungal pharmacology, oleuropein acts through several pathways. First, this compound can inhibit key enzymes in the synthesis of fungal cell walls, which leads to disruption of their growth and cell division. Second, by inducing oxidative stress and increasing the production of reactive oxygen species (ROS) in the fungal cells, it causes structural and functional destruction of cellular components. In vitro studies have indicated that oleuropein can effectively inhibit the growth of fungi such as *Candida albicans*, *Aspergillus Niger*, and *Trichophyton rubrum*. In a study by Bisignano et al. (2001), oleuropein caused a significant reduction in fungal colonies at acceptable concentrations in terms of toxicity without reporting cytotoxicity to human cells. Such findings make oleuropein a suitable candidate for use in topical formulations, especially in cases where the goal is to treat resistant superficial fungi.

3.2. Hydroxytyrosol:

Hydroxytyrosol, a product formed when oleuropein breaks down, is a small phenolic compound that has strong antioxidant abilities. This compound, unlike oleuropein, lacks a glycosidic moiety and therefore has greater permeability in cell membranes. This property allows Hydroxytyrosol to quickly cross the stratum corneum of the skin and reach deeper areas, which is of great importance in topical formulations. The suggested ways Hydroxytyrosol fights fungi include blocking enzymes that help fungi grow, damaging their cell membranes, and disrupting their communication processes. In addition, Hydroxytyrosol, with its antioxidant properties, can reduce inflammation caused by fungal infection and facilitate the tissue repair process. In studies on tough strains of *Candida glabrata* and *Aspergillus fumigatus*, it has been found that Hydroxytyrosol can greatly slow down the growth of these fungi, especially when used together with other herbal antifungal agents or synthetic drugs. This synergistic effect can be the basis for the design of new therapeutic combinations that reduce the dose of chemical drugs while maintaining the effectiveness of the treatment. The totality of the available evidence indicates that oleuropein and Hydroxytyrosol are complementary to each other not only in terms of chemical structure but also in terms of biological action mechanisms and play an important role in the antifungal activity of olive oil. These compounds have become an effective multi-mechanism agent in topical treatment by utilizing different pathways, such as cell structure destruction, oxidative stress induction, and interference with fungal biological pathways. A detailed understanding of these mechanisms and identification of effective and safe doses of these compounds in topical formulations is an important step in the development of plant-based drugs and combating drug resistance in fungal infections.

4. POSSIBLE MECHANISMS FOR THE ANTIFUNGAL ACTIVITY OF COMPOUNDS IN OLIVE OIL

The antifungal efficacy of olive oil, unlike many chemical pharmaceutical agents that have a single mechanism, is due to the multi-mechanism activity of its bioactive compounds. These compounds, which include healthy fats, antioxidants like oleuropein and Hydroxytyrosol, vitamin E, and squalene, work in various ways to stop harmful fungi from growing and spreading. Even though some of these ways olive oil works against fungi still need to be studied more closely in labs and require better clinical proof, the information we have so far helps us understand how this oil fights fungal infections.

4.1. Disruption of the integrity of the fungal cell membrane:

Compounds in olive oil, especially polyphenols such as oleuropein and Hydroxytyrosol, is the disruption of the structure and function of the fungal cell membrane. The fungal cell membrane is mainly composed of phospholipids, membrane proteins, and ergosterol, which play a fundamental role in maintaining structural integrity and regulating ionic and molecular exchanges. Phenolic compounds in olive oil penetrate the membrane, increasing its permeability and, as a result, disrupting cellular homeostasis. In vitro studies have shown that direct contact between olive oil extracts and active compounds with fungi such as *Candida albicans* leads to the leakage of intracellular contents such as electrolytes, proteins, and nucleic acids. This disruption in membrane permeability not only prevents the growth and proliferation of the fungal cell, but in some cases also induces programmed cell death (apoptosis-like death). Electron microscopic studies have also confirmed the physical destruction of the membrane, the loss of the normal cell shape, and the formation of pores on the cell surface after exposure to phenolic compounds of olive oil. In addition, changes in the lipid content of the membrane and the oxidation of phospholipid components under the influence of the antioxidant activity of olive oil compounds may also play an important role in this process. These effects are similar to the mechanism of action of some common antifungal drugs such as amphotericin B and

azoles, with the difference that plant compounds are often associated with lower toxicity to human cells. This feature makes olive oil a potential option for use in complementary therapies or topical formulations.

4.2. Inhibition of ergosterol biosynthesis:

Some studies show that phenolic compounds in olive oil, especially Hydroxytyrosol and oleuropein, can interfere with the biosynthesis of ergosterol, an essential component of fungal cell membranes. Ergosterol plays a similar role in fungi as cholesterol does in mammalian cells, maintaining membrane fluidity, integrity, and function. By disrupting key enzymatic steps in the ergosterol biosynthesis pathway—particularly those catalyzed by lanosterol 14 α -demethylase (CYP51)—these compounds can compromise membrane structure and function, resulting in increased permeability, leakage of cellular contents, and ultimately cell death. This mode of action is comparable to that of standard azole antifungals, such as fluconazole and itraconazole, suggesting that olive oil-derived phenolics may exert synergistic or complementary effects when used alongside conventional therapies. Furthermore, the selective targeting of ergosterol synthesis may reduce cytotoxic effects on host cells, making such natural compounds promising candidates for antifungal formulations with improved safety profiles.

4.3. Induction of oxidative stress in fungal cells:

Proteases, lipases, and phospholipases are examples of fungal hydrolytic enzymes that are essential to the pathogenicity of *Candida* species and dermatophytes because they promote adhesion, tissue invasion, and nutrient uptake. Olive oil phenolics, especially Hydroxytyrosol and oleuropein, have been shown in numerous *in vitro* investigations to be able to inhibit the activity of these enzymes. For example, it has been demonstrated that Hydroxytyrosol inhibits the activity of secreted aspartyl proteinases (SAPs), which are important virulence factors in mucosal invasion in *Candida albicans*. A decrease in fungal growth and tissue penetration seems to be associated with this inhibition, which also seems to be dose-dependent. Moreover, polyphenolic compounds may interfere with the function of fungal hydrolases by interacting with their active sites or necessary cofactors, which would hinder the organism's capacity to colonize host tissues. These results imply that olive oil's antifungal properties extend beyond its direct fungicidal action and include disruption of vital enzymatic systems required for pathogenicity.

4.4. Inhibition of fungal hydrolytic enzymes:

Fungal hydrolytic enzymes, like proteases, lipases, and phospholipases, are very important for the ability of dermatophytes and *Candida* species to cause disease because they help with sticking to surfaces, invading tissues, and getting nutrients. Several lab studies have shown that olive oil compounds, especially Hydroxytyrosol and oleuropein, can block the activity of these enzymes. For example, Hydroxytyrosol has been found to reduce the activity of secreted aspartyl proteinases (SAPs) in *Candida albicans*, which are important factors that help the fungus invade tissues. This inhibition appears to be both dose-dependent and correlated with a reduction in fungal growth and tissue penetration. Additionally, polyphenolic compounds can interact with important parts of fungal enzymes, which may stop these enzymes from working properly, making it harder for the fungus to invade host tissues. These findings suggest that the antifungal effect of olive oil goes beyond just killing fungi; it also disrupts important enzyme systems that the fungi need to cause infection.

4.5. Enhancement of the host immune response:

Certain parts of olive oil, especially polyphenols like Hydroxytyrosol and oleuropein, have

been shown to help the immune system fight off fungal infections. By enhancing the ability of immune cells like neutrophils and macrophages to engulf and destroy pathogens, these compounds boost the body's natural defenses. Additionally, phenolics from olive oil can change the production of cytokines, promoting a Th1-type response, which is usually more effective against fungal infections. By increasing the ability of immune cells to engulf and destroy pathogens and boosting the production of reactive oxygen species (ROS), these compounds can enhance the function of important immune cells like neutrophils and macrophages, which are crucial for fighting off fungal infections. Additionally, compounds from olive oil can change the way the body produces cytokines, promoting a Th1-type response that is usually more effective against fungal infections. These bioactive might also prepare immune cells in the skin, like Langerhans cells, to recognize and respond more effectively to fungal substances, based on lab studies. Even though there isn't much direct clinical evidence, these findings suggest that using olive oil could be a promising way to boost the immune system and help fight fungal infections.

4.6. Synergistic effect with antifungal drugs:

Evidence from combination studies suggests that some beneficial parts of olive oil—especially phenolic compounds like oleuropein and Hydroxytyrosol—might make traditional antifungal medicines work better. These compounds seem to work together with azole-class drugs (like fluconazole and ketoconazole) by making it easier for the drugs to enter the fungus or by blocking the fungus's ability to get rid of the drugs, which helps the drugs work better. For example, lab studies have shown that treating *Candida albicans* with Hydroxytyrosol and fluconazole together greatly lowers the amount of fluconazole needed to stop the fungus from growing, showing that their antifungal effects work better together. This combined effect might not only decrease the number of synthetic antifungals needed—thereby lowering side effects and the chance of resistance—but also expand their effectiveness against a wider range of fungi. While these findings are promising, further in vivo and clinical investigations are necessary to confirm the therapeutic potential of such combinations in clinical settings.

5. IN VIVO AND CLINICAL EXPERIMENTAL EVIDENCE SUPPORTING THE ANTIFUNGAL PROPERTIES OF OLIVE OIL

Several in vitro studies have confirmed the antifungal efficacy of compounds present in olive oil; however, evaluation of the performance of these compounds in vivo and ultimately in the human setting is essential for their clinical validation. A review of studies on animals and early human tests indicates that olive oil and its beneficial parts, especially oleuropein and Hydroxytyrosol, could be very effective in treating skin and mucosal fungal infections. In animal models, several studies have demonstrated the positive effect of topical formulations containing active olive oil compounds in inhibiting pathogenic fungi. For example, Zorić et al. (2013) reported in a study on mice infected with *Candida albicans* that topical application of a cream containing Hydroxytyrosol significantly reduced the fungal load, improved the histopathological status of the skin, and reduced the inflammatory response. These findings not only indicate the direct efficacy of Hydroxytyrosol but also indicate its role in accelerating the process of damaged tissue repair [Zorić et al., 2013]. In another study, Somova et al. (2003) investigated the effect of oleuropein-rich olive leaf extract on dermatophytosis induced in a rabbit model. The results of this study also demonstrated an improvement in clinical symptoms, which included a reduction in erythema, scaling, and inflammation, as well as inhibition of fungal growth in the treated areas. These data strengthen the potential of olive plant extracts as effective options for topical treatments [Somova et al., 2003]. Clinical evidence is also limited but promising. In a preliminary double-blind trial, Recio et al. (2009) investigated the efficacy of a topical cream containing a combination of olive oil, beeswax, and honey in the treatment of vulvovaginal candidiasis. This cream was able to reduce the patients' symptoms, including

itching, discharge, and inflammation, to a comparable extent to clotrimazole, without any specific side effects being reported. These findings suggest the possibility of using natural compounds containing olive oil in complementary or alternative treatments for female mucosal infections [Recio et al., 2009]. Also, in a randomized trial conducted by Shokri et al. (2018), a topical ointment containing olive leaf extract was used to treat dermatophytosis in patients. The results of this study showed that the intervention group experienced a significant improvement in clinical symptoms and a reduction in fungal burden compared to the control group (placebo), with no serious adverse events reported. This study is one of the few studies that has directly evaluated the clinical antifungal effect of olive oil [Shokri et al., 2018]. Overall, although there are still insufficient clinical studies to draw definitive conclusions in this area, the available experimental evidence suggests that olive oil and its active compounds could be considered safe, effective, and adjunctive options for the topical treatment of fungal infections of the skin and mucosa. Because these compounds have antioxidant, anti-inflammatory, and various beneficial properties, it would be important to carry out large, controlled clinical trials to help develop pharmaceutical products based on olive oil.

6. COMPARING THE ANTIFUNGAL PROPERTIES OF OLIVE OIL WITH COMMON ANTIFUNGAL DRUGS:

Synthetic antifungal agents, including azoles (e.g., clotrimazole, fluconazole), polyenes (e.g., amphotericin B), and allylamines (e.g., terbinafine), are the primary therapeutic alternatives for several cutaneous, mucosal, and systemic fungal infections. These pharmaceuticals operate via distinct methods, including the inhibition of ergosterol production, disruption of cellular membranes, or the inhibition of squalene epoxidase. Notwithstanding early success, the evolution of drug resistance, systemic toxicity, local discomfort, and elevated costs underscore the necessity to explore and create safer complementary or alternative medicines. In this context, bioactive chemicals found in olive oil, particularly oleuropein and Hydroxytyrosol, have garnered significant interest from researchers as natural multi-mechanism medicines. Numerous comparative in vitro investigations have demonstrated that these compounds can have benefits comparable to or even surpassing certain conventional antifungal medications, particularly at elevated concentrations or in enhanced formulations. A study by Bisignano et al. (1999) compared the inhibitory effects of Hydroxytyrosol and oleuropein on the development of *Candida albicans* and *Aspergillus Niger* with that of clotrimazole. The findings indicated that these herbal substances, at particular concentrations (25–100 µg/ml), generated substantial zones of inhibition that coincided with the inhibition zone of clotrimazole (10 µg/disk) [Bisignano et al., 1999].

Gómez-Muñoz et al. (2021) shown in combination research (checkerboard assay) that the concurrent administration of fluconazole and olive phenolic extract lowered the MIC of fluconazole by almost fourfold against resistant *C. albicans*. The synergistic impact is probably attributable to the enhanced entry of the medicine into the fungal cell facilitated by lipophilic olive chemicals [Gómez-Muñoz et al., 2021]. Besides efficacy, the safety profile of olive oil has an additional benefit over many synthetic pharmaceuticals. Fluconazole and terbinafine, while highly efficacious in systemic therapy, may occasionally induce adverse effects including hepatic injury, dermal eruptions, or gastrointestinal disturbances. Conversely, the topical application of olive oil and its derivatives, even in elevated quantities, has been deemed safe in the majority of animal and human trials (Omar, 2010; Recio et al., 2009). Furthermore, olive chemicals, owing to their multitargeted characteristics, diminish the probability of drug resistance and can be utilized for prolonged and sustainable treatment.

Comparative data indicate that olive oil and its phenolic compounds are not only as effective as certain common antifungal medications but also possess the potential to serve as complementary or alternative treatments for specific fungal infections of the skin and mucosa, due to their high safety profile, anti-inflammatory properties, and suitability for topical

formulations. Nevertheless, additional randomized and direct clinical trials are required to evaluate the efficacy and tolerability of these substances in comparison to current medications.

7. TOPICAL FORMULATIONS CONTAINING OLIVE OIL

Given the proven antifungal, antioxidant, and anti-inflammatory properties of olive oil, its use in topical formulations as a natural alternative or complement to conventional treatments has increasingly attracted the attention of researchers and the pharmaceutical industry. Olive oil is used not only as a bioactive agent but also as a suitable base or lipid phase in semi-solid formulations such as creams, ointments, gels, and lotions. Among these dosage forms, creams have been the most widely used, as they are suitable for the proper delivery of both polar and non-polar compounds, and they also show acceptable physicochemical stability in the presence of vegetable oils. Olive oil-based creams are usually of the oil-in-water (O/W) or water-in-oil (W/O) type. In some studies, the addition of skin penetration enhancers (such as mild surfactants, fatty alcohols, or essential oils) to olive oil has been shown to increase the bioavailability of the active ingredients and enhance the antifungal efficacy of the formulation.

A study by Ali et al. (2019) showed that a cream formulation containing 10% olive oil combined with thyme extract had significant inhibitory activity against *Candida albicans*, and its efficacy was comparable to clotrimazole. Also, Hashem et al. (2021) reported that topical application of a cream containing the compound oleuropein (a phenolic component of olive oil) in an animal model of dermatophytosis resulted in a clear reduction in inflammation, erythema, and scaling. Among the main challenges in olive oil formulation are its sensitivity to oxidation and the effects of light, heat, and pH on the stability of its phenolic compounds.

To overcome this problem, the use of novel delivery systems such as nano emulsions, liposomes, and biocompatible polymer hydrogels has been proposed, which, in addition to increasing stability, also improve skin penetration and efficacy. Overall, the development and optimization of topical formulations containing olive oil is not only important from the perspective of treating fungal skin infections but also, given the high acceptability of natural compounds among patients, can help increase treatment acceptance and reduce the incidence of side effects.

8. COMPATIBILITY AND STABILITY OF OLIVE OIL IN DIFFERENT BASES OF TOPICAL FORMULATIONS

Compatibility and stability of olive oil in different bases of topical formulations Numerous studies have focused on the chemical and physical stability of olive oil, which is one of the most important parameters in designing topical formulations. Olive oil can go bad because it has unsaturated fatty acids, like oleic acid and linoleic acid, which can make it less effective and cause a bad smell in the final products. However, the presence of natural antioxidant compounds such as Hydroxytyrosol, tocopherol, and oleocanthal in the composition of olive oil relatively compensates for this weakness (Servili et al., 2009). In fat-based formulations (such as W/O creams or oily ointments), olive oil has good compatibility, and its stability is increased by the addition of natural or synthetic antioxidants such as butylated hydroxytoluene (BHT) (Gómez-Alonso et al., 2003).

In contrast, stability is reduced in aqueous or O/W emulsion bases due to greater exposure to oxygen and moisture, which also increases the need for careful pH control and the use of appropriate emulsifiers. Accelerated stability testing studies have shown that olive oil undergoes chemical degradation at high temperatures and in direct light, but at lower temperatures and in opaque, light-tight packaging, it maintains excellent stability for up to six months or more (Psomiadou & Tsimidou, 2002). Furthermore, the addition of stabilizing

compounds such as ascorbyl palmitate and citric acid has improved the storage quality of olive oil in semi-solid bases in some studies (Bianchi, 2003). From a pharmaceutical perspective, olive oil is well compatible with many base compounds such as petrolatum, lanolin, glycerin, stearyl alcohol, and silicones, but it may cause discoloration or sedimentation in combination with some ionic emulsifiers and low-pH materials, which must be controlled in terms of formulation.

9. LIMITATIONS AND CHALLENGES IN THE PHARMACEUTICAL USE OF OLIVE OIL IN TOPICAL FORMULATIONS

Despite the growing evidence supporting the antifungal effects of bioactive compounds present in olive oil, the clinical and pharmaceutical application of this natural compound still faces several limitations and challenges. These challenges are not only related to biopharmaceutical aspects but also include technological, qualitative, and research considerations.

9.1. Problems with the Skin Absorption of Polar Compounds

One important challenge in using olive oil in topical products is that some of its active compounds, such as Hydroxytyrosol and oleuropein, are relatively poorly absorbed into the deeper layers of the skin. These compounds are often polar and do not easily cross the lipophilic barrier of the stratum corneum (Scognamiglio et al., 2016). Even though using tiny carriers like nanoliposomes or nano emulsions can help the skin absorb olive oil better, these technologies still need more work to ensure they are safe and stable.

9.2. Chemical instability of some phenolic compounds

Polyphenolic compounds such as Hydroxytyrosol, especially in the presence of light, oxygen, and high temperature, undergo rapid oxidation. This instability can lead to a decrease in the pharmacological efficacy of the formulation as well as the production of side compounds with the potential to irritate the skin (Covas et al., 2010). Therefore, the selection of complementary antioxidants, controlled storage conditions, and light-resistant packaging are of significant importance.

9.3. Chemical differences due to the source of olive oil extraction

The chemical composition of olive oil is strongly influenced by ecological factors, genetics, extraction method, and processing. For example, the content of phenols, free fatty acids, and volatiles can vary significantly between different olive varieties (*Olea europaea* L.) and even between different harvests from the same geographical area (Bendini et al., 2007). This heterogeneity leads to non-uniformity in the efficacy of formulations and makes quality control in mass production difficult.

9.4. Lack of human clinical data

Although in vitro and in vivo evidence supports the antifungal properties of olive oil, direct clinical data in humans are very limited. Most of the available human studies focus on its restorative or antioxidant effects and not on its antifungal efficacy (Valls et al., 2015). Therefore, there is an urgent need to design randomized, double-blind, controlled trials that evaluate the efficacy of olive oil in the treatment of fungal skin infections.

9.5. Regulatory Challenges and Clinical Acceptance

The lack of precise pharmaceutical standards to define the quality, purity, and effective dosage of olive oil for topical applications is an obstacle to its widespread commercialization as a

pharmaceutical product. Currently, many olives oil-containing formulations are classified as cosmetic-hygiene products or natural supplements rather than officially licensed drugs, which prevents them from entering clinical treatments (European Medicines Agency, 2020).

CONCLUSION

The incorporation of olive oil in topical formulations as a natural antifungal agent has introduced a noteworthy perspective in complementary medicine and topical therapy. In vitro and animal studies demonstrate that the bioactive constituents of this oil, such as oleuropein, Hydroxytyrosol, and unsaturated fatty acids, exhibit considerable antifungal efficacy against *Candida albicans*, *Aspergillus* spp., and various other fungal infections. The various mechanisms by which these chemicals operate—such as disrupting the fungal cell membrane, inducing oxidative stress, and inhibiting critical enzymes—indicate their potential utility in treatment, particularly in the context of increasing drug resistance. The absence of comprehensive and regulated clinical evidence in humans is a significant barrier to the therapeutic advancement of these drugs. While there are some preliminary reports regarding the efficacy of olive oil-infused creams in superficial skin infections, these findings are not yet clinically applicable due to their initial designs, small sample numbers, and absence of a standardized control group. Thus, it appears that undertaking clinical trials with double-blind, randomized, and multicenter designs, aimed at establishing the effective dose, long-term safety, and direct comparison with standard antifungal medications, is an essential requirement. Conversely, the pharmaceutical characteristics of olive oil, including its chemical and physical stability over many bases, particularly with exposure to light, heat, and oxidants, necessitate careful evaluation. The quality of olive oil, influenced by olive variety, extraction technique, and purity, can substantially affect the ultimate medicinal outcomes. Consequently, the standardization of raw materials and the optimization of formulations incorporating this oil will be pivotal in guaranteeing clinical efficacy. The findings suggest that olive oil has significant potential in treating superficial fungal infections; however, to facilitate its clinical and official use, it is essential to address the current research deficiencies in pharmacokinetics, safety, stability, and human efficacy through more comprehensive studies. Only then may this natural substance be deemed suitable for inclusion in official pharmacopoeias as a scientific, standardized, and dependable entity.

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