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PREFACE

The continuity of human life in a healthy and high-quality manner primarily depends on an adequate and balanced diet. Nutrition is the intake and utilisation of nutrients that are necessary for the growth, development, and long-term healthy and productive life of an individual. Adequate and balanced nutrition is defined as the intake of sufficient and balanced amounts of nutrients necessary for the growth and renewal of the body, and their proper utilisation in the body. Food is not only a biological need, but also a way of living that carries deep cultural, geographical, and social imprints. When viewed from a cultural and social perspective, food is a means of communication, an expression of identity, belonging, love, and life. Geographical indications, on the other hand, reveal the effects of the relationship people have with nature and environmental conditions on eating habits. Nowadays, nutritional science is no longer just about chemical reactions consisting of calories, proteins, or vitamins. In recent years, research has moved beyond macro- and micronutrient analysis to multidisciplinary approaches that take into account the cultural and geographical identity of foods and their bioactive content. The factors influencing human health have a very variable structure, and sustainable diets, respect for nature and animals, cultural values, geographical production conditions, organic foods, functional foods with natural bioactive components, and safe food systems are the cornerstones of this structure.

It is important to evaluate foods that are considered as cultural heritage not only from a gastronomic perspective but also in terms of sustainability, bio-functionality, and public health. Climate, soil, water resources, agriculture, and biodiversity determine the characteristics of the products grown and their transformation into nutritious food. With examples ranging from mountain villages to seasides, how geography and our people shape cuisine is explained in this book. While the sections of the book trace cheeses from different cultures and regions, information is also provided on the bioactive compounds that shape nutrition. A wide range of topics are discussed, from geographically indicated cheeses from Anatolia to Thrace, to powerful antioxidant compounds obtained from olives such as oleuropein, from the effects of soluble fibres such as beta-glucan on the immune system to traditional dietary habits. The aim of the book is not only to compile scientific data on nutrition, but also to bring together traditional, culturally based knowledge with modern science. I believe that the book will be a holistic resource for scientists.

In the light of science, we hope to understand better the values coming from nature and the living beings breathing here…

27/04/2025

EDITOR
Prof. Dr. Tulay OZCAN

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CHAPTER 1

GEOGRAPHICALLY INDICATED CHEESES FROM THRACE TO ANATOLIA

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INTRODUCTION

The significance of plant-based and animal-derived foods in nutrition, which are the most essential and fundamental requirement for the continuity of human life, is substantial. Turkiye is a country where the diversity of agricultural and animal products is due to its geographical location. In addition, its rich culinary culture consists of the coexistence of societies of different cultures. This cultural richness is quite efficient in the advertisement and tourism of traditional food products throughout the country. Products are geographically marked to protect the rich cultural, social and local heritage, and registrations made by the Turkish Patent Institute in our country (Kantaroğlu and Demirbaş, 2018).

Cheese is one of the products in the category of geographically indicated products and is widely consumed. Cheese, which is a part of daily nutrition, stands out with its nutritional value and longest storage capacity, as well as its diversity among milk and milk products. When historical records were examined, cheese is a sign of cultural richness and has a large share in traditional products (Ozcan et al., 2022).

Traditional foods are products that should be transferred to new generations without harming their original characteristics as products that carry the legacy of civilisations. In this context, the concept of geographic indication gains importance. A geographical indication is a concept that emerged due to the need for consumers to know the origin of the food they eat, that which can easily access foods specific to various regions in the globalisation process (Gökovalı, 2007). The purpose of the geographical indication is to ensure the production of the product subject to registration and the protection of these products. "Geographical indication" is one of the international regulations to protect local products from imitation and to eliminate the information asymmetry between the consumer and the producer. Consumers purchase the products at higher prices due to the high-quality guarantee offered, and a significant income increase is provided to the producers. Therefore, there is an opportunity to contribute significantly to rural development, promotion, and sales of local products (Ertan, 2010).

1.1 Geographical Indication

Local products have been protected by geographical indications at national and international levels for protection against imitations of local products and not to be exposed to unfair competition (Kan and Gülçubuk, 2008). Geographic indications are signs on products in order to have a significant geographical origin and derive their quality and fame. Geographical origin can be a village, a town, a region, or a country. In geographical indication registration, the quality that region-specific features bring to the product and the subjectivity that distinguishes it from other similar products are the main objectives (Ayber, 2005). Products and different manufacturing techniques specific to people living in that region have emerged for distinctive locations of Turkiye due to geographical location, climate, different soil structure and diversity of cultural heritage. This difference demonstrates that Turkiye has a product variety that can be the subject of geographical indication (Gökovalı, 2007).

The protection of products with geographical indication provides advantages such as increasing marketing opportunities, increasing income by protecting the producer, economic gain, and orientation of the rural population towards different business areas (Gökovalı, 2007). Today, the registration of geographic indication can be performed in two ways: Protected Designation of Origin (PDO); is the name given to products whose production, processing, and other operations must all take place in a geographical area with defined borders, while the Protected Geographical Indication (PGI) is defined as the name given to products whose production, processing, and at least one of the other operations must take place in a geographical area with defined borders (Anonymous, 2019a). Protected designations of origin products can only acquire their characteristics if they are produced within the region. Products of protected geographical indication are produced in another region, provided that at least one of their qualities originates from the district. However, the production methods and the quality of the product must be identical (Anonymous, 2019b).

1.2 Geographical Indication Cheeses of Turkiye

Cheese, which is the most preferred among milk and dairy products and has the highest product diversity, gains different physicochemical properties with production methods depending on the type of milk used in production. Many technological processes such as heat treatment, coagulation, salting, drying, and ripening provide cheeses with the desired flavour and aroma profile as well as characteristic features (Hayaloğlu et al., 2007). In Turkiye, various local cheeses have been produced with conventional production techniques depending on geographical conditions, cultural habits, and differences in animal species and breeds. Although most of these are produced/consumed in quantities to meet the demand in the region where they are produced, some of them are known throughout the country and provide added value by being converted into commercial products (Cantürk and Çakmakçı, 2019; Keser et al., 2022).

Cheeses, whose consumption figures are limited to the region where they are produced, have commercial potential, but they are products with limited borders. These cheeses are known by the name of the city or region where they are produced and have unique flavour characteristics. The dairy industry has a great responsibility to make these cheeses more widely known and their consumption widespread. When it comes to manufactured production, while it is to preserve the taste, flavour, and aroma profile of local cheeses, it should not cause changes in the original structure of the product. In our country, some traditional cheeses remained limited in various regions and had partially been abandoned as the socio-economic conditions of the district changed. In this regard, it is essential to determine the technical characteristics and various elements of cheeses processed with traditional methods in several regions of our country through research to be performed to be registered (Küpelikılınç, 2020). Erzurum Civil cheese and Diyarbakır Braided cheese are among the more well-known geographically indicated cheeses and have succeeded in exceeding regional production. Cheeses such as Tulum cheese, Antep Sıkma Cheese, Antakya Sürkü, Erzurum Moldy Civil cheese, Yozgat Çanak cheese and Antakya Moldy Sürkü are among the cheeses that cannot exceed regional production but have received geographical indication. These cheeses are loved and consumed by the people of the region in which they are produced. However, the production of these cheeses remains low because they are not well-known outside the region (Saygılı et al., 2020). Cheeses with geographical indication in Turkiye are listed as follows and some characteristics of cheeses are given in Table 1.

1.2.1 Antep cheese/ Gaziantep cheese / Antep Sıkma cheese (Antep Sıkma peyniri)

Antep cheese is a kind of local cheese produced in Gaziantep and bearing the name of the province. Antep cheese is traditionally crafted from the milk of small ruminants grazed on the pastures of Gaziantep province. It is also referred to as "pişken" or "kelle" in Gaziantep. The appearance of Antep cheese is characterized by homogeneity, non-porosity, smoothness, firmness, non-crumbling texture upon cutting, semi-hardness, flexibility, and easy dispersal in the mouth. When chewed, it leaves a squeaky sensation. Its color ranges from grey to white (Anonymous, 2009a). Antep cheese has an irregular oval shape, resembling the palm of a hand. This shape is a result of the traditional method of shaping cheeses during production (Anonymous, 2019a). Antep cheese, when its curd is boiled, is consumed either fresh or after maturing in brine for 2-3 months at temperatures of 3-5ºC (Hayaloğlu et al., 2008; Kamber and Terzi, 2008).

1.2.2 Diyarbakır Braided cheese (Diyarbakır Örgü peyniri)

Diyarbakır Braided cheese is generally produced from sheep milk in the spring months, or a mixture of goat and cow milk. In terms of composition, it is similar to White cheese, and in terms of production technology, it resembles Kashar cheese. Cheese is high in fat content, homogeneous, with plastic curd, elastic texture, semi-hard, unique characteristic taste and aroma, high nutritional value, and has gained consumer preference with its distinctive braided shape. Furthermore, the cheese is creamy white or slightly yellowish, and it can be separated by hand into thread-like strands (Anonymous, 2019a). Although this cheese is consumed fresh, it is mainly available for consumption after maturing in brine containing approximately 10-12% NaCl (at least 90 days at 4-6°C) (Anonymous, 2010a).

1.2.3 Erzurum Civil cheese (Erzurum Civil peyniri)

Civil cheese is an original cheese variety in which acid, rennet, and heat treatment are used together. It is produced under names such as "Çeçil cheese", "Tel cheese", "İplik cheese" and "Çekme cheese" in the Eastern and Northeastern regions of Turkiye, especially in Erzurum (Çakmakçı et al., 2014; Arslaner and Salık, 2020). Civil cheese is manufactured from milk acquired from animals grazing on various grasslands in the pastures amidst the high mountains of Erzurum province. The production of Erzurum Civil cheese involves several steps. Firstly, the milk is passed through a separator to remove its fat content, which results in skimmed milk. Subsequently, after undergoing a specific level of acidification, the skimmed milk is fermented using liquid rennet. Afterwards, the curd formed by heating the product is mixed and kneaded. This cheese is hung on hangers and is obtained as a result of forming a string. This cheese can also be classified as skim or low-fat cheese (Anonymous, 2009b). Erzurum Civil cheese has been produced using only skimmed milk, rennet, and salt, without any additives such as starter culture or $CaCl_2$. Civil cheese is white because it is fat-free and can be used for dietary purposes for people who must eat away from milk fat. The most important feature that distinguishes this cheese is its non-cylindrical filamentous string structure due to the suspension process. This specific feature allows Erzurum Civil cheese to have a lower salt content and distinguishes it from similar string cheeses (Anonymous, 2009b).

1.2.4 Erzurum Mouldy Civil cheese (Erzurum Küflü Civil peyniri (Göğermiş)

Göğermiş cheese is a mature cheese variety with a unique taste, obtained by crumbling Erzurum Civil cheese and mixing it with Lor cheese, pressing it into food-grade plastic containers, removing the whey, and naturally cultivating mould on it (Anonymous, 2010b; Çakmakçı et al., 2012; Çakmakçı et al., 2014). It is stated that non-fat or low-fat cheeses, such as Civil and curd cheese, are rich in protein, calcium and phosphorus. These cheeses are important in the nutrition of children and the elderly and they can meet the quality animal protein needs of the society that tends to be fed lean foods (Anonymous, 2018d). Cheeses with low-fat or reduced-fat content, such as Civil and Lor cheese, have a similar taste to France's Roquefort cheese. Although made from skimmed milk, they were perceived as a fatty variety due to the biochemical reactions that occur during the maturation processes. These cheeses had been extensively studied in all aspects through projects supported by TUBITAK (The Scientific and Technological Research Council of Turkiye), and the strains of *Penicillium roqueforti* that can act as starter moulds had been identified, revealing all their characteristics (Çakmakçı et al., 2012; Çakmakçı et al., 2014; Çakmakçı et al., 2015). In recent years, studies on Mouldy Civil cheese have shown the use of specific non-toxin-producing strains of *Penicillium roqueforti*, obtained by mould isolation and identification, to achieve controlled mould development (Çakmakçı et al., 2014; Çakmakçı et al., 2015).

1.2.5 Yozgat Çanak cheese (Yozgat Çanak peyniri)

This cheese is a low-ripe and semi-skimmed cheese specific to Yozgat, produced from milk obtained from sheep, goats, and cows fed by the natural vegetation and water resources of Yozgat province and its districts (Anonymous, 2017). The product also derives its original name from its packaging. It is matured by burying it in sand after being pressed into a bowl made of soil. It is important in terms of production that the sand in which it is buried during maturation is fine and less pebbly, cool and slightly humid.

1.2.6 Antakya Sürkü cheese (Antakya Sürkü, Çökelek)

Antakya Sürkü Cheese is first precipitated by boiling cow's milk with advanced acidity or buttermilk for the production of Antakya Sürkü (Çökelek) cheese. This cheese has been produced by adding and kneading wild thyme, locally known as ‘zahter’, collected from the mountains of the region, along with salt, pepper paste, optional spices (red chilli, mint, cumin, coriander, coriander, mahaleb, allspice, ginger, nutmeg, cloves, black pepper, cinnamon, basil, fennel, nigella) and garlic (Durmaz et al., 2004; Hayaloğlu and Fox, 2008; Anonymous, 2018b). Since the cheese is shaped by hand, it has a conical structure the size of a pear. “Sürk”, which also means “Çökelek” in Arabic, is usually consumed fresh for breakfast. Antakya Sürkü cheese gains its characteristic feature with its conical shape and orange color. In addition, it contains salty, sour, and bitter tastes together. (Anonymous, 2018b; Anonymous, 2019a).

1.2.7 Antakya Mouldy Sürkü (Antakya Küflü Sürkü)

After receiving its registration, Antakya Mouldy Sürkü (Çökelek), also referred to as "cooked" Sürkü, has obtained a geographical indication. In cheese that matures with the presence of mould, there are alterations in appearance, taste, and aroma. However, unlike other mouldy cheeses, Antakya Mouldy Sürkü (Çökelek) is consumed after removing the moulds from its surface. Although hard crust formation had been observed outside, this type of “Çökelek” exhibits a color ranging from dark red to brown, and industrial production for this variety yet (Anonymous, 2018c).

1.2.8 Gümüşhane Deleme cheese (Gümüşhane Deleme peyniri)

Gümüşhane Deleme cheese is pre-processed and produced by cutting/coagulation of naturally acidified cow's milk. It is a homogeneous, non-porous, slippery, meltable, semi-hard, slightly sour taste and high milk-flavoured cheese that was obtained by boiling, kneading, and shaping with skimmed milk. The prepared cheese can be consumed fresh or after being pressed into moulds, it can mature underground for a minimum of 3 months before consumption (Anonymous, 2021a).

1.2.9 Manyas Kelle cheese (Manyas Kelle peyniri)

Manyas Kelle cheese is a full-fat or semi-fat hard cheese produced from the milk of sheep and cows obtained from animals nourished by the natural vegetation and water sources of the Manyas district in Balıkesir. It has a hard, 2-3 mm thick rind with a yellow-white color, a compact and porous structure, and a distinctive taste and aroma (slightly acidic and salty). The cheese matures in brine and exhibits unique characteristics (Anonim, 2020b). Manyas Kelle cheese is matured for a minimum of 3 months. The salting and maturation process in brine contributes to the development of the characteristic properties and porous texture of Manyas Kelle cheese. It is known as Manyas Kelle cheese and also called Mihalic, Maglıc, primarily made from raw sheep's milk for over 250 years in the Balıkesir and Bursa provinces (Hayaloğlu et al., 2008; Aday and Karagül-Yüceer, 2014; Ozcan and Kurdal, 2012).

1.2.10 Maraş Parmak/Sıkma cheese (Maraş Parmak/Sıkma peyniri)

Maraş Parmak/Sıkma cheese has been produced from pasteurized cow/goat/sheep milk or a combination of them. It is a type of cheese that has been shaped into strips approximately two fingers wide (around 2-3 cm) in hot water. After production, Maraş Parmak/Sıkma cheese can be consumed without any further processing, and it is also preferred in the production of pastries, casseroles, and unsalted desserts (Anonymous, 2021b).

1.2.11 Sakarya Abhaz cheese (Sakarya Abaza peyniri)

Sakarya Abhaz cheese was shaped by the culture of the Abhaz people who settled in Sakarya province 700 years ago. This cheese is a ripened cheese with characteristics between kashar cheese and dil cheese, with a fibrous structure, amber-yellow color, and a generally braided appearance. It is a mature cheese with a fibrous texture and an amber-yellow color. Its appearance is typically in the form of a braid or pattern. It creeps into hot water because of its fibrous structure. The distinctive properties of the cheese are due to the omasum yeast used in its production, seasonings (optionally black cumin and thyme), and the traditional production method (Anonymous, 2021c).

1.2.12 Vakfikebir Külek cheese (Vakfikebir Külek peyniri)

Vakfikebir Külek cheese is a traditional type of cheese obtained by pressing the cheese and cottage cheese produced from cow or sheep's milk tightly in layers in wooden containers called külek and maturing under the ground or in hazelnut shells. The distinctive characteristics of this cheese are due to the traditional omasum rennet used in its production and the "külek" made from the spruce trees used for packaging. The külek used in the production of Vakfıkebir Külek cheese has been produced from spruce trees that do not cause odour and taste transfer to the cheese. The cheeses are buried in soil (not hard and sandy) or hazelnut shells and matured for 3-6 months. After ripening, the cheese can be consumed directly or vacuum packed and stored at 4°C. After maturation (3-6 months), it has a typical aged cheese flavour (Anonymous, 2021d).

1.2.13 Urfa Cheese/Şanlıurfa cheese (Urfa peyniri/Şanlıurfa peyniri)

Urfa cheese / Şanlıurfa cheese is a type of cheese known by the name of Şanlıurfa province and it has a reputation with the specified geographical border. It is obtained from raw cow, sheep, and goat milk, or a combination of these kinds of milk, using unique methods. Urfa cheese ripened in brine is produced by heat treatment of raw milk, and this cheese matures in brine for at least 120 days from the date of production and is offered to the market. During the production of Urfa cheese, the moisture content of the product has initially been reduced by applying dry salting or boiling. It has ensured that it has the desired hard, firm, and less brittle structure by salting the cheese. In addition, it has ensured that it is elastic and less sticky inside and outside with the boiling process. One of the distinguishing characteristics of Urfa cheese is its shape. To give the cheese its unique shape, cheese cloths called "parzın" are used in the production in the region. After breaking the curd formed during cheese production, it is placed in the "parzın" to remove the whey, and the cheese is partially shaped into a cylindrical or conical form, specific to the cheese (Anonymous, 2021e).

1.2.14 Çankırı Küpecik cheese (Çankırı Küpecik peyniri)

Küpecik cheese is a local cheese variety produced almost everywhere in the Çankırı province. In the production of Çankırı Küpecik cheese, no heat treatment is applied to the curd. The factors contributing to the distinctive characteristics of Çankırı Küpecik cheese are the following: the use of specific yeast, pressing the cheese into glazed clay pots, sealing the openings of the pots with cotton cloth, and ageing the cheese in sand. During the first 15 days, it has remained mature for at least 120 days by continuing to change and control the gland once every 3 or 4 days (Anonymous, 2021f).

1.2.15 İvrindi Kelle cheese (İvrindi Kelle peyniri)

İvrindi Kelle cheese has produced using sheep, goat and cow milk, or a mixture thereof. İvrindi Kelle cheese is a type of cheese with a hard, crusty outer shell that can range in color from yellow to white. It has a smooth and porous texture and falls primarily into the category of hard cheese, with some variations of semi-hardness. It has matured in brine during the ageing process. Omasum yeast had been used in the production stage. It matures in brine for at least 120 days from the date of production. Its porous structure formed during the maturation process (Anonymous, 2022a).

1.2.16 İzmir Tulum cheese (İzmir Tulum peyniri)

İzmir Tulum cheese is a type of cheese obtained from animals grown in the Aydın, Balıkesir, İzmir, and Manisa provinces and produced according to the local method using 50% sheep, 25% goat and 25% cow milk and matured for at least 4 months. In the production of Izmir tulum cheese, 70-80% of the milk obtained from goats and sheep grazing on pastures in January and June is used. The milk of the animals of this geography contains volatile phenolic compounds characteristic of the vegetation and especially volatile fatty acids from thyme. İzmir Tulum cheese is creamy yellow in color, semi-hard, and has a brittle structure and homogeneous pores (Anonymous, 2022b).

1.2.17 Malatya cheese (Malatya peyniri)

Malatya cheese is a cylindrical-shaped cheese with a diameter of 10-15 cm and a thickness of 2-3 cm, with grooves on it, making a sound when chewed, semi-hard structure, and porcelain white-light yellowish color. The grooves on it originate from printing tools made of reed. In its production, Malatya cheese can be made using raw cow or sheep milk or a combination of these milks. Alternatively, milk that has been pasteurized with a heat treatment not exceeding 70°C can also be used. Although starter culture is not used in raw milk, it can be used in production with pasteurised milk production. Malatya cheese is produced by boiling in water or whey at temperatures above 85°C. As a result, it possesses a characteristic texture that produces a crunching sound when bitten into, and it can be cooked on a non-stick pan or over an open fire without melting (Anonymous, 2022c).

1.2.18 Yüksekova Çirek cheese (Yüksekova Çirek peyniri)

Yüksekova Çirek cheese is exclusively produced using sheep milk during the spring and summer months. After the curd, the cheese is manually opened into thin sheets that resemble yufka (a type of Turkish pastry dough). Afterwards, a mixture of lor cheese is spread over the sheets and the cheese is rolled up into a cylindrical shape. The curd cheese used in production is produced using whey from the previous production of Yüksekova Çirek Cheese. On the geographical border, Yüksekova Çirek Cheese is also called "penire çırık" or "penire çırkırı", which means "elastic or boiled cheese". Yüksekova Çirek Cheese can be stored at +4°C and out of the light for 7-15 days (Anonymous, 2022d).

1.2.19 Atlantı Dededağ Tulum cheese (Atlantı Dededağ Tulum peyniri)

Atlantı Dededağ Tulum cheese has a rich historical background that dates back to ancient times. Its name is derived from the Atlantı Plain, located on the geographical border, and the adjacent Dede mountain. The geographical frontier is of significant importance in the local culinary culture. It is unique to the geographical border in terms of kneading boiled curd with baked rock salt and preparation of overalls. Cheese is produced using milk obtained from sheep raised within the geographical border. Consequently, all stages of production for the Atlantı Dededağ Tulum cheese are carried out within this geographical boundary due to its close association with the region (Anonymous, 2023a).

1.2.20 Ağrı Tulum cheese (Ağrı Tulum peyniri)

Ağrı Tulum Cheese is produced in the Ağrı plain and Patnos plain of Ağrı province, located at an average altitude of 1640 meters. Cheese is manufactured by blending cow milk and Akkaraman/Morkaraman breed sheep milk, with the composition of the milk mixture comprising 90-95% sheep milk and 5-10% cow milk. The curd is pressed into a leather sack or plastic container and aged for a minimum of 4 months, resulting in a semi-soft, full-fat Tulum cheese. The cheese is made from raw milk, and neither pasteurization nor thermization is applied during production.

The curd pressing continues until the whey is expelled through the pores of the leather. In the case of plastic containers, perforations are made using a sharp needle ("biz") to facilitate the drainage of whey. The curd, whether in leather sacks or plastic containers, is stored in cold storage at temperatures ranging from -2°C to 0°C for at least 4 months for maturation (Anonymous, 2024a).

1.2.21 Ayvalık Kelle cheese (Ayvalık Kelle peyniri)

Ayvalık Kelle cheese is produced using a mixture of sheep, goat, and cow milk, or a combination of these. It is a brined cheese with a hard rind, varying in color from yellow to white, and has a firm, hole-free, and porous texture. Depending on the degree of hardness, it is classified primarily as a hard cheese, with a smaller portion classified as semi-hard. The milk composition is determined by the producer, but at least 10% and no more than 30% of sheep and/or goat milk is used. Raw milk is heated in cooking vats in a temperature range of 57-68°C for at least 15 seconds to ensure a longer shelf life. Maturation is a key factor in the cheese's characteristics, as it causes the pore size to increase and spread uniformly up to 8 cm in diameter. The cheese hardens further during maturation. Ayvalık Kelle cheese is distinctive for its basket shape and relatively low salt content after maturation. The cheese is brined in a 10-12% salt solution for at least 120 days after production, with the development of the porous structure occurring during the maturation phase (Anonymous, 2024b).

1.2.22 Savaştepe Mihaliç Kelle cheese (Savaştepe Mihaliç Kelle peyniri)

Savaştepe Mihaliç Kelle cheese is produced in the Savaştepe district of Balıkesir province using a mixture of sheep and cow milk or exclusively cow milk. It is a brined cheese with a hard rind, ranging from yellow to white, with a firm, hole-free, and porous texture. It is predominantly classified as a hard cheese, with a small portion being semi-hard. Sheep milk is sourced primarily from hybrid breeds of

Kıvırcık Merinos, with peak production occurring from April to June. During periods of low sheep milk production, cow milk is used exclusively. When sheep and cow milk are used, sheep milk constitutes at least 40% of the mixture. Traditional curd shaping methods are used, with the curd being boiled, collected in straining cloths, suspended on hooks, and pierced with sticks to allow whey drainage. The curd is then shaped into a "basket" form. The cheese undergoes fermentation in a brine solution at room temperature for 5-10 days, followed by maturation at 4°C for a minimum of 120 days. The maturation process leads to the formation of characteristic pores, generally no larger than 10 mm (Anonymous, 2024c).

1.2.23 Mengen cheese (Mengen peyniri)

Mengen cheese is a low-fat, semi-hard cheese produced in the Mengen region of Bolu province, using either cow or sheep milk. It has a light yellow color and cylindrical shape, reminiscent of Kashkaval cheese. The milk is pasteurized at a minimum temperature of 63°C for 30 minutes. Heating continues until the whey temperature reaches approximately 50-55°C.

The curd begins to coagulate under heat and is then manually collected and placed into cylindrical cheese molds with perforated bottoms to facilitate draining. Cheese is dry-salted on the exterior and stored at 4°C for one day. The shelf life of this cheese is generally around two months (Anonymous, 2023b).

1.2.24 Antakya Künefelik cheese (Antakya Künefelik peyniri)

Antakya Künefelik Cheese, traditionally made from the milk of small ruminants, is now exclusively produced from cow milk due to a decline in small ruminant populations and increased demand. It can be salted or unsalted. The unsalted version lacks salt and has a short shelf life, lasting only a few days depending on storage conditions. The salted version, also known as "chestnut type," has a high salt content, which extends its shelf life to up to 6 months at room temperature and up to 1 year under refrigeration. Despite the differences in salt content, both variants share similar pH levels due to their functional property of stretchability. The unsalted variety is particularly known for its elastic texture and the "chicken breast" like structure that forms when pH reaches 4.9-5.2 during production. It also exhibits stretchability when heated above 65°C. Both salted and unsalted versions are used exclusively in cooking, such as in künefe preparation, where the cooking temperature exceeds 75°C, thus eliminating potential microbiological risks associated with raw milk (Anonymous, 2021g).

1.2.25 Bergama Tulum cheese (Bergama Tulum peyniri)

Bergama Tulum Cheese is produced on the Kozak Plateau (Madra mountains) of the Bergama district, using cow milk or a mixture of cow, sheep, and goat milk. It is a full-fat, semi-hard, porous cheese that is matured in brine. The milk mixture typically comprises 40-50% cow milk, 30-40% sheep milk, and 20-30% goat milk. The cheese is named after the traditional method of pressing curd into a leather sack, a technique brought about by the nomadic Yörük people of Central

Asia. However, modern production often involves maturing cheese in metal containers. Bergama Tulum cheese has a high dry matter content (approximately 58%) and fat content (approximately 30.5%). Its distinctive flavor is enhanced by local plant species from the Kozak plateau, which contribute terpenes and other compounds (Anonymous, 2024d).

1.2.26 Elbistan Kelle cheese (Elbistan Kelle peyniri)

Elbistan Kelle cheese is produced by coagulating milk at the appropriate fermentation temperature using rennet, followed by fermentation and boiling of the curd. The curd is then salted, placed in food-safe containers, and shaped before maturation. It is a white, cream, or pale yellow cheese with a firm, partially porous texture and a salty taste. Elbistan Kelle cheese belongs to the class of cheeses matured in brine and can be classified as either hard or semi-hard, depending on its firmness. Typically, equal amounts of cow and sheep milk are used in production, although it can also be made exclusively from sheep or cow milk (Anonymous, 2023c).

1.2.27 Kars Gruyere Cheese (Kars Gravyer peyniri)

Kars Gruyere cheese is a hard, firm-textured, porous cheese produced in Kars province using raw or pasteurized cow's milk. It is aged 6-12 months and has a strong taste. Both industrial and traditional production methods are used, with the traditional method omitting starter cultures. The rind is hard and homogeneous, ranging in color from golden yellow to light brown, while the interior is ivory to pale yellow. The cheese has evenly distributed holes, typically no larger than 1 cm in diameter. Cheese wheels usually measure 55-70 cm in diameter, 15-17 cm in height, and weigh 55-85 kg. Its flavor is mildly salty, slightly sweet, creamy, nutty, and robust (Anonymous, 2024e).

1.2.28 Talas Cumin Cheese (Talas Çörekotlu Çömlek peyniri)

Talas Cumin cheese is produced by coagulating milk at the appropriate fermentation temperature using rennet. The curd undergoes fermentation, is crumbled, salted, and then tightly pressed into food-safe clay pots or containers for maturation. This cheese is characterized by a white, cream, or pale yellow color, with a firm, non-porous structure, a salty taste, and a distinct cumin flavour. Cow milk is primarily used in production, though up to 25% sheep or goat milk may be included, depending on producer preference. Cumin is derived from the seeds of *Nigella sativa* L. and *Nigella damascena* L. (A maximum of 50 grams of cumin is used per 1 kg of cheese). The cheese matures for at least 4 months in a cool environment before being ready for consumption (Anonymous, 2024f).

1.2.29 Muş Aged Kashkaval cheese (Muş Eski Kaşar peyniri)

Muş Aged Kashkaval cheese is a creamy-colored cheese produced from the milk of sheep that graze on endemic plants in the region, with goat and cow milk added to balance the flavour. The typical milk composition is 45-50% sheep milk, 30-35% cow milk, and 15-20% goat milk. The milk is heated to 32°C, and rennet is added to form curd. The curd is then heated with steam to raise the temperature to

38°C, followed by draining. It is pressed with cloths for 25-30 minutes and shaped into large molds. Molds are pressed for 2-3 hours before briefly boiling in a water bath.

The curd is kneaded and dry-salted four times during a pre-aging process that lasts 24 hours. The cheese matures for 35-40 days in air circulation, followed by cold storage on wax paper for 4-6 months. After maturation, the cheese is packaged and ready for sale (Anonymous, 2023d).

1.2.30 Kepsut Bükdere Mouldy Katık cheese (Kepsut Bükdere Küflü Katık peyniri)

It is a type of moldy cheese produced by straining and salting yogurt obtained from goat and sheep milk and filling it into goat or goat skins and ripening it, and its color varies from yellowish cream to white. It has thin strips of blue mold veins inside. The distinguishing feature of the cheese is the use of oak trees in the preparation of the leather skins in which it is ripened.

The strained and salted yogurt is placed tightly into the skins with sticks made of oak trees, so that there is no gap. Kepsut Bükdere Moldy Katık cheese is ripened at 10-20°C for approximately 9 months and stored at 4°C for 12 months (Anonymous, 2025).

Table 1.a. Some Characteristics of Turkiye's CI Registered Cheeses

Type of Cheese	pH	Acidity %LA	DM (%)	Protein (%)	Fat (%)	Ash (%)	Salt (%)	References
Antep Sıkma Cheese	6.50 6.50	1.75 -	60.20 50.00	20.30 17.50	23.30 19.00	- -	9.90 1.00	Anonymous, 2009a, Anonymous , 2009a
Diyarbakır Braided Cheese	- 5.40 5.57 5.40	1.11* - 0.46 -	47.75 57.47 54.43 53.17	21.69 23.55 25.20 26.18	17.86 23.50 20.57 17.70	8.01 - 8.77 9.29	6.03 4.82 7.67 8.29	Anonymous, 2010a, Hayaloğlu and Karabulut, 2013, Hatipoğlu, 2014, Hatipoğlu and Çelik, 2021
Erzurum Civil Cheese	6.32 4.53 5.47	0.73* 0.78 2.39	40.35 36.58 35.19	32.20 22.49 32.40	0.30 0.25 2.30	7.8 - -	6.14 4.68 -	Anonymous , 2009b, Cambaztepe et al., 2009, Yıldız et al., 2010
Erzurum Mouldy Civil Cheese	5.60 6.48 5.25 6.51	1.70 0.77 0.72 0.48	65.00 48.18 46.97 -	35.00 36.95 36.55 -	6.00 3.45 1.72 -	- 5.6 - -	5.00 5.13 7.21 7.34	Anonymous , 2010b, Çakmakçı et al., 2012,, Çakmakçı et al., 2014, Arslan, 2020

Table 1.b. Some Characteristics of Turkiye's CI Registered Cheeses

Type of Cheese	pH	Acidity %LA	DM (%)	Protein (%)	Fat (%)	Ash (%)	Salt (%)	References
Yozgat Çanak Cheese	- 4.77 -	1.62 - 2.23	51.49 53.52 64.12	26.61 27.53 -	13.56 19.58 46.00	6.68 - -	6.10 3.34 8.48	Akyüz and Gülümser (Çakmakçı), 1984 Hayaloğlu and Karabulut, 2013
Malatya Cheese	5.8-6.1	-	43-45.7	-	18.8-20.8	-	4-5.2	Anonymous, 2022c
Antakya Sürkü (Çökeleği)	5.81 4.49 4.40 4.36	1.44 1.04 1.77 1.04	49.82 32.27 37.40 34.80	26.43 17.56 22.00 22.00	14.66 9.90 7.40 7.40	- 4.42 4.70 4.80	5.36 - 3.50 3.50	Durmaz et al., 2004, Ördek, 2015, Anonymous, 2018b, Anonymous, 2018c
Antakya Mouldy Sürkü Cheese	4.94 5.25 4.76	1.14 1.62 1.44	44.32 46.91 45.20	19.03 19.45 20.10	8.99 8.81 9.50	7.96 5.90 6.20	8.35 - 6.80	Güler, 1994, Ördek, 2015, Anonymous, 2018c
Manyas Kelle Cheese	5.44 5.51 -	- 0.56 -	58.75 60.4 -	24.58 22.0 -	25.54 27.4 -	- 7.54 -	6.38 5.92 -	Hayaloğlu and Karabulut, 2013, Aday and Karagul Yuceer, 2014, Anonymous, 2020b
Maraş Parmak/ Sıkma Cheese	- 5.69 5.7	1.71 0.59 0.7	53.00 57.04 50.00	20.25 22.30 22.00	43.87 33.26 23.00	- 11.46 -	6.12 - 6.5	Ceylan et al., 2003, Küpelikılınç, 2020, Anonymous, 2021d**

Table 1.c. Some Characteristics of Turkiye's CI Registered Cheeses

Type of Cheese	pH	Acidity %LA	DM (%)	Protein (%)	Fat (%)	Ash (%)	Salt (%)	References
Sakarya Abhaz (Abaza) Cheese	-	-	65.00	27.00	25.00	-	-	Anonymous, 2021f**
Vakfıkebir Külek Cheese	5.3	3.00	45.00	27.5	10-45	-	10.0<	Anonymous, 2021g**
Urfa Cheese / Şanlıurfa Cheese	1.23 0.29 -	1.23 0.29 -	48.33 48.52 -	17.53 - -	22.96 22.02 -	2.10 9.58 -	6.80 9.29 -	Yetişmeyen and Yıldız, 2003, Yalçın et al., 2007, Anonymous, 2021e
Çankırı Küpecik Cheese	6.3	2.3	55.00	26.29	25	2.45	5.8	Anonymous, 2021f**
İvrindi Kelle Cheese	-	-	-	-	25/45	-	7.5	Anonymous, 2022a
İzmir Tulum Cheese	4.36 4.92	0.98 1.45	56.52 71.85	24.48 27.50	24.38 32.00	- -	3.53 5.27	Akpınar et al., 2017 Anonymous, 2022b**
Yüksekova Çirek	5.18	0.77	46.92	20,0	21.69	3.27	2,81	Anonymous, 2022d
Kepsut Bükdere Mouldy Katık Cheese	4.6-4.7	1.75-1.90	55.00	19.00-21.00	24.75 28.05	-	1.65-2.20	Anonymous, 2025

LA: Lactic acid, DM: Dry matter, **R: References, **: The highest average values reported in the relevant research, -: No analysis *: Calculated from the values given in °SH and/or dry matter in the relevant research

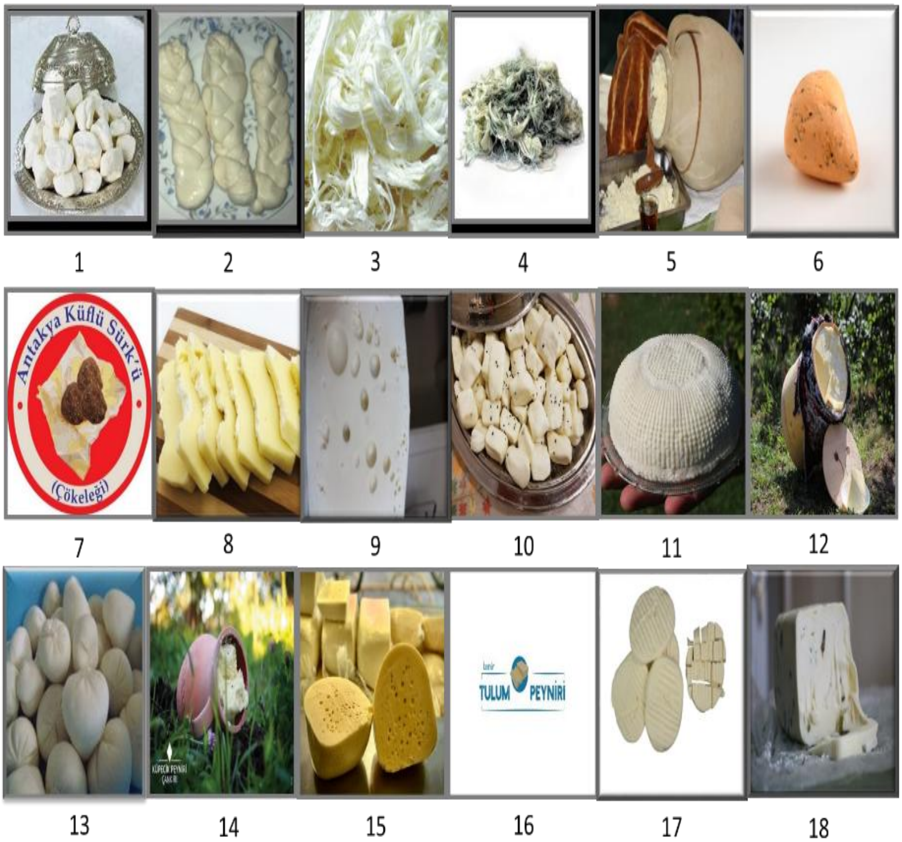

Fig. 1a. 1: Antep Sıkma cheese, **2:** Diyarbakır Braided cheese, **3:** Erzurum Civil cheese, **4:** Erzurum Mouldy Civil cheese, **5:** Yozgat Çanak cheese, **6:** Antakya Sürkü cheese, **7:** Antakya Mouldy Sürkü, **8:** Gümüşhane Deleme cheese, **9:** Manyas Kelle cheese, **10:** Maraş Parmak/Sıkma cheese, **11:** Sakarya Ahbaz Cheese (Abaza), **12:** Vakfikebir Külek cheese, **13:** Urfa Cheese/Şanlıurfa cheese, **14:** Çankırı Küpecik cheese, **15:** İvrindi Kelle cheese, **16:** İzmir Tulum cheese, **17:** Malatya cheese, **18:** Yüksekova Çirek cheese. (TÜRK PATENT VE MARKA KURUMU).

Fig. 1b. 19: Atlantı Dededağ Tulum cheese, **20**: Ağrı Tulum cheese, **21:** Ayvalık Kelle cheese, **22:** Savaştepe Mihaliç Kelle cheese, **23:** Mengen cheese, **24:** Antakya Künefelik cheese, **25:** Bergama Tulum cheese, **26:** Elbistan Kelle cheese, **27:** Kars Gruyere cheese, **28:** Talas Cumin cheese, **29:** Muş Aged Kashkaval cheese, **30:** Kepsut Bükdere Mouldy Katık cheese (TÜRK PATENT VE MARKA KURUMU).

CONCLUSION

Turkiye has significant potential in terms of local product diversity. Each region has a unique product, and these products are named with the same name as the geographical region that has been referenced. The registration of these products with geographical indications is of importance from economic, political, and tourist points of view. When considering the whole country, dairy products, with their wide variety of varieties, stand out among the geographically indicated products in our country. Our ever-increasing variety of cheeses not only contributes to the growth of tourism activities but also meets the demands of consumers seeking natural, reliable, and high-quality products due to their superior nutritional characteristics. In this regard, necessary efforts must be initiated for the industrial-scale production of our country's rich traditional products. The production of geographically indicated products on an industrial scale, without compromising their distinctive characteristics, can facilitate easier access for consumers and satisfy producers. There are many varieties with different characteristics that may be at risk of extinction in Turkiye. It is necessary to classify our country's cheeses based on their different characteristics, develop and standardize production technologies, obtain geographical indications for a greater number of cheeses, establish a regular and updatable database of their specific features and compositions, and promote them to the world. Additionally, 11 cheese varieties have applied for geographic indication registration. The increase in the number of geographical indications for cheeses would play a significant role in the development of unrecognized cheese varieties and undiscovered flavours, as well as facilitating the transition of rich traditional products into the industrial realm. This would create momentum across the entire food sector and have important effects on the development of the country. Furthermore, awareness of the right to use geographical indications will increase the demand for geographically indicated products among consumers who seek to consume high-quality goods, as they recognize geographical indications as symbols of quality.

Authors' Contribution

The authors contributed equally to the article.

Declaration of Conflict of Interest

There is no conflict of interest between the authors.

Declaration of Research and Publication Ethics

Research and publication ethics were complied with in the study.

REFERENCES

Aday, S., and Karagül Yüceer, Y. (2014). Physicochemical and sensory properties of Mihalic cheese. *International Journal of Food Properties*, *17*(10), 2207-2227.

Akpinar, A., Yerlikaya, O., Kınık, Ö., Korel, F., Kahraman., C., and Uysal., H. R. (2017). Some Physicochemical Characteristics and Aroma Compounds of Izmir Tulum Cheese produced with different milk types. *Ege Üniversitesi Ziraat Fakültesi Dergisi*, *54* (1), 27-35.

Akyüz, N., ve Gülümser (Çakmakçı), S. (1984). Yozgat Çanak peynirinin yapılışı, bileşimi ve olgunlaştırılması. *Gıda*, *9*(4), 231-238.

Anonymous (2009a) TÜRKPATENT. Antep Sıkma Peynirinin Cİ Tescil Belgesi (Tescil No:356), https://www.ci.gov.tr/

Anonymous (2009b) TÜRKPATENT. Erzurum Civil Peynirinin Cİ Tescil Belgesi (Tescil No:116), https://www.ci.gov.tr/

Anonymous (2010a) TÜRKPATENT. Diyarbakır Örgü Peynirinin Cİ Tescil Belgesi (Tescil No:170), https://www.ci.gov.tr/

Anonymous (2010b) TÜRKPATENT. Erzurum Küflü Civil Peynirinin Cİ Tescil Belgesi (Tescil No:164), https://www.ci.gov.tr/

Anonymous (2017) TÜRKPATENT. Yozgat Çanak Peyniri Cİ Tescil Belgesi (Tescil No:281), https://www.ci.gov.tr/

Anonymous (2018b). TÜRKPATENT. Antakya Sürkü (Çökelek) Cİ Tescil Belgesi (Tescil No:330), https://www.ci.gov.tr/

Anonymous (2018c). TÜRKPATENT. Antakya Küflü Sürkü Cİ Tescil Belgesi (Tescil No:359), https://www.ci.gov.tr/

Anonymous (2018d) Coğrafi işaretli et ve süt ürünleri. https://www.esk.gov.tr/tr/10872/Sut (Erişim Tarihi: 21.01.2022).

Anonymous (2019a) Türkiye Patent Enstitüsü. Coğrafi işaretler ve geleneksel ürün adları başvuru kılavuzu. https://www.turkpatent.gov.tr/TURKPATENT

Anonymous (2019b) Türkiye Esnaf ve Sanatkârları Konfederasyonu (2019). Sınai Mülkiyet Hakları Bilgi Sitesi.

Anonymous (2020b). TÜRKPATENT. Manyas Kelle Peyniri Cİ Tescil Belgesi (Tescil No:628), https://www.ci.gov.tr/

Anonymous (2021a). TÜRKPATENT. Gümüşhane Deleme Peyniri Cİ Tescil Belgesi (Tescil No:694), https://www.ci.gov.tr/

Anonymous (2021b). TÜRKPATENT. Maraş Parmak/Sıkma Peyniri Cİ Tescil Belgesi (Tescil No:727), https://www.ci.gov.tr/

Anonymous (2021c) TÜRKPATENT. Sakarya Abhaz (Abaza) Peyniri Cİ Tescil Belgesi (Tescil No:746), https://www.ci.gov.tr/

Anonymous (2021d) TÜRKPATENT. Vakfıkebir Külek Peyniri Cİ Tescil Belgesi (Tescil No:764), https://www.ci.gov.tr/

Anonymous (2021e) TÜRKPATENT. Urfa Peyniri/Şanlıurfa Peyniri Cİ Tescil Belgesi (Tescil No:807), https://www.ci.gov.tr/

Anonymous (2021f) TÜRKPATENT. Çankırı Küpecik Peyniri Cİ Tescil Belgesi (Tescil No:907), https://www.ci.gov.tr/

Anonymous (2021g). TÜRKPATENT. Antakya Künefelik Peyniri Cİ Tescil Belgesi (Tescil No:979), https://www.ci.gov.tr/

Anonymous (2022a). TÜRKPATENT. İvrindi Kelle Peyniri Cİ Tescil Belgesi (Tescil No:1025), https://www.ci.gov.tr/

Anonymous (2022b) TÜRKPATENT. İzmir Tulum Peyniri Cİ Tescil

Belgesi (Tescil No:1006), https://www.ci.gov.tr/
Anonymous (2022c). TÜRKPATENT. Malatya Peyniri Cİ Tescil Belgesi (Tescil No:1164), https://www.ci.gov.tr/
Anonymous (2022d). TÜRKPATENT. Yüksekova Çirek Peyniri Cİ Tescil Belgesi (Tescil No:1086), https://www.ci.gov.tr/
Anonymous (2023a). TÜRKPATENT. Atlantı Dededağ Tulum Peyniri Cİ Tescil Belgesi (Tescil No: 1327), https://www.ci.gov.tr/
Anonymous (2023b). TÜRKPATENT. Mengen Peyniri Cİ Tescil Belgesi (Tescil No:1482), https://www.ci.gov.tr/
Anonymous (2023c). TÜRKPATENT. Elbistan Kelle Peyniri Cİ Tescil Belgesi (Tescil No:1500), https://www.ci.gov.tr/
Anonymous (2023d). TÜRKPATENT. Muş Eski Kaşarı Cİ Tescil Belgesi (Tescil No:1393), https://www.ci.gov.tr/
Anonymous (2024a). TÜRKPATENT. Ağrı Tulum Peyniri Cİ Tescil Belgesi (Tescil No:1565), https://www.ci.gov.tr/
Anonymous (2024b). TÜRKPATENT. Ayvalık Kelle Peyniri/Ayvalık Sepet Peyniri Cİ Tescil Belgesi (Tescil No:1664), https://www.ci.gov.tr/
Anonymous (2024c). TÜRKPATENT. Savaştepe Mihaliç Kelle Peyniri Cİ Tescil Belgesi (Tescil No:1405), https://www.ci.gov.tr/
Anonymous (2024d). TÜRKPATENT. Bergama Tulum Peyniri Cİ Tescil Belgesi (Tescil No:1597), https://www.ci.gov.tr/
Anonymous (2024e). TÜRKPATENT. Kars Gravyer Peyniri Cİ Tescil Belgesi (Tescil No:1640), https://www.ci.gov.tr/
Anonymous (2024f). TÜRKPATENT. Talas Çörekotlu Çömlek Peyniri Cİ Tescil Belgesi (Tescil No:1560), https://www.ci.gov.tr/

Anonymous (2025). TÜRKPATENT. Kepsut Bükdere Küflü Katık Peyniri Cİ Tescil Belgesi (Tescil No:1683), https://www.ci.gov.tr/

Arslan, N. (2020). Erzurum Küflü Civil Peyniri'nin (Gögermiş Peynir) laktik asit bakteri mikrobiyotası ile bazı mikrobiyolojik ve fizikokimyasal özelliklerinin belirlenmesi (Yüksek Lisans Tezi). Atatürk Üniversitesi Fen Bilimleri Enstitüsü, Erzurum.

Arslaner, A., ve Salık, M. A. (2020). Bayburt Civil peynirinin bazı kimyasal, biyokimyasal ve mikrobiyolojik özellikleri ile mineral ve ağır metal içerikleri. *Gıda*, *45*(3), 433-447.

Ayber, İ. (2005). Sınai Mülkiyet Hakları ile ilgili uluslararası kuruluşlar (WIPO DTÖ, AB, TPE.). Uzmanlık Tezi, *Türk Patent Enstitüsü Markalar Dairesi Başkanlığı, Ankara*.

Cambaztepe, F., Çakmakçı, S., and Dağdemir, E. (2009). Effect of some technological parameters on microbiological, chemical and sensory qualities of Civil cheese during ripening. *International Journal of Dairy Technology*, *62*(4), 541-548.

Cantürk, A., ve Çakmakçı, S. (2019). Erzurum çevresindeki peynir işletmelerinde kullanılan peynir mayalarının mikrobiyolojik, duyusal ve teknolojik özellikleri. *Akademik Gıda*, *17*(1), 30-37.

Ceylan, Z. G., Türkoglu, H., and Dayisoylu, K. S. (2003). The microbıologıcal and Chemical Qualıty of sıkma cheese produced in Turkey. *Pakıstan Journal of Nutrition*, *2*(2), 95-96.

Çakmakçı, S., Gündoğdu E., Hayaloğlu A. A., Dağdemir, E., Gürses, M., Çetin, B., and Tahmas-Kahyaoğlu D. (2012). Chemical and microbiological status and volatile profiles of mouldy Civil cheese, a Turkish mold-ripened variety. *International Journal of Food*

Science and Technology, *47*(11), 2405-2412.

Çakmakçı, S., Gürses, M., Hayaloğlu, A. A., Çetin, B., Şekerci, P., and Dağdemir, E. (2015). Mycotoxin production capability of *Penicillium roqueforti* strains isolated from mould-ripened traditional Turkish Civil cheese. *Food Additives and Contaminants: Part A*, *32*(2), 245-249.

Çakmakçı, S., Hayaloğlu, A. A., Dağdemir, E., Cetin, B., Gürses, M., and Tahmas- Kahyaoğlu, D. (2014). Effects of *Penicillium roqueforti* and whey cheese on gross composition, microbiology and proteolysis of mould-ripened Civil cheese during ripening. *International Journal of Dairy Technology*, *67*(4), 594-603.

Durmaz, H., Tarakçı, Z., Sağun, E., ve Aygün, O. (2004). Sürk'ün kimyasal ve duyusal nitelikleri. *Fırat Üniversitesi Sağlık Bilimleri* Dergisi, *18*(2), 85-90.

Ertan, A. (2010). Prestijli tarım ürünlerinin pazarlanmasında kalite ve coğrafi işaretler kavramlarının tutundurulması ve bu bağlamda tarım satış kooperatiflerinin önemi. *Süleyman Demirel Üniversitesi Sosyal Bilimler Dergisi*, *2*(12).

Gökovalı, U. (2007). Coğrafi işaretler ve ekonomik etkileri: Türkiye örneği. *İktisadi ve İdari Bilimler Dergisi*, *21*(2), 141-160.

Güler, M. B. (1994). Hatay Yöresi Sürk (Küflü Çökelek) ve Carra (Testi) peynirlerinin üretimi, özellikleri ve standardizasyon olanakları üzerine bazı araştırmalar (Doktora Tezi), Çukurova Üniversitesi, Fen Bilimleri Enstitüsü, Adana.

Hatipoğlu, A. (2014). Geleneksel Diyarbakır Örgü peynirinin karakteristik özelliklerinin tespit edilmesi ve gıda güvenliği açısından değerlendirilmesi (Doktora Tezi), Harran Üniversitesi, Fen Bilimleri Enstitüsü, Şanlıurfa.

Hatipoğlu, A., ve Çelik, Ş. (2021). Küçük aile işletmelerinde üretilen Diyarbakır Örgü peynirinin bileşim ve bazı biyokimyasal özellikleri. *Afyon Kocatepe Üniversitesi Fen ve Mühendislik Bilimleri Dergisi*, 21, 829-836.

Hayaloğlu, A. A, Fox, P. F., Güven, M., and Çakmakçı, S. (2007). Cheeses of Turkey: 1. Varieties ripened in goat-skin bags. *Lait*, 87, 79-95.

Hayaloğlu, A. A., Ozer, B. H., and Fox, P. F. (2008). Cheeses of Turkey: 2. Varieties ripened under brine. *Dairy Science and Technology*, *88*(2), 225- 244.

Hayaloğlu, A. A., ve Fox, P. F. (2008). Cheeses of Turkey: 3. Varieties containing herbs or spices. *Dairy Science and Technology*, 88, 245-256.

Hayaloğlu, A. A., and Karabulut, İ. (2013). Primary and secondary proteolysis in eleven Turkish cheese varieties. *International Journal of Food Properties*, *16*(8), 1663-1675.

Kamber, U., and Terzi, G. (2008). The traditional cheeses of Turkey: Southeast Anatolia region. *Food Reviews International*, *24*(1), 62-73.

Kan, M., ve Gülçubuk, B. (2008) Kırsal ekonominin canlanmasında ve yerel sahiplenmesinde coğrafi işaretler. *Uludağ Üniversitesi Ziraat Fakültesi Dergisi*, *22*(2), 57- 66.

Kantaroğlu, M., ve Demirbaş, N. (2018). Türkiye'de coğrafi işaretli gıda üretim potansiyelinin değerlendirilmesi. VIII. IBANESS

Kongreler serisi, Plovdiv, Bulgaristan, Nisan, 21-22, 514-520.

Keser, G., Ozcan, T., Ciniviz, M., and Yilmaz-Ersan, L. (2022). Genetic heritage and traditional cheeses. 1st International Traditional Food and Sustainable Food Systems Symposium, August,10, Mersin.

Küpelikılınç, E. E. (2020). Geleneksel helete peynirinin genel özellikleri (Yüksek lisans tezi), Kahramanmaraş Sütçü İmam Üniversitesi Fen Bilimleri Enstitüsü, Kahramanmaraş.

Ozcan, T. and Kurdal. E. (2012). The effects of using a starter culture, lipase and protease enzymes on ripening of Mihalic cheese. *International Journal of Dairy Technology*, *65*(4): 585-593.

Ozcan, T., Yilmaz-Ersan, L., and Keser, R. A. (2022). The perspective of geographically indicated dairy products. 1st International Traditional Food and Sustainable Food Systems Symposium, August,10, Mersin.

Ördek, R. (2015). Hatay ilinde satılan sürklerin kaliteleri üzerine araştırmalar/Studies on the quality of surk sold in Hatay province (Doktora tezi) Sağlık Bilimleri Enstitüsü, Hatay.

Saygılı, D., Demirci, H., ve Samav, U. (2020). Coğrafi İşaretli Türkiye Peynirleri. *Aydın Gastronomy*, 13-19

Yalçın, S., Ardıç, M., ve Nizamlıoğlu, M. (2007). Urfa Peynirinin bazı kalite nitelikleri. *Atatürk Üniversitesi Veteriner Bilimleri Dergisi*. *2*(3), 90-95.

Yetişmeyen, A., ve Yıldız, F. (2003). Urfa peynirlerinin mikrobiyolojik, kimyasal ve duyusal niteliklerinin saptanması. *Gıda*, *28*(3), 287-294.

Yıldız, F., Yetişemiyen, A., Şenel, E., Durlu Özkaya, F., Öztekin, Ş., ve Şanlı, E. (2010). Some properties of Civil cheese: A type of traditional Turkish cheese. *International Journal of Dairy Technology*, *63*(4),575-580.

CHAPTER 2

TRADITIONAL TURKISH CHEESE REGISTERED AS DESIGNATION OF ORIGIN

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INTRODUCTION

When regional food products protected by geographical indications and the richness of regional products are evaluated together, it becomes clear that there is significant production potential for the national economy in Turkiye. In addition to creating employment and added value for potential products, geographical indication can contribute to the sustainability of production in production regions (Kantaroğlu & Demirbaş, 2018). The definition of geographical indication includes signs indicating the product identified with the region, area, region, or country of origin regarding a distinctive quality, reputation, or other characteristics. Geographical indications are also registered as the name of the origin or source indication according to the characteristics (Anonymous, 2017a).

The names that define products that originate from a region, area, or, in exceptional cases, a country with defined geographical boundaries derive all or all of their main characteristics from natural and human elements specific to this geographical area and whose production, processing, and other processes take place within the boundaries of this geographical area are called designations of origin. The names that define products that originate from a region, area or country with defined geographical boundaries are identified with this geographical area in terms of distinctive quality, reputation, or other characteristics and whose production, processing, and different processes take place within the limits of a defined geographical area are called indications of origin (Anonymous, 2017a).

All the main characteristics and characteristics of the product subject to the designation of origin must originate from a geography with specific boundaries. The second feature is that the product's production process, subject to the designation of origin, must take place entirely within a geography with boundaries. The product's connection and geographical origin are powerful in origin names (Karaca, 2016). In Turkiye, 14 of 44 cheeses with geographical indication have been registered as originating. This study summarises the distinguishing features and physicochemical properties of the cheeses that have received geographical indications and have been registered as origins.

Ezine Cheese (Ezine Peyniri)

Ezine cheese is a popular cheese variety that has been produced on a large scale and consumed abundantly in Turkiye (Uymaz et al., 2019). Ezine cheese is produced from mixtures of full-fat cow, sheep, and goat milk among the white cheeses in Turkiye. The most distinctive feature of Ezine cheese is animal milk fed with fatty and aromatic herbs grown in the region. In the production of this cheese, milk obtained from animal breeds (Tahirova, Chios, Dağlıç breed sheep, Holstein breed cow, Karakeçi, and Turkish Saanen goat breed) is used in March and July (Anonymous, 2006). Starter culture and calcium chloride are not used in production (Uymaz et al., 2019). Ezine cheese, which obtained geographical indication status in 2007, has a pale yellow color leaning towards white and possesses a soft to medium firmness with a non-brittle texture (Durlu-Ozkaya & Gun, 2007). The distinctive characteristics of Ezine cheese arise from the milk mixture used in its production, the cheese culture prepared from calf rennet in whey (PAS), sea salt, and the production method used. Ezine cheese may have a creamy taste due to milk fat and a cooked milk taste and aroma due to heat treatment (Anonymous, 2006).

Kargı Tulum Cheese (Kargı Tulum Peyniri)

Kargı Tulum cheese is produced from cow, sheep, and goat milk grown in Kargı district of Çorum province. Furthermore, this cheese is a full-fat tulum cheese served for consumption after it has matured for at least 4 months. Kargı Tulum cheese is produced with traditional methods on a small scale in homes, family-type businesses, and dairy farms in the region. It is a good example of traditional food (Dinkçi et al., 2012). The region has rich vegetation due to the high rainfall. There are more than 70 endemic plants in Kargı plateau. Eight of them are unique to Kargı. Since the milk used in the production of Kargı Tulum cheese is processed into cheese without removing fat, the cheese has a high-fat content and appears yellowish. Kargı Tulum cheese has a semi-hard textural structure. There is also a special production of tulum used in Kargı Tulum cheese. The white sheepskin is salted and left to dry in the sun for 3 months during the summer. After the sheepskin is dried, the wool is tagged. Afterwards, the sheepskins are soaked and subjected to a pre-washing process. The sheepskin surface is mixed with cheese, juice, flour, and dough. It is kept this way for about one day. Subsequently, the sheepskin is cleaned and washed. The skins are cut into sizes for cheese filling and left to dry again. Skins prepared this way are ready to be used as overalls (Anonymous, 2021b).

Edirne White Cheese (Edirne Beyaz Peyniri)

The Edirne White cheese, mostly known as "Salamura" or "Teneke" cheese, is primarily produced in the Thrace, Marmara, Aegean, and Central Anatolia regions. The unique taste, aroma, and texture of these cheeses were influenced by various factors, such as the geographical conditions of each region, the local plant habitat, the breed of animals raised, and the different technological processes applied. The most important distinguishing characteristic of production technology is the absence of additives or supplement substances other than milk, yeast, and salt in the production process (Anonymous, 2019). It is our country's most widely consumed geographical indication cheese variety (Saygılı et al., 2020).

Antakya Carra Cheese (Antakya Carra Peyniri)

Antakya Carra Cheese is obtained from the milk of cows or goats raised within the geographical boundaries. Afterwards, the cottage cheese produced from cow's milk is pressed into a glazed or unglazed pot/earthenware jug (Carra) in layers so that no air is left. Subsequently, the mouth of this pot is sealed. Finally, the pot is buried in the ground with the mouth of the vessel down (Anonymous, 2021c). After the mouth of the pot is closed/sealed with a mortar prepared from a mixture of salt, wood ash, olive oil, and water, the prepared cheeses are ripened for at least 4 months. The distinctive characteristic of this cheese comes from the mountain thyme, known locally as ‘Zahter’, along with the use of cumin and the pots used for packaging. Antakya Carra cheese, depending on the season and animal breed, exhibits a white-cream color, a firm and brittle texture, and is rich in salty and aromatic components (Careri et al., 1996; Hayaloglu & Fox, 2008; Anonymous, 2021c).

Karaman Divle Obruk Tulum Cheese (Karaman Divle Obruğu Tulum Peyniri)

It is made from the milk obtained from goats, cows, and sheep fed completely naturally (dried clover, hay, or roughage in seasons when they cannot go out to pasture) in the highlands within the borders of the Ayrancı district of Karaman province. First, the raw milk of the Tulum cheese is mixed in a ratio of 1/1/8 (goat/cow/sheep). Then, it is pressed into a leather Tulum prepared from goat or lamb skin and matured in Divle Obruğu for 5-6 months. Subsequently, it is offered for consumption (Anonymous, 2017b). This cheese, which has the general characteristics of Tulum cheese, is a white cream, high in fat content, and exhibits a distinctive aroma and flavor. The main characteristic distinguishing this product from other Tulum cheeses is its maturation process in a cave called "Obruk." Obruk is a natural cold storage facility, providing a temperature of 4ºC and relative humidity of 80% within the cave (Kamber & Terzi, 2008a; Anonim, 2017b). The Tulum cheeses placed in this Obruk, which has a unique mould flora, develop blue, white and brick-red moulds for about one month. After the mould has dried, the outer surface of the overalls turns a brick-red color. This process shows that the cheese is fully matured. This ripening period lasts 5-6 months (Kamber & Terzi, 2008a; Morul & Isleyici, 2012; Anonymous, 2017b; Anonymous, 2018a).

Kars Kashar Cheese (Kars Kaşar Peyniri)

The milk used in the production of Kashar cheese is obtained from animals grazing on pastures in the Kars and Ardahan provinces, where there are around 1600 flowering plants. Kars Kashar cheese is classified within the cheeses produced by boiling the curd. It has a whitish cross-sectional surface, a slightly salty taste, and a texture that easily crumbles in the mouth. Kashar cheese is called 'Fresh Kashar cheese' in the pre-maturation stage before it is taken to cold storage and is marketed as 'Old Kashar cheese' after the third month (Anonymous, 2019a). When fresh Kashar cheese comes out of the mould, it has a whitish color and tastes slightly salty, bland, and milky. It takes a yellowish color by forming a crust within a week. Old Kashar is harder, slightly salty, more aromatic, and readily dispersed in the mouth (Anonymous, 2014).

Pınarbaşı Uzunyayla Circassian Cheese (Pınarbaşı Uzunyayla Çerkes Peyniri)

Pınarbaşı Uzunyayla Circassian cheese is a traditional cheese variety produced by the Circassians who migrated from the Caucasus region after 1850. It has also continued its production while maintaining its authenticity to the present day. Pınarbaşı Uzunyayla Circassian cheese is a traditional cheese variety produced from full-fat cow or sheep milk in the geographical area mentioned. At the boiling point of the milk, fermented whey is added and coagulated with the effect of acid and heat, and the resulting clot is moulded into baskets. Its outer surface is salted with coarse rock salt, and it forms a crust in a short time. It is exposed to north winds in its natural environment, fresh, or where it is produced. It is a semi-hard traditional cheese that can last long and is consumed after resting in its natural environment for about fifteen days. The cheese has a smooth and even appearance. Initially, it has a matte, pale white color resembling white cheese, but it turns creamy or straw-yellow after a week. During maturation, it develops a firm and oily rind due to oxidation. Over time, the rind forms a dark yellow color (Anonymous, 2021a).

Kırklareli White Cheese (Kırklareli Beyaz Peyniri)

Kırklareli White cheese is a type of cheese produced from a mixture of sheep (30-45%), goat (25-45%), and cow (15-30%) milk, which is grown in the pastures and meadows of Kırklareli. This cheese is consumed after maturing in brine. These cheeses are ripened for at least six months at 4ºC after being filled with brine (6-7% NaCl) and sealed (Anonymous, 2020a; Aşkın, 2020). Kırklareli white cheese is obtained from natural omasum yeast. The pasteurization temperature (63-65°C) is usually kept low. A specific portion of the natural flora derived from the milk remains alive at these temperature parameters, preserving the flavor of the milk to a great extent. Since the maturation of the product takes place with these bacteria from the natural flora of milk, the aroma and flavor show more characteristic features than the white cheeses produced in other regions (Anonymous, 2020a).

Malkara Old Kashar Cheese (Malkara Eksi Kaşar Peyniri)

The famous work of Evliya Çelebi has been the subject of Seyahatname; it stated that Malkara is a famous place for its kashkaval (Kashar cheese). Malkara Old Kashar cheese is a local cheese variety produced in Malkara, located on the old road from Thessaloniki to Istanbul. It was produced from the milk of sheep, goats, and cows fed with *Lathyrus* L. (damson), *Medicago minima* L. Bart (wild clover), *Medicago polymorpha* L. (hairy clover), *Medicago falcata* L. (yellow-flowered clover), *Avenaelatius* L. (high-meadow oats), *Thymuslongicaulis* C. Presl (long-stemmed thyme), which are predominantly native to the region.

Its dark straw-yellow color has a firm texture and a fully ripened cylindrical form (Anonymous, 2019; Karaca, 2016). From a sensory perspective, it exhibits a salty, umami, and sour taste, with cooked, creamy-buttery, sulfur, whey, rancid, animalistic, yeast/mould, fruity, and nutty aromas (Anonymous, 2017c).

Van Herby Cheese (Van Otlu Peyniri)

Van Herby cheese has been produced in Van and Hakkari provinces for more than 200 years from sheep, cow, or goat's milk or a mixture thereof with the addition of approximately 20-25 herbs grown in the region and surrounding provinces such as Sirmo, Thyme, Siyabo and Heliz (Coşkun et al., 1996; Tarakci et al., 2004; Hayaloglu & Fox, 2008). It has a color ranging from white to yellowish, depending on the variation in milk and herbs. It is moderately firm and salty, with a predominant aroma of garlic and thyme. After salting, it is consumed fresh or aged in brine, making it a type of cheese (Kamber & Terzi, 2008b; Anonymous, 2018b). Cheese's distinct color, taste, aroma, and appearance originate from the herbs used in its production (Yenipınar et al., 2014).

Hanak String Cheese (Hanak Tel Peyniri)

Hanak String cheese is a bright and light yellow colored wire cheese with each wire measuring 0.6-3.8 mm thick, obtained by fermenting the milk obtained from the "Anatolian Brown" breed, which is a hybrid of the native Eastern Anatolian Red and Brown Swiss breeds raised in the Hanak district of Ardahan province, with rennet, processing the prepared cheese dough, and brining. It is cylindrical and rope-shaped, quite flexible, and has high stretchability. Hanak String cheese consists of thin strings (fibres) that extend up to approximately 6 m and do not stick together. 1 kg of Hanak String cheese is obtained from 13 litres of milk. In the production of Hanak String cheese, the cheese fibres are made independent of each other by pulling and kneading processes. In Hanak String cheese, the wire cheese mass consists of a gland resembling a large skein of rope, and each string in this rope remains without sticking to each other. Its sensory properties include shredded wheat, string skin, or thin rod pasta; it is slightly yellowish and bright in color, flexible in textural properties, and highly able to stretch. Since a large amount of rock salt is used in the brine process, the shelf life of Hanak String cheese is 2 years (Anonymous, 2023a).

Erzincan Tulum Cheese (Erzincan Tulum Peyniri)

Erzincan Tulum cheese is white and cream-colored, does not spread quickly, and its unique aroma originating from its ingredients is easily felt when taken into the mouth; it is semi-hard, homogeneous in structure, and has a distinct acidic taste. It is produced from raw milk obtained from Akkaraman sheep or by mixing a maximum of 5% of Morkaraman sheep's or goat milk into Akkaraman sheep's milk. Since raw milk is used in production, the ripening period is at least 4 months. The distinctive features of Erzincan Tulum cheese: It is produced by using at least 95% sheep milk, traditionally produced rennet from lamb or calf, and spring salt (salt produced by crystallizing natural saltwater solution with natural evaporation method in summer months) in its composition and by pressing it tightly into food-compatible packaging material or goat and sheep skin Tulum cheeses. Rennet is used in the production of Erzincan Tulum cheese. It is obtained by adding 6-7 dried lamb rennet or 3-4 calf rennet to approximately 25-30 litres of whey and waiting for 1 week. The milk fermented with animal rennet is strained and then kept for one day, then placed in 50 kg bags and turned upside down every day for approximately 10 days to drain completely. Cheeses crumbled in chrome vats are salted with 2-2.5% spring salt from the Kemah district of Erzincan province and tightly into bags. The mouths of the bags are sewn and stacked on top of each other. After waiting approximately 10 days, the cheeses, which are drained, are stored in cold storage (Anonymous, 2001).

Kırklareli Old Kashar Cheese (Kırklareli Eski Kaşar Peyniri)

Kırklareli Old Kashar cheese is an old Kashar cheese produced in Kırklareli province using milk and natural rennet obtained from animals raised in Kırklareli province. Only cow milk can be used in its production, or a mixture of 30-45% sheep's milk, 25-40% goat's milk, and 15-30% cow's milk can be used. Wheat, legumes, broad-leaved grasses, and shrubs found in the pastures of Kırklareli province cause an increase in dry matter, fat, and aroma components in milk and cheese. The milk is fermented with rennet and left for 60 minutes to reach curd maturity, then broken into 1 cm diameter pieces. The curd separated from the cheese water is cut into large pieces and fermented to be processed quickly during the boiling phase and to smooth the cheese dough. After passing through the grating machine 2-3 times, when the acidity reaches pH 5.20-5.10, it is boiled for 10 minutes in boiling water at 65-75°C. It is placed in 12 kg wheel-shaped Kashar molds and left for pre-ripening in resting rooms for 20-30 days. Kırklareli Old Kashar cheese, whose pre-ripening is completed, is placed in specially produced linen sacks suitable for contact with food and left for at least 6 months in cold storage at 2-4°C and more than 90% relative humidity for the main ripening (Anonymous, 2023b).

Çayeli Koloti Cheese (Çayeli Koloti Peyniri)

It is a cheese produced from the milk of jersey and cross-bred cows in the Cayeli district of Rize Province. Çayeli Koloti cheese is off-white in color, flat, and thin. Koloti is a container with a water drain hole at the bottom, cut into specific sizes from the trunks of pine trees growing in the highlands of Çayeli. The locals ripen the cheese in these containers. The cheese gets its woody aroma from these containers. For this reason, this cheese is called Koloti cheese. Skim milk is ripened in cauldrons for half a day to one day. The measure of ripening is milk coagulation when heated to 40-45°C. While the milk in the cauldron continues to be heated on low heat, it is stirred with a suitable wooden spoon for contact with food. When heat treatment is applied to the cheese, a fist-sized piece is taken from the cheese that has reached the consistency of bread dough, crushed by hand on a straining cloth, taken out, and kneaded 3 times until it reaches 73-75°C. After the cooled cheese is salted, it is stored in a pine Koloti container below 10°C for at least 3 months. It is taken out of this container and offered for sale (Anonymous, 2022).

Table 1.a. Some Characteristics of Turkiye's CI Registered Cheeses

Type of Cheese	pH	Acidity (%LA)	DM (%)	Protein (%)	Fat (%)	Ash (%)	Salt (%)	References
Edirne White Cheese	4.88	1.05	39.42	13.97	19.17*	-	7.34*	Öner & Karahan, 2006
	5.00	-	40.00	-	8.00	-	10.0	Anonymous, 2007
	4.61	1.51	35.54	-	16.50	-	3.01	Aydemir, 2018
	5.10	0.83	45.4*	17.10	23.50	4.10	2.98	Salum et al., 2018
Ezine Cheese	5.72	1.60	52.00	-	-	-	-	Anonymous, 2006
	4.95	1.10	42.92	17.55	22.47	5.35	4.68	Özsoy, 2012
	4.95	-	49.98	19.10	25.25	-	3.91	Hayaloğlu & Karabulut, 2013
	4.92	0.62*	48.91	-	25.0*	-	3.58*	Uymaz et al., 2019
Karaman Divle Obruk Tulum Cheese	5.42	1.07	56.27	25.90	23.46	4.96	3.99	Morul & İşleyici, 2012
	5.49	-	60.13	27.62	25.92	-	2.46	Hayaloğlu & Karabulut, 2013
	5.14	2.72	56.25	31.07	19.50	-	3.80	Anonymous, 2017b
Kars Kashar Cheese	-	1.52	60.04	27.23	26.88	4.74	3.30	Aydemir, 2010
	-	2.29	63.50	29.00	33.34	5.30	3.50	Anonymous, 2014
	5.61	1.09	60.36	25.85	29.71	3.93	2.20	Koboyeva, 2018
	5.04	1.63	56.37	-	28.09	-	3.73	Çetinkaya, 2021
Malkara Old Kashar Cheese	-	-	60.00	-	45.00	-	3.5	Anonymous, 2017c
	5.34	0.87	68.92	32.51	31.8	3.88	3.88	Subaşı, 2021
Van Herby Cheese	4.55	1.84	55.41	21.22	24.37	-	6.64	Tarakçı et al., 2004
	4.66	-	53.32	20.86	20.42	-	5.52	Hayaloğlu & Karabulut, 2013
	-	-	47.78	25.52	19.21	7.4	6.90	Anonymous, 2018b
	5.10	1.41	51.94	17.24	24.88	8.43	6.12	Kara & Köse, 2020

Table 1.b. Some Characteristics of Turkiye's CI Registered Cheeses

Type of Cheese	pH	Acidity (%LA)	DM (%)	Protein (%)	Fat (%)	Ash (%)	Salt (%)	References
Erzincan Tulum Cheese	5.30	1.88	66.22	24.63	34.96	5.82	4.66	Tekinşen & Akar, 2017**
Kırklareli Old Kashar	-	-	65	20	29.75	-	-	Anonymous, 2023b**
Çayeli Koloti Cheese	-	-	52	40	12	-	5.2	Anonymous, 2022**
Antakya Carra Cheese	5.63	0.85	53.43	24.86	18.87	-	8.84	Güler, 1994
	6.56	0.32	65.35	14.76	13.87	-	4.49	Aygün et al., 2005
	5.20	-	58.70	-	26.80	-	7.80	Anonymous, 2021c
Kargı Tulum Cheese	-	0.62	65.34	21.37	20.53	-	3.69	Dinkçi et al., 2012
	4.64	1.41	61.71	20.17	30.28	4.67	4.76	Kiraz, 2018
	4.5	2.55	-	-	25.00	-	-	Akbulut Çakır et al., 2021
	-	0.9	70.00	25.00	33.00	3.5	3.5	Anonymous, 2021b**
Kırklareli White Cheese	4.90	-	49.00	27.00	17.00	-	-	Anonymous, 2020a
	4.66	1.77	50.20	18.38	28.60	2.46	5.59	Aşkın, 2020
Pınarbaşı Uzunyayla Circassian Cheese	-	-	59.17	24.03	32.9	-	3.97	Anonymous, 2021a**
	-	-	62.79	23.27	34.90	-	4.00	Anonymous, 2021a**

LA: Lactic acid, DM: Dry matter, **R: References, **: The highest average values reported in the relevant research, -: No analysis *: Calculated from the values given in °SH and/or dry matter in the relevant research

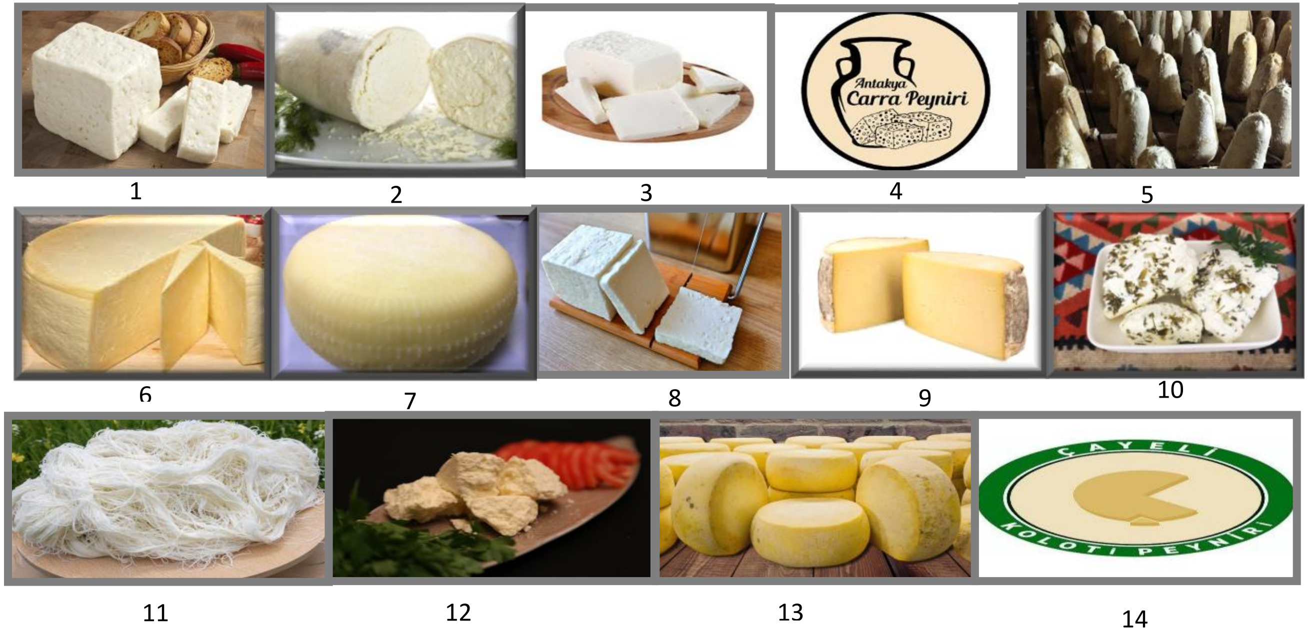


Fig. 1. 1. Ezine Cheese, 2: Kargı Tulum Cheese, 3: Edirne White Cheese, 4: Antakya Carra Cheese, 5: Karaman Divle Obruk Tulum Cheese, 6: Kars Kashar Cheese, 7: Pınarbaşı Uzunyayla Circassian Cheese, 8: Kırklareli White Cheese, 9: Malkara Old Kashar Cheese, 10: Van Herby Cheese, 11: Hanak String Cheese, 12: Erzincan Tulum Cheese, 13: Kırklareli Old Kashar Cheese, 14: Cayeli Koloti Cheese (TÜRK PATENT VE MARKA KURUMU)

CONCLUSION

As in the world, the production of traditional cheeses and their recognition by different consumer groups are critical in our country. Our traditional cheese variety contributes to gastronomy tourism and meets consumers' natural, reliable, and quality product demands with its nutritional features. Protecting our traditional cheeses with geographical indication and especially protecting local production businesses to bring unknown flavors to light is very important in gastronomy tourism. For this purpose, introducing traditional cheeses with geographical indications throughout the country without losing their unique characteristics and producing them industrially will allow consumers to access these products more efficiently and provide added value to producers. In addition, the microflora of cheeses made with traditional methods, the identification of the microbiological diversity of cheeses with geographical indications, and the industrial evaluation and protection of these cultures are also important. To provide the expected benefits of geographically indicated cheeses, researching to reveal the difference between the product and carrying out promotional activities on national and international platforms (festivals, catering promotions, TV programs, public service announcements, posters, brochures, traditional product promotion, etc.) will further contribute to the branding of these products.

Authors' Contribution

The authors contributed equally to the article.

Declaration of Conflict of Interest

There is no conflict of interest between the authors.

Declaration of Research and Publication Ethics

Research and publication ethics were complied with in the study.

REFERENCES

Akbulut Çakır, Ç., Büyüksırıt Bedir, T., and İstanbullu Paksoy, Ö. (2021). Determınatıon of some chemıcal, textural and mıcrobıologıcal propertıes of kargı tulum cheese. *Euroasia Journal of Mathematics, Engineering, Natural and Medical Sciences International Indexed and Refereed*, *8*(17), 131.

Anonymous (2001). TÜRKPATENT. Erzincan Tulum Peyniri Cİ Tescil Belgesi (Tescil No:30), https://www.ci.gov.tr/

Anonymous (2006) TÜRKPATENT. Ezine Peynirinin Cİ Tescil Belgesi (Tescil No:86), https://www.ci.gov.tr/

Anonymous (2007) TÜRKPATENT. Edirne Beyaz Peynirinin Cİ Tescil Belgesi (Tescil No:93), https://www.ci.gov.tr/

Anonymous (2014). TÜRKPATENT. Kars Kaşarının Cİ Tescil Belgesi (Tescil No:190), https://www.ci.gov.tr/

Anonymous (2017a). Sınai Mülkiyet Kanunu. (2017, 10 Ocak). Resmi Gazete (Sayı: 29944). Erişim adresi: https://www.mevzuat.gov.tr/mevzuat?MevzuatNo=6769&MevzuatTur=1&MevzuatTertip=5

Anonymous (2017b) TÜRKPATENT. Karaman Divle Obruğu Tulum Peynirinin Cİ Tescil Belgesi (Tescil No:270), https://www.ci.gov.tr/

Anonymous (2017c) TÜRKPATENT. Malkara Eski Kaşar Peynirinin Cİ Tescil Belgesi (Tescil No:261), https://www.ci.gov.tr/

Anonymous (2018a) Coğrafi işaretli et ve süt ürünleri. https://www.esk.gov.tr/tr/10872/Sut (Erişim Tarihi: 04.02.2025).

Anonymous (2018b). TÜRKPATENT. Van Otlu Peynirinin Cİ Tescil Belgesi (Tescil No:405), https://www.ci.gov.tr/

Anonymous (2019). Türkiye Patent Enstitüsü Coğrafi İşaretler ve Geleneksel Ürün Adları Başvuru Kılavuzu. https://www.turkpatent.gov.tr/TURKPATENT/resources/temp/6B3F914C-E72C-437C8A30-F50C51DE0A23.pdf

Anonymous (2020a). TÜRKPATENT. Kırklareli Beyaz Peyniri Cİ Tescil Belgesi (Tescil No:636), https://www.ci.gov.tr/

Anonymous (2021a) TÜRKPATENT. Pınarbaşı Uzunyayla Çerkes Peyniri Cİ Tescil Belgesi (Tescil No:727), https://www.ci.gov.tr/

Anonymous (2021b). TÜRKPATENT. Kargı Tulum Peyniri Peyniri Cİ Tescil Belgesi (Tescil No:933), https://www.ci.gov.tr/

Anonymous (2021c). TÜRKPATENT. Antakya Carra Peyniri Cİ Tescil Belgesi (Tescil No:679), https://www.ci.gov.tr/

Anonymous (2022). TÜRKPATENT. Çayeli Koloti Peyniri Cİ Tescil Belgesi (Tescil No:1199), https://www.ci.gov.tr/

Anonymous (2023a). TÜRKPATENT. Hanak Tel Peyniri Cİ Tescil Belgesi (Tescil No:1563), https://www.ci.gov.tr/

Anonymous (2023b). TÜRKPATENT. Kırklareli Eski Kaşar Peyniri Cİ Tescil Belgesi (Tescil No:1408), https://www.ci.gov.tr/

Aşkın, B. (2020). Some properties of Kırklareli ripened white cheese. *Milk Science International*, *73*(3), 16-22.

Aydemir, O. (2010). Kars Kaşar Peynirinin Karakterizasyonu (Doktora tezi). Ondokuz Mayıs Üniversitesi Fen Bilimleri Enstitüsü, Kars.

Aydemir, O. (2018). Proteolysis and lipolysis of white-brined (Beyaz) cheese during storage: Effect of milk pasteurization temperature. *Journal of Food Processing Preservation*, *42*(5), 1-6.

Aygün, O., Aslantaş, Ö., ve Öner, S. (2005). A survey on the microbiological quality of Carra, a traditional Turkish cheese. *Journal of Food Engineering*, 66, 401-404.

Careri, M., Spagnoli, S., Panari, G., Zannoni, M., & Barbieri, G. (1996). Chemical parameters of the non-volatile fraction of ripened ParmigianoReggiano cheese. *International Dairy* Journal, *6*(2), 147-155.

Coşkun, H., Bakırcı, İ., & Işık, Ş. (1996). A study on the determination of herb-addition rate in Van herby cheese. *Yüzüncü Yıl Üniversitesi Ziraat Fakültesi Dergisi, 6*(4), 97- 103.

Çetinkaya, A. (2021). Kars piyasasında satışa sunulan yoğurt, beyaz peynir ve kars kaşar peynirlerinin fiziksel ve kimyasal özelliklerinin incelenmesi. *Gıda the journal of food*, *6*(5), 1233-1242.

Dinkçi, N., G, Ünal., S, Akalın., S, Varol., & S, Gönç (2012). Kargı Tulum Peynirinin Kimyasal ve Mikrobiyolojik Özellikleri. *Ege Üniversitesi Ziraat Fakultesi Dergisi*, *49*(3), 287-292.

Durlu-Özkaya, F., & Gün, İ. (2007). Anadolu'da peynir kültürü. ICANAS, Uluslararası Asya ve Kuzey Afrika Çalışmaları Kongresi, 10-15 Eylül, Ankara, Türkiye. Özet kitabı, s.485.

Güler, M. B. (1994). Hatay Yöresi Sürk (Küflü Çökelek) ve Carra (Testi) Peynirlerinin Üretimi, Özellikleri ve Standardizasyon Olanakları Üzerine Bazı Araştırmalar (Doktora Tezi), Çukurova Üniversitesi, Fen Bilimleri Enstitüsü, Adana.

Hayaloglu, A. A., & Fox, P. F. (2008). Cheeses of Turkiye: 3. Varieties containing herbs or spices. *Dairy Science and Technology*, 88, 245-256.

Hayaloglu, A. A., & Karabulut, İ. (2013). Primary and secondary proteolysis in eleven Turkish cheese varieties. *International Journal of Food Properties*, *16*(8), 1663-1675.

Kamber, U., & Terzi, G. (2008a). The traditional cheeses of Turkiye: Central Anatolian region. *Food Reviews* International, *24*(1), 74-94.

Kamber, U., & Terzi, G. (2008b). The traditional cheeses of Turkiye: Southeast Anatolia region. *Food Reviews* International, *24*(1), 62-73.

Kantaroğlu, M., & Demirbaş, N. (2018). Türkiye'de coğrafi işaretli gıda üretim potansiyelinin değerlendirilmesi. VIII. IBANESS Kongreler serisi, Plovdiv, Bulgaristan, Nisan, 21-22, 514-520.

Kara, S., & Köse, Ş. (2020). Geleneksel yöntemle üretilen otlu peynirlerin bazı kalite özelliklerinin ve biyoaktivitesinin belirlenmesi. *Gıda*, *45*(5), 942- 953.

Karaca, O. B. (2016). Geleneksel peynirlerimizin gastronomi turizmindeki önemi. *Journal of Tourism and Gastronomy* Studies, *4*(2), 17-39.

Kiraz, Ş. (2018). Çorum yöresinde üretilen geleneksel kargı tulum peynirlerinin bazı bileşim özeliklerinin belirlenmesi (Yüksek lisans tezi), Hitit Üniversitesi Fen Bilimleri Enstitüsü, Çorum.

Koboyeva, F. (2018). Dağ ve Ova İşletmelerinde Farklı Mevsimlerde Üretilen Taze Kars Kaşarlarının Bazı Kalite Özellikleri (Yüksek lisans tezi), Çukurova Üniversitesi Fen Bilimleri Enstitüsü, Adana.

Morul, F., ve İşleyici, Ö. (2012) Tulum peynirinin kimyasal ve mikrobiyolojik özellikleri. *Yüzüncü Yıl Üniversitesi Veteriner Fakültesi Dergisi*, *23*(2), 71- 76.

Öner, Z., & Karahan, A. G. (2006). Changes in the microbiological and chemical characteristics of an artisanal Turkish white cheese during ripening. *LWT-Food Science and Technology*, *39*(5), 449- 454.

Özsoy, N. (2012). Isıl işlemin Ezine peynirinin özellikleri üzerine etkisi. Yüksek Lisans Tezi. Çanakkale Onsekiz Mart Üniversitesi, Fen Bilimleri Enstitüsü, 95 s.

Salum, P., Govce, G., Kendirci, P., Bas, D., & Erbay, Z. (2018). Composition, proteolysis, lipolysis, volatile compound profile and sensory characteristics of ripened white cheeses manufactured in different geographical regions of Turkiye. *International Dairy* Journal, 87, 26- 36.

Saygılı, D., Demirci, H., ve Samav, U. (2020). Coğrafi İşaretli Türkiye Peynirleri. *Aydın Gastronomy*, 13-19

Subaşı, K. (2021). Coğrafi işaretli ezine ve edirne beyaz peynirleri ile malkara eski kaşar peynirlerinin bazı fizikokimyasal özelliklerinin ve yağ asidi bileşimlerinin belirlenmesi (Yüksek lisans tezi), Tekirdağ Namık Kemal Üniversitesi Fen Bilimleri Enstitüsü, Tekirdağ.

Tarakçı, Z., Coşkun, H., & Tunçtürk, Y. (2004). Some properties of fresh and ripened herby cheese, a traditional variety produced in Turkiye. *Food Technology Biotechnology*, *42*(1), 47- 50.

Tekinşen, K. K. ve Akar, D. (2017). Erzincan Tulum Peyniri. Atatürk Üniversitesi *Veteriner Bilimleri Dergisi*, 12(2), 218-226

Uymaz, B., Akçelik, N., & Yüksel, Z. (2019). Physicochemical and microbiological characterization of protected designation of origin Ezine cheese: Assessment of non- starterlactic acid bacterial diversity with antimicrobial activity. *Food Science of Animal*

Resources, *39*(5), 804- 819.

Yenipınar, U., Köşker, H., ve Karacaoğlu, S. (2014). Turizmde yerel yiyeceklerin önemi ve coğrafi işaretleme: Van otlu peyniri. *Journal of Tourism and Gastronomy Studies*, *2*(2), 13- 23.

CHAPTER 3

NUTRITIONAL INSIGHTS ON OLEUROPEIN: A NATURAL HEALTH BOOSTER

Ibrahim CANBEY

INTRODUCTION

The role of secondary metabolites (SM(s)) in biological functions and properties is highly significant. Despite being present in plants in minor quantities, these compounds exert substantial effects on bioactivity, such as antioxidative function and preventing effect on the growth of microorganism (Elshafie et al., 2023; Messa et al., 2024; Sun et al., 2024; Zhao et al., 2024; Anchimowicz et al., 2025). SMs are categorized into three principal classes: phenolic compounds, terpenoids, and nitrogenous substances. These metabolites exhibit broad spectrum of biological functions, making them useful as flavor enhancers, food additives, and agents for plant disease management. Additionally, they have a vital function in enhancing plant defenses against herbivores and facilitating cellular adaptation to physiological stress conditions (Kabera et al., 2014; Elshafie et al., 2023; Anchimowicz et al., 2025).

One of the most prominent plant species containing such bioactive SMs are the olives. The olive tree (OT) (*Olea europaea* L.), cultivated in various regions of the world with a Mediterranean climate, holds great economic and nutritional value. Its fruits are processed into table olives and olive oil (OO) (Cavalheiro et al., 2015; Nunes et al., 2016; Issaoui & Delgado, 2017; Kritikou et al., 2020; Mousavi et al., 2022). Olives and their derived products are integral to the Mediterranean diet due to their nutritional value and bioactive compounds, which contribute to human health (Issaoui & Delgado, 2017; Riolo et al., 2022; Barazani et al., 2023; Vijakumaran et al., 2023; Canbey et al., 2024; Marrero et al., 2024).

Rich in bioactive compounds, olives possess antioxidative, anti-inflammatory, and cancer-preventive properties, along with antiviral activity (Mousavi et al., 2022). However, limited studies have explored the potential benefits of these compounds on respiratory disorders (Vijakumaran et al., 2023). Among these compounds, minor bioactive substances are critical contributors to the health-promoting effects of olives. Notably, the antioxidant properties of OO make it the healthiest choice among vegetable oils (Yubero-Serrano et al., 2019; Lozano-Castellón et al., 2020; Guclu et al., 2021). The Mediterranean climate, characterized by mild temperatures and abundant sunlight, supports the accumulation of phenolic compounds in the fruit and leaves of OTs (Erbay & Icier, 2010; Kritikou et al., 2020).

During the production of OO, phenolic compounds from the fruits are transferred into the oil, enriching its bioactive profile. Olive leaves, a secondary product of pruning and producing of OO, are especially rich in phenolic compounds (Nicolì et al., 2019; Medfai et al., 2020). The quality of OO is often assessed by analyzing its content of fatty acids, phytosterols, polyphenols, squalene, and tocopherols (Cayuela &

García, 2018; Mousavi et al., 2019; Miho et al., 2021). Nutraceutical compounds in olives, primarily concentrated in the fruit pulp, allow for rapid screening of genotypes, aiding in the identification of those with the potential to produce high-quality oil (Velasco et al., 2014; Mousavi et al., 2022). Among the bioactive compounds in olives, oleuropein (OLE) is particularly notable. This bioactive SM is renowned for its antioxidative, anti-inflammatory, and neural-, oncological-, cardioprotective properties, etc. (Otero et al., 2021; Asghariazar et al., 2022; Canbey et al., 2024; Christodoulou et al., 2024; García-Molina et al., 2024; Hu et al., 2024).

The objective of this chapter is to provide a comprehensive analysis of the biological perspective of OLE, the significant polyphenolic compound found in olives. The study explores the bioactivities attributed to this compound, including antioxidant, anti-inflammatory, anticancer, antimicrobial effects, etc. By highlighting its therapeutic potential in disease prevention and treatment, this study underscores its significance in human health and their possible applications in the food and pharmaceutical industries.

1. The Characteristics of Oleuropein

Olives and their derived products are rich in phenolic compounds, which significantly influence their chemical, nutritional, and organoleptic properties (Fernández-Bolaños et al., 2008). The levels of this SM varies depending on the olive cultivar, fruit ripeness, climatic conditions, and harvesting techniques. Among the bioactive phenolic compounds present in *Olea europaea L.*, OLE a secoiridoid glycoside, initially identified in 1908 by Bourquelot and Vintilesco, is synthesized from ligstroside and is distributed throughout the OT, with its highest concentrations in the green-stage drupe and leaves (Figure 1) (Sayadi & Manel, 2016; Coppa et al., 2020; Kritikou et al., 2020; Munekata et al., 2020; Otero et al., 2021; Canbey et al., 2024; Filardo et al., 2024; García-Molina et al., 2024; Marrone et al., 2024; Soldo et al., 2024). The concentrations of OLE significantly vary due to factors, such as genotype (variety), plant organ, climate, the degree of ripeness at harvest, agricultural practices, processing methods, and olive-based product (Hassen et al., 2015; Canbey et al., 2024).

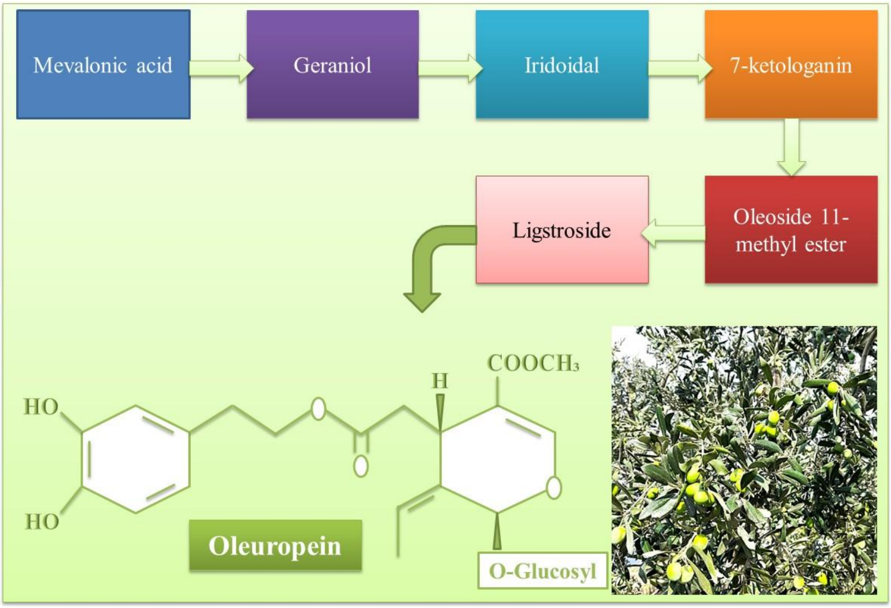


Figure 1. The formation and chemical structure of OLE (Kritikou et al., 2020; Asghariazar et al., 2022; Frumuzachi et al., 2024).

OLE was characterized as a non-crystalline, highly bitter compound, soluble in alcohol and moderately soluble in water, and it is responsible for the characteristic bitterness of olives and is distributed across various parts of the OT, including the branches, buds, flowers, fruits, leaves, and roots, in varying concentrations. The pronounced bitterness of OLE is attributed to its high concentrations in young olive drupes (as much as 140 mg per gram of dry matter) and leaves (between 60 and 80 mg per gram of dry matter) (Omar, 2010; Carrera-González et al., 2013; Barbaro et al., 2014; Tasioula-Margari & Tsabolatidou, 2015; Ambra et al., 2017a and 2017b; Miho et al., 2021; Ercelik et al., 2023; Mumcu, 2023; Asghar et al., 2024; Canbey et al., 2024).

OLE is most abundant in OTs, unripe fruits and leaves (Sun et al., 2017a and 2017b; Cavaca et al., 2020; Canbey et al., 2024). Besides fruits and leaves, it is also found in extra virgin olive oil (EVOO), roots of OT, and mill waste of olive (Leri, 2016; Asghar et al., 2024; Canbey et al., 2024). Conventionally, OLE is extracted from olive fruits and leaves and is also employed in the partial synthesis of oleacein (Costanzo et al., 2018).

OLE undergoes degradation through enzymatic and chemical processes. The enzymatic breakdown of OLE is catalyzed by enzymes, including β-glycosidase and esterase, yielding derivatives such as HT, elenolic acid, and glucose (Omar, 2010; Grewal et al., 2020; Canbey et al., 2024; García-Molina et al., 2024; Messa et al., 2024). Acid-catalyzed hydrolysis, a widely utilized method in laboratory and industrial applications, is another pathway for producing free HT from OLE (Xu et al., 2018; Messa et al., 2024). During olive ripening, olive processing and OO production, OLE content decreases as it is hydrolyzed into its derivatives, with HT being the major breakdown product (Erbay & Icier, 2010; Charoenprasert & Mitchell, 2012; Santos et al., 2012; Carrera-González et al., 2013; Talhaoui et al., 2015; Leri, 2016; Ramírez et al., 2016; Britton et al., 2019; Plastina et al., 2019; Romani et al., 2019; Otero et al., 2021; Canbey et al., 2024; Messa et al., 2024; Soldo et al., 2024). Elenolic acid, a structural component of OLE, is esterified to HT's catechol group and glycosidically bonded to glucose (Messa et al., 2024).

In summary, OLE is pivotal phenolic compound in olives and their derivatives, demonstrating significant bioactivity. This secondary metabolite is primarily associated with the bitter taste and antioxidative properties of unripe olives and leaves. Understanding the degradation pathways and molecular mechanisms underlying the bioactivity of this compounds not only highlights their therapeutic potential but also underscores its applicability in the culinary and pharmaceutical applications.

2. The Bioactivity of Oleuropein on Human Health

Phenolic compounds exhibit crucial biological properties, imparting essential bioactive characteristics to the plants in which they are present, and especially show significant functions in the chemically, organoleptically, and nutritionally widely in olive and OO (Huang & Sumpio, 2008; Fernández-Bolaños et al., 2008; Zhang et al., 2022). In this context, OLE, which is important SM found in varying concentrations in the olive drupe, oil (especially EVOO), and leaves, exhibit a range of biological functions and properties, and it contributes to the bioactivity of the plant's various parts, enhancing its value in terms of biological activity (Tarabanis et al., 2023; Batarfi et al., 2024; Frumuzachi et al., 2024). OLE is recognized for its multifunctional pharmacological and biological effects, including its antioxidant, inflammation-reducing, fighting againts microorganisms, virus and cancer, and protecting heart health, as well as lipid-regulating properties (Nediani et al., 2019; Emma et al., 2021; Otero et al., 2021; Fayez et al., 2023; Canbey et al., 2024; Filardo et al., 2024; Deng et al., 2025).

Clinical studies have demonstrated that the consumption of EVOO, due to its unique bioactive compounds, exhibits a range of significant biological activities (Christodoulou et al., 2024). These include atherosclerosis-inhibiting properties (Nocella et al., 2017), inflammation-preventing activities (George et al., 2019; Longhi et al., 2021; Marrone et al., 2023), antioxidative capacities (Venturini et al., 2015; Kumar & Goel, 2019; Sarapis et al., 2022), cancer-inhibiting effects (Kumar & Goel, 2019; Deng et al., 2025), improved glucose regulation (Guasch-Ferré et al., 2020; Tuccinardi et al., 2022), enhanced lipid catabolism and synthesis (George et al., 2019), and lowered arterial pressure (Christodoulou et al., 2024; Marrone et al., 2023). In addition, incorporating EVOO as the primary dietary fat source appears to be associated with a decreased comprehensive cancer susceptibility, specifically affecting the gastrointestinal tract, prostate, and breast (Di Daniele et al., 2017; Romani et al., 2019; Romani et al., 2020; Vanni et al., 2021). The anticancer properties of EVOO, along with those of its specific components or isolated bioactive compounds, have been extensively investigated and demonstrated in both experiments (*in vitro*) using cell cultures and studies (*in vivo*) conducted on animal models and within clinical trials (Cusimano et al., 2017; Carpi et al., 2020; Cuyàs et al., 2020; Emma et al., 2021; Benedetto et al., 2022; Marrone et al., 2024). Besides EVOO, derivatives from leaves of olive hold significant economic importance due to bioactive compounds like OLE, and various formulations are commonly available in the marketplace, including dried whole leaves used as herbal infusions, capsules, powders produced from desiccated plant material, tablets, extracts in liquid form, and dietary supplements (Özcan & Matthäus, 2017; Arslan et al., 2021).

The growing global attention towards OLE is driven by their diverse health benefits and broad physiological activities (Batarfi et al., 2024; Frumuzachi et al., 2024). This SM have inhibitory functions on cancer types (bladder, brain, breast, cervical, colorectal, gastric, hematologic, liver, lung, prostate, skin, thyroid regions, etc.). Research on these bioactive substances is ongoing, with several studies emphasizing the need for more detailed exploration of their action mechanisms, particularly in the context of cancer treatment. The encouraging outcomes observed in in both vitro and in vivo investigations provide a solid foundation for continued research, particularly in pediatric oncology, where there is an ongoing demand for safer and less toxic treatment options (Imran et al., 2018; Karković Marković et al., 2019; Nediani et al., 2019; Castejón et al., 2020; Pojero et al., 2022; Pojero et al, 2023; Canbey et al., 2024; Gervasi & Pojero, 2024; Goncalves et al., 2024).

Moreover, it was underscored that the anticancer activities of OLE are influenced by its concentration, exposure duration, and the specific cancer type (Morana et al., 2016; Deng et al., 2025). Furthermore, the activity of OLE on antiproliferation has been demonstrated in studies (*in vitro - in vivo*). For example, it was reported that OLE exerts antiproliferative effects on seminomatous cell cultures (TCAM-2 and SEM-1) by inhibiting NF-κB activity in an in vitro setting (Bossio et al., 2022).

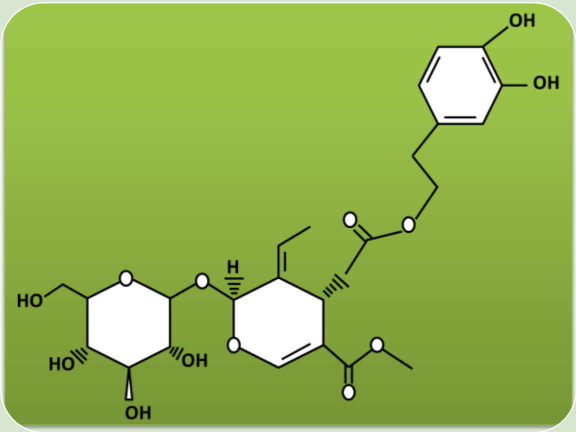
In a preclinical model of mammary tumor, it was found that administering OLE at a quantity of 125 mg per kilogram significantly reduced metastasis in the lung tissue and surrounding pulmonary structures (Ci et al., 2016). In addition, the suppression of COX-2 by OLE in colon and rectal cancer has been connected to the suppression of the Wnt/β- catenin pathway activation (Giner et al., 2016). Indeed, many investigations have determined that Wnt/β-catenin hyperactivation plays a role in various cancers, including stomach, colon, and uterine malignancies (Giner et al., 2016; Deng et al., 2020). Besides, OLE also shows promise in prostate malignancy intervention. It was determined in a study (*in vitro*) that OLE, in combination with doxorubicin (DXR), effectively displayed inhibitory effect on PC-3 cell growth and stimulated autophagy (Papachristodoulou et al., 2016).

Notably, the concurrent approach of DXR and OLE exhibited stronger anticancer effects than DXR alone while mitigating potential side effects, such as DXR-induced cardiotoxicity (Andreadou et al., 2014).

Thus, OLE not only displays oncoprotective properties but also enhances the efficacy of cancer-treatment agents, enabling the use of lower drug doses and minimizing adverse effects (Shamshoum et al., 2017; Imran et al., 2018; Noce et al., 2023).

Supporting this role, it was investigated OLE's adjuvant potential in A375 human melanocytic carcinoma cells, demonstrating that OLE at 500 μM induces apoptosis, while at 250 μM, it interferes with cell proliferation and disrupts the pAKT/pS6 signaling pathway. These findings affirm the synergistic importances of OLE when combined with conventional cancer drugs in targeting skin cancer cells (Ruzzolini et al., 2018).

Further research has highlighted OLE's broad health-promoting functions, such as preventing inflammation, oxidation, cancer, and neurodegeneration, while also safeguarding health of heart, underscoring its therapeutic potential in treating various human diseases (Kontogianni & Gerothanassis, 2011; Filardo et al., 2024; Hu et al., 2024). The biological activities and functions of OLE are summarized in Figure 2.



Anticancer (Asghariazar et al., 2022; Rishmawi et al., 2022; Asghariazar et al., 2024; Gervasi & Pojero, 2024; Iantomasi et al., 2024; Magyari-Pavel et al., 2024; Salvo & Tuttolomondo, 2025); **antitumor, pro-apoptotic and anti-proliferative activities against several cancer cell lines in humans** (Bulotta et al., 2013; Casaburi et al., 2013; Barbaro et al., 2014; Antognelli et al., 2019; Bayat et al., 2019); **cardioprotective** (Tsoumani et al., 2021; Iantomasi et al., 2024; Magyari-Pavel et al., 2024; Salvo & Tuttolomondo, 2025); **anti-inflammatory** (Silvestrini et al., 2023; Hu et al., 2024; Iantomasi et al., 2024; Şahin et al., 2024; Jahan et al., 2025; Li et al., 2025); **antioxidant** (Allaw et al., 2021; Karimi et al., 2021; García-Molina et al., 2024; Hu et al., 2024; Iantomasi et al., 2024; Şahin et al., 2024; Jahan et al., 2025; Li et al., 2025); **suppressing reactive oxygen species** (Geyikoğlu et al., 2017; Imran et al., 2018; Al-Shaal et al., 2019; Salvo & Tuttolomondo, 2025); **antimicrobial** (Al-Rimawi et al., 2024; Magyari-Pavel et al., 2024; Jahan et al., 2025); **antihypertensive** (Vogel et al., 2015; Romero et al., 2016; Al-Rejaboo et al., 2025); **antidiabetic** (Da Porto et al., 2021; Saad, 2023; Iantomasi et al., 2024); **hypoglycemic** (Ahmadvand et al., 2014; Vogel et al., 2015; Zheng et al., 2021); **hypolipidemic** (Andreadou et al., 2006; Jemai et al., 2008; Ahmadvand et al., 2014); **antiobesity** (Oi-Kano et al., 2017; Saad, 2023; Ilgaz et al., 2025); **wound-healing activity on skin, etc.** (Allaw et al., 2021; Magyari-Pavel et al., 2024).

Figure 2. The biological functions of OLE (Asghariazar et al., 2022; Batarfi et al., 2024; Canbey et al., 2024; Christodoulou et al., 2024; Frumuzachi et al., 2024; Goncalves et al., 2024).

Several scientific studies have further demonstrated that OLE exhibits antioxidative and inflammation-preventing activities (Hassen et al., 2015; Canbey et al., 2024; Deng et al., 2025; Jahan et al., 2025; Li et al., 2025), in addition to its effects on lowering blood pressure, reducing blood sugar levels (Cristiano et al., 2021), and decreasing uric acid levels (Wan et al., 2018; Otero et al., 2021).

Moreover, OLE has been shown to possess a range of health-promoting pharmacological properties, including growth of microbe-inhibiting, protective against virus, and tumor-suppressing effects, along with its ability to prevent elevated LDL levels in the bloodstream (Canbey et al., 2024; Filardo et al., 2024). The bioactive compound is also effective in addressing various diseases, as illustrated in Figure 3 (Otero et al., 2021).

The cancer-, obesity-, and diabetes-preventive effects, as well as the cardio-, neuro-, gastro-, and hepatoprotective activities shown in Figure 3, are attributed to the antioxidative and and anti-swelling characteristics of OLE (Hassen et al., 2015; Canbey et al., 2024).

Alzheimer disease	• Grossi et al., 2013; Cordero et al., 2018; Leri et al., 2019
Cancer	• Torić et al., 2019; Castejón et al., 2020; Asgharzade et al., 2021; Hamed et al., 2021; Ramírez-Expósito et al., 2021; Salvo & Tuttolomondo, 2025
Cerebral hemorrhage	• Shi et al., 2017; Zhang et al., 2018
Cholesterol	• Jemai et al., 2008; Hadrich et al., 2016; Malliou et al., 2018; Ahamad et al., 2019; Frumuzachi et al., 2024
Cystitis	• Boeira et al., 2011; Sinanoglu et al.,2012; Moraes et al., 2013; Sherif et al., 2016
Diabetes mellitus	• Murotomi et al., 2015; Sangi et al., 2015; Annunziata et al, 2018; Kerimi et al., 2019; Benlarbi et al., 2020
Hepatitis B	• Zhao et al., 2009; Fujiwara et al., 2017; Al-hafidh & Filardo et al., 2024; Shaibani & Rafieirad, 2024; Zheng et al., 2024
Hypertension	• Romero et al., 2016; Lockyer et al., 2017; Sun et al., 2017a and 2017b; Ivanov et al., 2018; Ahamad et al., 2019; Nediani et al., 2019
Inflammatory Bowel Diseases	• Fakhraei et al., 2014; Vezza et al., 2017; Mattioli et al., 2022; Filardo et al., 2024
Myocarditis	• Killeen et al., 2014; Tiedje et al., 2014; Amoah et al., 2015; Zhang et al., 2017; Tsoumani et al., 2021
Obesity	• Hadrich et al., 2016; Oi-Kano et al., 2017; Malliou et al., 2018; Ahamad et al., 2019; Vezza et al., 2019
Parkinson	• Pasban-Aliabadi et al., 2013; Sarbishegi et al., 2014; Di Rosa et al. 2018

Figure 3. The biological effects of OLE on some health problems (Otero et al., 2021).

OLE has been explored for its distinctive impact on autophagic processes and the formation of amyloid fibrils (Leri & Bucciantini, 2016; Nediani et al., 2019; Canbey et al., 2024). Additionally, OLE offers beneficial effects on the skin, particularly by promoting hair growth during the anagen stage in the telogen skin of C57BL/6N mice. This hair growth stimulation is linked to the activation of the Wnt10b/β-catenin signaling pathway and an increase in the gene expression of IGF-1, VEGF, HGF, and KGF in the skin tissues of mice (Tong et al., 2015). Both OLE and its derivative, HT, demonstrate limited skin permeability but exhibit cytoprotective properties by reducing oxidative stress (OS)-induced cytotoxicity in human dermal fibroblast cells (Li et al., 2022). OLE-based creams also display properties that prevent inflammation, oxidation, aging, and offer photoprotection, all contributing to facial revitalization. Notable improvements, such as enhanced texture of skin, hydration, and barrier function, are observed within one month of treatment, with further benefits evident after two months (Wanitphakdeedecha et al., 2020). Furthermore, OLE helps reduce elevated levels of serum creatinine, myeloperoxidase, nitric oxide (NO), and urea in diabetic rats while inhibiting leukocyte infiltration and kidney scarring. OS is a key factor in the pathological pathways leading to diabetic damage, inflammation, and cancer (Ahmadvand et al., 2017). Moreover, OLE enhances the polarization of Th1 cells and the production of immune-related genes, including IFN-γ, TGF-β1, IL-10, and IL-12β, while also suppressing the synthesis of the IL-1β gene (Kyriazis et al., 2016).

2.1. Antimicrobial effects of oleuropein

OLE exhibits numerous significant biological functions, with antimicrobial activity being particularly prominent (Bensehaila et al., 2022; Deng et al., 2025; Jahan et al., 2025). Although the exact mechanisms underlying its antimicrobial effects are not yet fully understood, it is suggested that phenolic compounds like OLE can denature proteins, disrupt lipid bilayers, degrade murein layers, impair transmembrane permeability, and cause leakage of cytosolic and intracellular components, such as glutamate, inorganic phosphate, and potassium. These processes collectively slow down and inhibit microbial growth (Sanchez et al., 2007; Lee & Lee, 2010). Additionally, the ability of hydroxyl groups in phenolic chemicals to bind to the active sites of key enzymes and alter microbial metabolic pathways provides another mechanism for their antimicrobial activity (Gyawali & Ibrahim, 2014).

Research has demonstrated that OLE exhibits antimicrobial properties effective against a diverse range of microorganisms, such as *Bacillus cereus*, *B. subtilis*, *Escherichia coli*, *Campylobacter jejuni*, *Candida albicans*, *Vibrio parahaemolyticus*, *S. aureus* etc. (Aliabadi et al., 2012; Keskin et al., 2012; Gökmen et al., 2016; El-Sohaimy et al., 2021; Sánchez-Gutiérrez et al., 2021). One study revealed that OLE had a stronger antimicrobial effect on *Staphylococcus aureus* than on *Escherichia coli*, a difference attributed to changes in cellular morphology (Sanchez et al., 2007). Another study found that *Campylobacter jejuni*, *Helicobacter pylori*, and *Staphylococcus aureus* exhibited the highest sensitivity to OLE, while *Kl. pneumoniae*, *B. subtilis*, *E. coli*, *P. aeruginosa*, and *Serratia marcescens* showed the lowest sensitivity (Sudjana et al., 2009). Additionally, it was shown that OLE significantly inhibited the proliferation of all Gram (+) and Gram (-) species tested, except for *Bacillus cereus* CCM 99, *E. cloacae* ATCC 13047, and *E. aerogenes* ATCC 13048 (Keskin et al., 2012). Furthermore, another study suggested that OLE could be beneficial for treating and preventing infectious conditions, such as oral candidiasis caused by *Candida* species (Nasrollahi & Abolhasannezhad, 2015). The antifungal activity of OLE against *Candida dubliniensis* CBS 7987 and *C. albicans* ATCC 10231 strains was evaluated, revealing an MIC of 46.875 mg/mL for *C. albicans* and 62.5 mg/mL for *C. dubliniensis* (Zorić et al., 2016). In another study, it was observed that OLE, at a specific concentration, nearly completely suppressed the growth of significant microorganisms transmitted through food, such as *E. coli* O157:H7, *Listeria monocytogenes*, and *Salmonella enteritidis*. Additionally, it reduced motility in *Listeria monocytogenes*, associated in the lack of flagella as observed through scanning electron microscopy, and inhibited biofilm formation by these bacteria (Liu et al., 2017). Furthermore, the antimicrobial and antioxidant properties of OLE were investigated. Crude leaf extracts of olive, partially purified OLE, and fully purified OLE from the Domat, Edremit, and Trilye species were sourced. Among the tested microorganisms, *Staphylococcus aureus* exhibited the highest sensitivity to OLE extracts, while *Escherichia coli* O157:H7 showed the greatest resistance. Consequently, both crude extracts and OLE isolated from these extracts demonstrated potential for enhancing the shelf life of food products due to their antimicrobial and antioxidant properties (Topuz & Bayram, 2022). Additionally, another study investigated the antimicrobial effect of the hydromethanolic extract of *Olea oleaster* leaves against food-associated pathogens in minced beef, specifically *Salmonella enterica* serovar *Enteritidis* and Shiga toxin-producing *Escherichia coli* O157:H7 (Djenane et al., 2018). Application of this extract, identified as rich in OLE, resulted in a significant reduction in pathogen levels. OLE has thus been shown to possess potent antimicrobial properties (Topuz & Bayram, 2022).

A range of antibacterial functions of OLE has been thoroughly studied in various research studies. The antimicrobial effects of extract from olive leaves follow this order of effectiveness: *B. cereus*, *C. albicans* > *E. coli* > *S. aureus* > *P. aeruginosa*. Notably, no Gram (+) or Gram (-) bacteria were excluded from the study, underscoring the broad-spectrum efficacy of this extract. It demonstrates the ability to denature proteins and alter the penetrability of bacterial cell membranes (Ghomari et al., 2019). Olive leaves are rich in OLE, a compound with potent antibacterial activity against both Gram (+) and Gram (-) pathogens, as well as mycoplasma. Phenolic compounds, including OLE, exert their antibacterial effects primarily by disrupting bacterial membranes and/or altering cell peptidoglycans. Biophysical studies have investigated the interactions between OLE and the lipid components of bacterial membranes, providing insights into its mechanism of action.

Although the precise mechanism underlying the antibacterial effects of OLE remains incompletely understood, some researchers propose a link to the presence of the ortho-diphenolic system (catechol). According to Saija and Uccella's 2001 hypothesis, the glycoside group in OLE influences its ability to penetrate bacterial membranes and reach target sites within the cell. Additionally, OLE is hypothesized to interfere with the production of amino acids essential for microbial growth. Another proposed mechanism involves the induction of phagocytosis, an immune response that targets various microorganisms. OLE and its hydrolysis products have been shown to inhibit the growth of *S. enteritidis,* prevent the synthesis of *S. aureus* enterotoxin B, and block the germination and subsequent growth of *B. cereus* spores. Furthermore, OLE completely inhibits the growth of *B. cereus, E. coli*, and *K. pneumoniae*, as well as other polyphenolic substances like *p*-coumaric, *p*-hydroxybenzoic, and vanillic acids (Omar, 2010).

The observed antimicrobial activity in the extract can be attributed to its high concentration of polyphenols. OLE and HT have been reported to inhibit or slow the growth of several pathogenic microorganisms associated with the human gut and respiratory system, including *H. influenzae*, *M. catarrhalis*, *S. aureus*, *S. typhi*, *V. cholerae*, *V. parahaemolyticus,* and *V. alginolyticus* (Debib & Boukhatem, 2017).

Interestingly, Gram (-) bacteria exhibit lower susceptibility to phenolic compounds compared to Gram (+) bacteria. The heightened susceptibility of Gram (+) bacteria is attributed to the interaction of hydrophobic polyphenolic compounds with their lipid bilayers. In contrast, the hydrophilic nature of the outer membrane in Gram (-) bacteria contributes to their reduced sensitivity to polyphenols (Calo et al., 2015). A prior investigation further demonstrated that olive waste extract effectively inhibited the motility of *Escherichia coli*, highlighting the potential of olive-derived compounds as antimicrobial agents (Carraro et al., 2014).

2.2. Antifungal impacts of oleuropein

In addition to its antibacterial properties, OLE also displays significant antifungal activity (Canbey et al., 2024; Al-Rejaboo et al., 2025). In a study, OLE demonstrated antifungal efficacy against *Candida albicans* and three dermatophytes, namely *Microsporum canis*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum*. Based on these findings, it was proposed that OLE could be utilized in the treatment of opportunistic mycotic infections (Markin et al., 2003). However, contrasting results were reported in a subsequent study where OLE exhibited no antimicrobial action against fungi *C. albicans*, *C. glabrata*, *C. krusei*, and *Candida tropicalis* (Shialy et al., 2015).

The antifungal effects of OLE are believed to operate through multiple pathways, including enhancing the permeability of fungal cell membranes, inducing programmed cell death, and inhibiting filamentous growth. In an evaluation of extracts from olive leaves against 30 fungal isolates, including *Alternaria alternata*, *Aspergillus chevalieri*, *A. chrysogenum*, *A. elegans*, *A. flavus* (four strains), *A. fumigatus*, *A. nidulans*, *A. niger* (two strains), *A. oryzae*, and *A.*

parasiticus (three strains), OLE exhibited the most potent antifungal efficacy, effectively inhibiting 18 out of the 30 strains tested. The surfactant characteristics of OLE, which disrupt the integrity of the fungal plasma membrane and enhance its permeability, likely account for its fungus destroying function (Korukluoglu et al., 2008).

In vitro investigations of OLE against *C. albicans* revealed a minimum inhibitory concentration (MIC) of 12.5 mg/mL, with sub-inhibitory concentrations inducing controlled cell death. Antifungal agents generally target pathogenicity determinants critical for fungal pathogenesis. OLE has been shown to modulate the morphogenetic transformation of *C. albicans* by suppressing filamentous growth. Additionally, OLE suppresses the function of secreted aspartyl proteinases, enzymes released by *C. albicans* that are integral to fungal virulence. In hydrophobicity assays, OLE significantly reduced the cellular surface hydrophobicity of *C. albicans*, a crucial element in its attachment to host epithelial tissue cells, under both oxygenated and non-oxygenated conditions. Moreover, a reduction in the total sterol content within the fungal cell membrane has been identified as another mechanism contributing to OLE’s antifungal effects (Zorić et al., 2016).

OLE encapsulated in chitosan-based nanoparticles has demonstrated enhanced *in vitro* antifungal activity, effectively inhibiting fungal sprouting and development. The proposed mechanism of action involves electrostatic interactions between the amine groups of chitosan and negatively charged components of the fungal cell membrane, such as phospholipids, proteins, and amino acids, which are essential for sprouting. These cytotoxic effects, attributed to OLE, play a crucial role in its antifungal properties (Muzzalupo et al., 2020). Furthermore, OLE has been shown to induce cellular demise through self-destruction mechanisms and trigger structural alterations within the nucleus, reinforcing its potential as an antifungal agent (Alfahdawi & Alsewuidi, 2022).

2.3. Antiviral effects of oleuropein

Beyond its antibacterial and antifungal properties, olive leaves also demonstrate notable antiviral potential (Pennisi et al., 2023; Al-Rejaboo et al., 2025; Benamar et al., 2025). According to a U.S. patent, OLE exhibits significant antiviral activity against bovine rhinovirus, canine parvovirus, rotavirus, etc. (Omar, 2010).

A potential molecular target for extract from leaves of olive, particularly OLE, is the HIV-1 gp41 glycoprotein subunit, which displays an essential function in mediating the entry of HIV into host cells. To explore the interaction between HIV proteins and extract from leaves of olive, it was conducted an integrated theoretical and experimental study to elucidate its inhibitory mechanism at the molecular level (Lee-Huang et al., 2007).

Supporting these findings, research has demonstrated that hydroethanolic extracts from the leaves of *Olea oleaster* demonstrate antiviral activity on herpes simplex virus type 1 (HSV-1). These extracts effectively inhibited the virus during both the pre- and postinfections phases in Vero cells, without inducing cytotoxicity. The antiviral efficacy was attributed to phenolic compounds, such as OLE hexoside, epicatechin, and oleanolic acid (Ben-Amor et al., 2021).

Further investigations revealed that olive leaf extract and its principal active component, OLE, inhibit the salmonid rhabdovirus viral hemorrhagic septicemia virus (VHSV), which causes hemorrhagic infection. Pre-incubation of the virus with olive leaf extract or OLE reduced viral infectivity by 10% and 30%, respectively. Additionally, post-infection treatment of cell monolayers with olive leaf extract significantly reduced VHSV levels and viral protein buildup in a dose-dependent fashion. This virucidal effect was linked to the interference of viral envelope interactions, which inhibited cell-to-cell membrane merging induced by VHSV in non-infected cells (Micol et al., 2005).

OLE also exhibits inhibitory activity against human immunodeficiency virus (HIV) by disrupting viral entry, integration, and replication within host cells. For influenza virus, OLE inhibits hemagglutinin, thereby compromising the structural integrity of the virion envelope. Additionally, ethanolic extracts of olive leaves suppress metabolic activity and inhibit neuraminidase function, further contributing to antiviral activity (Salamanca et al., 2021).

In the context of HIV, OLE and its metabolites, including elenolic acid, aglycone, and HT, target the gp41 surface glycoprotein. By inducing hydrophobic interactions within the protein, these compounds create a crucial binding site at the N-terminus of the gp41 core N36 trimer, interfering with viral function (Bao et al., 2007).

Notably, the phenolic compounds in leaves of olive have shown efficacy against SARS-CoV-2 in various in vitro studies. These bioactive compounds not only neutralize the virus but also reduce inflammation, fever, and pain while modulating immune responses. OLE has demonstrated in silico activity against the Mpro/3Clpro protease, blocked ACE2 receptors, and enhanced viral inactivation *in vitro*. Furthermore, olive leaf and fruit extracts prevent platelet aggregation, extend prothrombin time, and inhibit intravascular clotting. Phenolic compounds such as HT and maslinic acid also downregulate inflammatory markers, including interleukins (IL-1β, IL-5, IL-6, IL-13, IL-17), TNF-α, and inducible NO synthase (iNOS). These actions mitigate the cytokine storm associated with severe respiratory conditions like asthma and COVID-19 and alleviate symptoms such as coughing (Abdelgawad et al., 2022).

2.4. The cardioprotective effects of oleuropein

OLE, a prominent polyphenolic compound found in olives, is recognized for its significant benefits to the cardiovascular system (Asghar et al., 2024; Al-Rejaboo et al., 2025; Salvo & Tuttolomondo, 2025). Additionally, this bioactive molecule inhibits the copper sulfate-induced oxidation of LDL cholesterol, preventing its accumulation in blood vessels. By promoting the production of hypochlorous acid, OLE facilitates the chlorination of apoB-100, which initiates LDL fatty acid oxidation. This mechanism effectively prevents the deposition of cholesterol in arterial walls (Bulotta et al., 2014). Comparable to the water-soluble form of α-tocopherol (vitamin E), OLE exhibits significant antioxidative activity (Manna et al., 2004).

Following cardiac injury and subsequent restoration of blood flow, OLE has been shown to enhance cardiac function. Its blood vessel widening, inflammation-reducing, and anti-thrombotic properties contribute to these effects (Esmailidehaj et al., 2016). Furthermore, OLE mitigates endothelial cell activation by reducing the lipopolysaccharide-induced synthesis of vascular adhesion molecule-1 (VCAM-1) in endothelial cells. As a direct heart-protective phytochemical, OLE safeguards the heart from cellular damage and OS by lowering key biomarkers, such as creatine kinase, an indicator of cellular injury, and glutathione, which reflects oxidative damage in the cardiovascular system (Bulotta et al., 2014).

Supporting these findings, studies on animal models of type 2 *Diabetes mellitus* and renal hypertension revealed that OLE offers cardiovascular benefits. These effects were most evident when given at a daily dosage of 60 milligrams per kilogram (Nekooeian et al., 2014). Such results highlight the potential of OLE as a therapeutic agent for addressing cardiovascular complications associated with metabolic and hypertensive conditions (Vogel et al., 2015).

Further research demonstrated that perfusing isolated rat hearts with OLE improved cardiac performance following ischemic reperfusion injury, providing additional evidence of its antioxidative properties (Esmailidehaj et al., 2016). Another study revealed that OLE alleviates cardiac damage associated with diabetic cardiomyopathy in a dose-dependent manner, likely by modulating inflammatory responses, redox imbalance, and programmed cell death (Asghari et al., 2022).

To further investigate OLE's cardioprotective mechanisms, a study examined its anti-inflammatory effects *in vivo*. Both OLE and postconditioning, alone or in combination, were shown to reduce the infiltration of inflammatory monocytes into cardiac tissue and lower circulating monocyte levels. The mechanism of OLE's function includes direct cardiomyocyte protection, significantly improving cell survival following simulated ischemia-reperfusion injury. Additionally, OLE enhances postconditioning's cardioprotective effects by enhancing the expression of the transcription factor Nrf-2 and its downstream effectors. Immediate administration of OLE during blood flow restriction, in conjunction with postconditioning, offers strong and complementary heart protection in preclinical IRI models. This is achieved by activating antioxidative defense genes via the Nrf-2 pathway, independent of traditional cardioprotective signaling pathways such as RISK, cGMP/PKG, and SAFE (Tsoumani et al., 2021).

2.5. The antioxidant effects of oleuropein

Similar to its antimicrobial properties, another significant biological characteristic of OLE is its potent antioxidant natüre (Leri et al., 2021; Al-Rejaboo et al., 2025; Deng et al., 2025; Anchimowicz et al., 2025; Ilgaz et al., 2025). The antioxidative properties of OLE are intrinsically linked to the HT moiety within its molecular structure, which plays a pivotal role in neutralizing reactive oxygen species. This functional group stabilizes free radicals, thereby preventing OS and supporting cellular defense mechanisms, underscoring its central role in the biological activity of OLE (Vogel et al., 2015; Canbey et al., 2024).

Olive leaves, with their high OLE content (Ilgaz et al., 2025), are particularly suited for applications leveraging these properties, as demonstrated by significant scientific studies. For instance, the antioxidant potential of various solvent extracts (supercritical fluid, methanolic, ethanolic, propanolic, isopropanolic, and ethyl acetate) derived from *Olea oleaster* leaves was assessed using methods, such as the DPPH radical scavenging assay, the Rancimat method, and peroxide value determination (Lafka et al., 2013). Among these, ethanol extracts were found most effective in neutralizing DPPH radicals and preventing oxidation in sunflower oil using the Rancimat method. Additionally, ethanol extracts provided superior protection for both VOO (virgin olive oil) and oil of sunflower against oxidative process, as evidenced by peroxide value determination. This remarkable antioxidative activity is attributed to biologically active compounds, such as OLE, caffeic acid, catechin, and luteolin (Lafka et al., 2013). Similarly, methanol extracts from *Olea oleaster* leaves exhibited significant antioxidative functions in assays, such as DPPH and FRAP, due to phenolic compounds like OLE, caffeic and chlorogenic acids, and rutin (Makowska-Wąs et al., 2017; Zighed et al., 2022). Furthermore, methanol extracts from *Olea oleaster* fruits demonstrated superior antioxidative performance compared to aqueous extracts in

DPPH, ABTS, metal-chelating, and FRAP assays. This enhanced function is linked to the high concentration of phenolic substances, including OLE, rutin, and oleoside (Kabach et al., 2022).

In addition to its natural presence in leaves, OLE has demonstrated potential as a natural antioxidant for food applications. The extract from leaves of olive has been shown to extend the shelf life of vegetable oils by enhancing oxidative stability and preserving nutrients and bioactive components. For example, the incorporation of these extracts into VOO reduced peroxide values and extinction coefficients during storage, while improving sensory properties, such as flavor and aroma over six months (Mumcu, 2023). In another study, OLE was added to EVOO derived from the "Chetoui" variety to enhance its nutritional profile and oxidative stability. The results confirmed that the addition preserved organic standards and did not compromise overall oil quality (Arfaoui et al., 2024). The extracts obtained from leaves were also used to fortify various oils and fats, including olive oil, sunflower oil, palm oil, and vegetable fats, improving their radical scavenging capacities and oxidative stability, outperforming synthetic antioxidants like BHT (Salta et al., 2007). In refined soybean oil, this extract at varying levels exhibited antioxidant activity comparable to 200 ppm BHT under enhanced storage conditions, highlighting its potential as a natural antioxidant (Hassan et al., 2022). Furthermore, the antioxidative effectiveness of these extracts obtained through different extraction methods was evaluated in canola oil over a five-week storage period at 60°C. The results demonstrated that incorporating olive leaf extract significantly improved the oxidative resistance of canola oil (Dauber et al., 2022).

The benefits of OLE extend beyond food applications. In human dental pulp stem cells, OLE mitigated methylglyoxal (MG)-induced glycation-related damage by enhancing the activity of glyoxalase 1, a key enzyme in MG detoxification. This process involves the redox-regulated transcription factor Nrf2, which reduces glycation damage and protects DPSCs from degeneration (Monache et al., 2021).

Finally, extracts obtained with methanol from olive processing waste demonstrated the highest radical-neutralizing activity and the lowest EC50 values among tested extracts (ethyl acetate and petroleum ether), with antioxidative effects increasing with concentration. The ability of OLE to neutralize free radicals and reduce phytotoxic effects is closely linked to the availability of hydroxyl groups in its phenolic compounds. Phenolic substances, including OLE, are well-documented for their antioxidative properties, effectively preventing oxidative damage to biomolecules (Czerwińska et al., 2012; Asghar et al., 2024; Canbey et al., 2024).

2.6. The antidiabetic functions of oleuropein

Another notable biological property of OLE is its antidiabetic activity (Akhtar et al., 2022; Canbey et al., 2024; Iantomasi et al., 2024). This bioactive compound acts on striated muscle by facilitating glucose uptake and modulating associated protein signaling pathways, thereby improving glucose regulation and enhancing insulin sensitivity (Iantomasi et al., 2024). This characteristic allows various parts of the olive containing OLE to be applied across multiple fields due to their biological properties. For instance, extracts obtained from the leaves of *Olea europaea* have demonstrated antidiabetic and antioxidant properties *in vitro* (Chigurupati et al., 2021). Furthermore, compounds such as OLE, phenolic acids, and oleanolic acid extracted from leaves of *Olea europaea* has been linked to these *in vitro* blood sugar-regulating and antioxidative properties (Sato et al., 2007).

It can be concluded that extracts derived from olive leaves, rich in OLE, combined with metformin represent a promising therapeutic strategy for managing type 2 diabetes due to their antioxidant properties. This underscores the potential of extracts from olive leaves as a standalone treatment or as an adjunctive agent within the therapeutic framework for type 2 diabetes (Mansour et al., 2023). Additionally, research involving olive leaf supplementation in rats fed a high-fat diet and administered with reduced dosage of streptozotocin showed a diminution in body mass and efficient regulation of high blood sugar (Guex et al., 2019).

Beyond the leaves, the fruit of the olive also holds pharmacological potential due to its OLE and other bioactive compounds. Recent *in vitro* studies have demonstrated the antidiabetic potential of methanol extracts derived from the fruits of *Olea oleaster*. These extracts exhibited significant inhibitory effects on α-amylase and α-glucosidase enzymes, even at lower quantities. This action is likely attributed to the extract's high phenolic content, including compounds, such as OLE glucoside, ligstroside, and oleoside (Kabach et al., 2022).

Moreover, a study investigated the effects of purified OLE extracted from *Olea europaea* leaves on rats with alloxan-induced type 1 diabetes. *Diabetes mellitus* was induced in male rats through a single intradermal alloxan administration at a dose of 100 mg per kg body weight. The findings revealed that OLE possesses significant hypoglycemic and antioxidant properties. As a naturally bioactive phytochemical, OLE exhibits antioxidative activity capable of mitigating the adverse effects of alloxan under diabetic conditions. This protective role is likely mediated by OLE's antioxidant properties, which reduce free radical damage induced by alloxan, reactivate pancreatic β-cells, and enhance both enzymatic and non-enzymatic antioxidant defenses. Consequently, OLE is proposed as a potential dietary supplement for managing type 1 diabetes. However, further studies are required to validate the therapeutic efficacy of OLE in human subjects with type 1 diabetes (Qadir et al., 2016).

2.7. The cytotoxic activities of oleuropein

In addition to its other biological functions, OLE exhibits cytotoxic activity (Canbey et al., 2024; Benamar et al., 2025). This cell-toxic effect is likely associated with the extract of methanol from the leaves of *Olea oleaster*, attributed to its abundance content of bioactive compounds, particularly phenolic acids and the predominant polyphenol, OLE (Makowska-Wąs et al., 2017).

Beyond OLE, the observed cell-toxic activity may also be linked to other constituents in the extract, such as rutin and verbascoside (Kabach et al., 2022), both of which are known to exhibit potent cytotoxic properties (Ruzzolini et al., 2018; Caparica et al., 2020; Şenol et al., 2021).

Furthermore, existing evidence indicates that OLE may exert inflammation-preventing function by reducing inflammatory cytokine levels in liver and adipose tissues. Additionally, OLE targets striated muscle to enhance glucose uptake and regulate associated protein signaling pathways, leading to improved glucose homeostasis and increased insulin sensitivity. While these findings suggest that OLE holds potential as an inflammation- and diabet-preventing agent, further animal studies and clinical trials are necessary to validate its therapeutic applications for managing metabolic disorders (Iantomasi et al., 2024).

The increasing emphasis on the health-promoting properties of natural foods has spurred advancements in precise and reliable analytical methodologies. These techniques enable the identification of functional components and support the molecular profiling of foods, contributing to the exploration of their bioactive potential (Kritikou et al., 2020).

3. Conclusion

Olive (*Olea europaea* L.) is a plant species with high nutritional and economic value, exhibiting very important biological properties thanks to the phenolics in its composition. Among the phenolic compounds it contains, the place of OLE is too high to be denied. This secondary metabolite is found in the leaves, fruits, and oil of the olive, and exhibits very important biological properties and functions. This compound, which is a very strong antioxidant, also exhibits many biological properties, such as antimicrobial, antifungal, antiviral, anti-inflammatory, heart health protective, antidiabetic and obesity preventing effects. Owing to these properties; it plays a role in preventing the formation of many diseases, including cardiovascular diseases, obesity, diabetes, Alzheimer's disease and cancer types.

Its favorable safety profile, coupled with its capacity to modulate key molecular mechanisms, positions OLE as a promising candidate for integration into functional foods, nutraceuticals, and even as a complementary strategy in clinical settings. Nevertheless, despite the promising preclinical data, further research is warranted to fully elucidate its pharmacokinetics, bioavailability, and long-term effects in humans. Well-designed clinical trials are essential to translate the existing experimental findings into practical therapeutic applications. Moreover, future studies should aim to explore the synergistic effects of OLE with other bioactive compounds, as well as the development of advanced delivery systems to enhance its therapeutic efficacy.

In conclusion, OLE represents a compelling example of how naturally occurring phytochemicals can contribute to human health. Its broad biological potential offers a valuable foundation for future pharmacological exploration and the development of novel strategies for disease prevention and health promotion.

REFERENCES

Abdelgawad, S. M., Hassab, M. A. E., Abourehab, M. A. S., Elkaeed, E. B., & Eldehna, W. M. (2022). Olive Leaves as a Potential Phytotherapy in the Treatment of COVID-19 Disease; A Mini-Review. Frontier Pharmacology, Vol. 13 (April, 2022), pp. 1–9.

Anchimowicz, J., Zielonka, P., & Jakiela, S. (2025). Plant Secondary Metabolites as Modulators of Mitochondrial Health: An Overview of Their Anti-Oxidant, Anti-Apoptotic, and Mitophagic Mechanisms. Int. J. Mol. Sci., Vol. 26 (December, 2024), pp. 1-34.

Ahamad, J., Toufeeq, I., Khan, M. A., Ameen, M. S. M., Anwer, E. T., Uthirapathy, S., Mir, S. R., & Ahmad, J. (2019). Oleuropein: A natural antioxidant molecule in the treatment of metabolic syndrome. Phytotherapy Research, Vol. 33, No. 12 (November, 2019), pp. 3112-3128.

Ahmadvand, H., Noori, A., Dehnoo, M. G., Bagheri, S., & Cheraghi, R. A. (2014). Hypoglycemic, hypolipidemic and antiatherogenic effects of oleuropein in alloxan-induced Type 1 diabetic rats, Asian Pacific Journal of Tropical Disease, Vol. 4, No. 1 (February, 2014), pp. S421-S425.

Ahmadvand, H., Shahsavari, G., Tavafi, M., Bagheri, S., Moradkhani, M. R., Kkorramabadi, R. M., Khosravi, P., Jafari, M., Zahabi, K., Eftekhar, R., Soleimaninejad, M., & Moghadam, S. (2017). Protective effects of oleuropein against renal injury oxidative damage in alloxan-induced diabetic rats; a histological and biochemical study. Journal Nephropathology, Vol. 6, No. 3 (November, 2017), pp. 204–209.

Akhtar, M. F., Ashraf, K. M., Saleem, A., Sharif, A., Zubair, H. M., & Anwar, F. (2022). Antidiabetic Potential and Antioxidant Activity of *Olea europaea* subsp. *Cuspidata* (Indian Olive) Seed Extracts. Hindawi Evidence-Based Complementary and Alternative Medicine, Vol. 2022, No. 1 (September, 2022), pp. 1-12.

Alfahdawi, I. H., & Alsewuidi, W. M. (2022). Effect of Oleuropein on Fungal Infection for Denture Wearers. Research Square, Vol. 1 (January, 2022), pp. 1–9.

Al-Hafidh, S. H. A., & Abdulwahid, A. A. (2024). Neurotoxic effects of type II-diabetes mellitus and the possible preventive effects of olive leaves supplement in male rats. Open Veterinary Journal, Vol. 14, No. 10 (October, 2024), pp. 2651-2661.

Aliabadi, M. A., Darsanaki, R. K., Rokhi, M. L., Nourbakhsh, M., & Raeisi, G. (2012). Antimicrobial activity of olive leaf aqueous extract, Annals of Biological Research, Vol. 3, No. 8 (May, 2012), pp. 4189-4191.

Allaw, M., Manca, M. L., Gòmez-Fernández, J. C., Pedraz, J. L., Terencio, M. C., Sales, O. D., Nacher, A., & Manconi, M. (2021). Oleuropein multicompartment nanovesicles enriched with collagen as a natural strategy for the treatment of skin wounds connected with oxidative stres. Nanomedicine, Vol. 16, No. 26 (May, 2021), 2363–2376.

Al-Rejaboo, M. A., Al-Tarjuman, J. K., Al-Dulaimi, F. K. Y., & Al-Sumaidaiea, B. Z. (2025). Fungi isolated from soils adjacent to olive trees in Nineveh Governorate. Regulatory Mechanisms in Biosystems, Vol. 16, No. 1 (January, 2025), pp. 1-7.

Al-Rimawi, F., Sbeih, M., Amayreh, M., Rahhal, B., & Mudalal, S. (2024). Evaluation of the antibacterial and antifungal properties of oleuropein, olea Europea leaf extract, and Thymus vulgaris oil. BMC Complementary Medicine and Therapies, Vol. 24, No. 1 (August, 2024), pp. 297.

Al-Shaal, S., Karabet, F., & Daghestani, M. (2019). Determination of the antioxidant properties of the Syrian olive leaves extracts and isolation oleuropein by HPLC techniques. Analytical and Bioanalytical Chemistry Research, Vol. 6, No. 1 (June 2019), pp. 97–110.

Ambra, R., Natella, F., Lucchetti, S., Forte, V., & Pastore, G. (2017a). α-Tocopherol, β-carotene, lutein, squalene and secoiridoids in seven monocultivar Italian extra-virgin olive oils. Int. J. Food Sci. Nutr., Vol. 68, No. 5 (December 8), pp. 538–545.

Ambra, R., Natella, F., Bello, C., Lucchetti, S., Forte, V., & Pastore, G. (2017b). Phenolics fate in table olives (Olea europaea L. cv. Nocellara del Belice) debittered using the Spanish and Castelvetrano methods. Food Research International, Vol. 100, No. 1 (October, 2017), pp. 369–376.

Amoah, B. P., Yang, H., Zhang, P., Su, Z., & Xu, H. (2015). Immunopathogenesis of myocarditis: the interplay between cardiac fibroblast cells, dendritic cells, macrophages and CD 4+ T cells. Scandinavian Journal of Immunology, Vol. 82, No. 1 (March, 2015), pp. 1-9.

Andreadou, I., Iliodromitis, E. K., Mikros, E., Constantinou, M., Agalias, A., Magiatis, P., Skaltsounis, A. L., Kamber, E., Tsantili-Kakoulidou, A., & Kremastinos, D. T. (2006). The olive constituent oleuropein exhibits anti-ischemic, antioxidative, and hypolipidemic effects in anesthetized Rabbits12. J. Nutr., Vol. 136, (August, 2006), pp. 2213–2219.

Andreadou, I., Mikros, E., Ioannidis, K., Sigala, F., Naka, K., Kostidis, S., Farmakis, D., Tenta, R., Kavantzas, N., Bibli, S. I., Gikas, E., Skaltsounis, L., Kremastinos, D. Th., & Iliodromitis, E. K. (2014). Oleuropein prevents doxorubicin-induced cardiomyopathy interfering with signaling molecules and cardiomyocyte metabolism. J. Mol. Cell. Cardiol., Vol. 69 (April 2014), pp. 4-16.

Annunziata, G., Maisto, M., Schisano, C., Barrea, L., Ciampaglia, R., & Novellinoet, E. (2018). Oleuropein as a novel anti-diabetic nutraceutical. An overview. Archives of Diabetes & Obesity, Vol. 1, No. 3 (August, 2018), 54-58.

Antognelli, C., Frosini, R., Santolla, M. F., Peirce, M. J., & Talesa, V. N. (2019). Oleuropein-induced apoptosis is mediated by mitochondrial glyoxalase 2 in nsclc A549 cells: a mechanistic inside and a possible novel nonenzymatic role for an ancient enzyme. Oxidative Medicine and Cellular Longevity, Vol. 2019 (July, 2019), pp. 1-10.

Arfaoui, M., Boulares, M., Bezzezi, A., Ayachi, S., Ghrab, M., Jouini, N. E., Hassouna, M., & Boudiche, S. (2024). Effect of the enrichment with natural antioxidants obtained by maceration or ultrasound-assisted extraction from olive leaves on organic extra virgin olive oil. Rivista Italiana Delle Sostanze Grasse, Vol. 99, No. 2 (November, 2024), pp. 121-129.

Arslan, E. E., Karademir, G., Berktaş, S. & Çam, M. (2021). Zeytin yaprağı ekstraktı içeren soğuk çay üretimi, Mühendislik Bilimleri ve Tasarım Dergisi, Vol 9, No. 3 (September, 2021), pp. 843-849.

Asghar, T., Asghar, T., Ashraf, T., Ashraf, A., Manzoor, A., Tariq, F., Buzdar, J. A., Ihsan, M., Maryam, S., & Nazir, S. (2024). Chapter 13 - Unlocking health benefits: the potential of olive leaf extracts in promoting well-being. Complementary and Alternative Medicine: Chinese/Traditional Medicine. Unique Scientific Publishers, Faisalabad, Pakistan, (August, 2024), pp. 85-96.

Asghari, A. A., Mahmoudabady, M., Shabab, S., & Niazmand, (2022). Anti-inflammatory, anti-oxidant and anti-apoptotic effects of olive leaf extract in cardiac tissue of diabetic rats. Journal of Pharmacy and Pharmacology, Vol., 74 (March, 2023), pp. 961–972.

Asghariazar, V., Mansoori, B., Kadkhodayi, M., Safarzadeh, E., Mohammadi, A., Baradaran, B. & Sakhinia, E. (2022). MicroRNA-143 act as a tumor suppressor microRNA in human lung cancer cells by inhibiting cell proliferation, invasion, and migration. Molecular Biology Reports, Vol. 49, No. 8 (August, 2022), pp. 7637–7647.

Asghariazar, V., Makaremi, S., Zare, E., Danesh, H., Matin, S., Fouladi, N., & Safarzadeh, E. (2024). Oleuropein induces apoptosis in gastric cancer cell lines by regulating mir-34a, mir-21, and related genes: an experimental and bioinformatic study. International Journal of Biological Macromolecules, Vol. 265, No. 1 (April, 2024), 130527.

Asgharzade, S., Sheikhshabani, S. H., Ghasempour, E., Heidari, R., Rahmati, S., Mohammadi, M., Jazarei, A., & Amini-Farsani, Z. (2021). The effect of oleuropein on apoptotic pathway regulators in breast cancer cells. European Journal of Pharmacology, Vol. 886 (November 2020), pp. 173509-173518.

Bao, J., Zhang, D. W., Zhang, J. Z. H., Huang, P. L., Huang, P. L., & Lee-Huang, S. (2007). Computational study of bindings of olive leaf extract (OLE) to HIV-1 fusion protein gp41. FEBS Letters, Vol. 581, No. 14 (May, 2009), 2737-2742.

Barazani, O., Dag, A., & Dunseth, Z. (2023). The history of olive cultivation in the southern Levant. Front. Plant. Sci., Vol. 14 (February 2023), pp. 1-10.

Barbaro, B., Toietta, G., Maggio, R., Arciello, M., Tarocchi, M., Galli, A., & Balsano, C. (2014). Effects of the olivederived polyphenol oleuropein on human health. International Journal of Molecular Sciences, Vol. 15, No. 10 (September-October), pp. 18508–18524.

Batarfi, W. A., Yunus, M. H. M., Hamid, A. A., Lee, Y. T., & Maarof, M. (2024). Hydroxytyrosol: A Promising Therapeutic Agent for Mitigating Inflammation and Apoptosis. Pharmaceutics, Vol. 16 (October-November, 2024), pp. 1504.

Bayat, S., Mansoori Derakhshan, S., Mansoori Derakhshan, N., Shekari Khaniani, M., & Alivand, M. R. (2019). Downregulation of HDAC2 and HDAC3 via oleuropein as a potent prevention and therapeutic agent in MCF-7 breast cancer cells," Journal of Cellular Biochemistry, Vol. 120, No. 6 (January, 2019), pp. 9172–9180.

Benamar, K., Koraichi, S. I., & Fikri-Benbrahi, K. (2025). Ethnobotany, phytochemistry, and biological properties of three naturally associated Mediterranean species. Journal of Applied Pharmaceutical Science, Vol. 15, No. 02 (February, 2025), pp. 019-036.

Ben-Amor, I., Musarra-Pizzo, M., Smeriglio, A., D'Arrigo, M., Pennisi, R., Attia, H., Gargouri, B., Trombetta, D., Mandalari, G., & Sciortino, M. T. (2021). Phytochemical characterization of Olea europea leaf extracts and assessment of their anti-microbial and anti-HSV-1 activity. Viruses, Vol. 13, No. 6 (April-June, 2021), pp. 1085–1100.

Benedetto, N., Calabrone, L., Gutmanska, K., Macri, N., Cerrito, M. G., Ricotta, R., Pelosi, G., Bruno, A., Noonan, D. M., & Albini, A. (2022). An Olive Oil Mill Wastewater Extract Improves Chemotherapeutic Activity Against Breast Cancer Cells While

Protecting From Cardiotoxicity. Front. Cardiovasc. Med., Vol. 9 (April, 2022), 867867.

Benlarbi, M., Jemai, H., Hajri, K., Mbarek, S., Amri, E., Jebbari, M., ... & Dhifi, W. (2020). Neuroprotective effects of oleuropein on retina photoreceptors cells primary culture and olive leaf extract and oleuropein inhibitory effects on aldose reductase in a diabetic model: *Meriones shawi*. Archives of Physiology and Biochemistry, Vol. 128, No. 3 (June, 2022), pp. 593-600.

Bensehaila, S., Ilias, F., Saadi, F., & Zaouadi, N. (2022). Phenolic Compounds and Antimicrobial Activity of Olive (Olea europaea L.) Leaves. Asian Journal of Dairy and Food Research, Vol. 41, No. 2 (June 2022), pp. 237-241.

Boeira, V. T., Leite, C. E., Santos, A. A., Edelweiss, M. I., Calixto, J. B., Campos, M. M., & Morrone, F. B. (2011). Effects of the hydroalcoholic extract of *Phyllanthus niruri* and its isolated compounds on cyclophosphamide-induced hemorrhagic cystitis in mouse. Naunyn-Schmiedeberg's Archives of Pharmacology, Vol. 384, No. 3 (September, 2011), pp. 265-275.

Bossio, S., Perri, A., Malivindi, R., Giordano, F., Rago, V., Mirabelli, M., Salatino, A., Brunetti, A., Greco, E. A., & Aversa, A. (2022). Oleuropein Counteracts Both the Proliferation and Migration of Intra- and Extragonadal Seminoma Cells. Nutrients, Vol. 14, No. 11 (May, 2022), 2323.

Britton, J., Davis, R., & O Connor, K. E. (2019). Chemical, physical and biotechnological approaches to the production of the potent antioxidant hydroxytyrosol. Applied Microbiology and Biotechnology, Vol. 103, No. 15 (August, 2019), pp. 5957-5974.

Bulotta, S., Corradino, R., Celano, M., D’Agostino, M., Maiuolo, J., Oliverio, M., Procopio, A., Iannone, M., Rotiroti, D., & Russo, D. (2011). Antiproliferative and Antioxidant Effects on Breast Cancer Cells of Oleuropein and Its Semisynthetic Peracetylated Derivatives. Food Chem., Vol. 127, No. 4 (August, 2011), pp. 1609–1614.

Bulotta, S., Corradino, R., Celano, M., Maiuolo, J., D'Agostino, M., Oliverio, M., Procopio, A., Filetti, S., & Russo, D. (2013).

Antioxidant and antigrowth action of peracetylated oleuropein in thyroid cancer cells. Journal of Molecular Endocrinology, Vol. 51, No. 1 (May, 2013), pp. 181–189.

Bulotta, S., Celano, M., Lepore, S. M., Montalcini, T., Pujia, A., & Russo, D. (2014). Beneficial effects of the olive oil phenolic components oleuropein and hydroxytyrosol: focus on protection against cardiovascular and metabolic diseases. Journal of Translational Medicine, Vol. 12, No. 1 (August, 2014), pp. 1–9.

Calo, J. R., Crandall, P. G., O'Bryan, C. A., & Ricke, S. C. (2015). Essential oils as antimicrobials in food systems - A review. Food Control, Vol. 54 (August, 2015), pp. 111–119.

Canbey, I., Yigit Cinar, A., & Gurbuz, O. (2024). The Biological Activities of Oleuropein and Hydroxytyrosol. Journal of Food Health and Technology Innovations, Vol. 7, No. 15 (December, 2024), 607-621.

Caparica, R., Júlio, A., Araújo, M. E. M., Baby, A. R., Fonte, P., Costa, J. G., & de Almeida, T. S. (2020). Anticancer activity of rutin and its combination with ionic liquids on renal cells. Biomolecules., Vol. 10, No. 2 (January, 2020), pp. 1–15.

Carpi, S., Polini, B., Manera, C., Digiacomo, M., Salsano, J. E., Macchia, M., Scoditti, E., & Nieri, P. (2020). miRNA Modulation and Antitumor Activity by the Extra-Virgin Olive Oil Polyphenol Oleacein in Human Melanoma Cells. Front. Pharmacol., Vol. 11 (September, 2020), 574317.

Carraro, L., Fasolato, L., Montemurro, F., Martino, M. E., Balzan, S., Servili, M., Novelli, E., & Cardazzo, B. (2014). Polyphenols from olive mill waste affect biofilm formation and motility in Escherichia coli K-12. Microbiology Biotechnology, Vol. 7, No. 3 (March 2014), pp. 265–275.

Carrera-González, M. P., Ramírez-Expósito, M. J., Mayas, M. D., & Martínez-Martos, J. M. (2013). Protective role of oleuropein and its metabolite hydroxytyrosol on cancer. Trends Food Sci., Vol. 31, No. 2 (June 2013), pp. 92–99.

Casaburi, I., Puoci, F., Chimento, A., Sirianni, R., Ruggiero, C., Avena, P., & Pezzi, V. (2013). Potential of olive oil phenols as chemopreventive and therapeutic agents against cancer: a review of in vitro studies. Molecular Nutrition & Food Research, Vol. 57, No. 1 (January, 2013), pp. 71–83.

Castejón, M. L., Montoya, T., Alarcón-de-la-Lastra, C., & Sánchez-Hidalgo, M. (2020). Potential Protective Role Exerted by Secoiridoids from Olea europaea L. in Cancer, Cardiovascular, Neurodegenerative, Aging-Related, and Immunoinflammatory Diseases. Antioxidants, Vol. 9, No. 2 (February, 2020), 1-38.

Cavaca, L. A. S., Lopez-Coca, I. M., Silvero, G., & Afonso, C. A. M. (2020). The olive-tree leaves as a source of high-added value molecules: Oleuropein. Studies in Natural Products Chemistry, Vol. 64 (January, 2020), pp. 131-180.

Cavalheiro, C. V., Picoloto, R. S., Cichoski, A. J., Wagner, R., de Menezes, C. R., Zepka, L. Q., Da Croce, D. M., & Barin, J. S. (2015). Olive leaves offer more than phenolic compounds – Fatty acids and mineral composition of varieties from Southern Brazil. Industrial Crops and Products, Vol. 71, No. 1 (September, 2015), 122-127.

Cayuela, J. A., & García, J. F. (2018). Nondestructive measurement of squalene in olive oil by near infrared spectroscopy. LWT, Vol. 88 (February, 2018), pp. 103–108.

Charoenprasert, S., & Mitchell, A. (2012). Factors Influencing Phenolic Compounds in Table Olives (*Olea europaea*). J. Agric. Food Chem., Vol. 60, No. 29 (June 2012), pp. 7081–7095.

Chigurupati, S., Alharbi, F. S., Almahmoud, S., Aldubayan, M., Almoshari, Y., Vijayabalan, S., Bhatia, S., Chinnam, S., & Venugopal, V. (2021). Molecular docking of phenolic compounds and screening of antioxidant and antidiabetic potential of *Olea europaea* L. Ethanolic leaves extract. Arabian Journal of Chemistry, Vol. 14, No. 11 (November, 2011), pp. 1-9.

Christodoulou, A., Nikolaou, P.-E., Symeonidi, L., Katogiannis, K., Pechlivani, L., Nikou, T., Varela, A., Chania, C., Zerikiotis, S., Efentakis, P., Vlachodimitropoulos, D., Katsoulas, N., Agapaki, A., Dimitriou, C., Tsoumani, M., Kostomitsopoulos, N., Davos, C. H., Skaltsounis, A. L., Tselepis, A., Halabalaki, M., Tseti, I., Iliodromitis, E. K., Ikonomidis, I., & Andreadou, I. (2024). Cardioprotective potential of oleuropein, hydroxytyrosol, oleocanthal and their combination: Unravelling complementary effects on acute myocardial infarction and metabolic syndrome. Redox Biology, Vol. 76 (October, 2024), pp. 1-19.

Ci, Y., Qiao, J., & Han, M. (2016). Molecular Mechanisms and Metabolomics of Natural Polyphenols Interfering with Breast Cancer Metastasis. Molecules, Vol. 21, No. 12 (December, 2016), pp. 1-27.

Coppa, C. F. S. C. C, Goncalves, B. L., Lee, S., Nunes, V., M. R., Gonçalves, C. B., Rodrigues, C. E. C., & Oliveira, C. A. F. (2020). Extraction of Oleuropein from Olive Leaves and Applicability in Foods. Qual. Assur. Saf. Crops Foods, Vol. 12, No. 4 (October, 2020), pp. 50–62.

Cordero, J. G., García-Escudero, R., Avila, J., Gargini, R., & García-Escudero, V. (2018). Benefit of oleuropein aglycone for Alzheimer’s disease by promoting autophagy. Oxidative Medicine and Cellular Longevity, Vol. 2018 (February, 2018), pp. 1-12.

Costanzo, P., Bonacci, S., Cariati, L., Nardi, M., Oliverio, M., & Procopio, A. (2018). Simple and efficient sustainable semi-synthesis of oleacein [2-(3,4-hydroxyphenyl) ethyl (3S,4E)-4-formyl-3-(2-oxoethyl)hex-4-enoate] as potential additive for edible oils. Food Chemistry, 245 (April 2018), pp. 410–414.

Cristiano, M. C., Froiio, F., Mancuso, A., Cosco, D., Dini, L., Di Marzio, L., Fresta, M., & Paolino, D. (2021). Oleuropein-Laded Ufasomes Improve the Nutraceutical Efficacy. Nanomaterials, Vol. 11, No. 1 (January, 2021), 105.

Cusimano, A., Balasus, D., Azzolina, A., Augello, G., Emma, M. R., Di Sano, C., Gramignoli, R., Strom, S. C., McCubrey, J. A., Montalto, G., & Cervello, M. (2017). Oleocanthal exerts antitumor effects on human liver and colon cancer cells through ROS generation. Int. J. Oncol., Vol. 51, No. 2 (June, 2017), pp. 533–544.

Cuyàs, E., Gumuzio, J., Lozano-Sanchez, J., Segura-Carretero, A., Verdura, S., Bosch-Barrera, J., Martin-Castillo, B., Nonell-Canals, A., Llebaria, A., Cabello, S., Serra, C., Sanchez-Martinez, M., Martin, Á. G., & Menendez, J. A. (2020). Mimetics of extra virgin olive oil phenols with anti-cancer stem cell activity. Aging, Vol. 12, No. 21 (November, 2020), pp. 21057–21075.

Czerwińska, M., Kiss, A. K., & Naruszewicz, M. (2011). A comparison of antioxidant activities of oleuropein and its dialdehydic derivative from olive oil, oleacein. Food Chemistry, Vol. 131 (November, 2011), pp. 940–947.

Da Porto, A., Brosolo, G., Casarsa, V., Bulfone, L., Scandolin, L., Catena, C., and Sechi, L. A. (2022). The Pivotal Role of Oleuropein in the Anti-Diabetic Action of the Mediterranean Diet: A Concise Review. Pharmaceutics, Vol 14 (December, 2021), pp. 1-12.

Dauber, C., Carreras, T., González, L., Gámbaro, A., Valdés, A., Ibañez, E., & Vieitez, I. (2022). Characterization and incorporation of extracts from olive leaves obtained through maceration and supercritical extraction in Canola oil: Oxidative stability evaluation. LWT, Vol. 160 (April, 2022), pp. 1-10.

Debib, A., & Boukhatem, M. N. (2017). Phenolic Content, Antioxidant and Antimicrobial Activities of "Chemlali" Olive Leaf (*Olea europaea* L.) Extracts. International Journal Pharmacology Phytochemistry Ethnomedicine, Vol. 6 (January, 2017), pp. 38–46.

Deng, L., Liang, H., & Han, Y. (2020). Cyclooxygenase-2 and beta-Catenin as Potential Diagnostic and Prognostic Markers in Endometrial Cancer. Front. Oncol., Vol. 10 No. 56 (February, 2020), pp. 1-10.

Deng, Y., Zhou, J., Qu, J., Wang, B., Xu, X., & Zhao, C. (2025). Deep Eutectic Solvents and Wall-Breaking Technique: A New Frontier in the Extraction of Oleuropein and Flavonoids from Olive Leaves with Superior Antioxidant and Antitumor Potential. Molecules, Vol. 30 (March, 2025), pp. 1-17.

Di Daniele, N., Noce, A., Vidiri, M. F., Moriconi, E., Marrone, G., Annicchiarico-Petruzzelli, M., D'Urso, G., Tesauro, M., Rovella, V., & De Lorenzo, A. (2017). Impact of Mediterranean diet on metabolic syndrome, cancer and longevity. Oncotarget, Vol. 8, No. 5 (January, 2017), pp. 8947–8979.

Di Rosa G, Saul N, Schmitz-Linneweber C, & Calabrese V. (2018). Olive oil polyphenols show beneficial effects in two c. elegans parkinson models. Pathophysiology, Vol. 25, No. 3 (September, 2018), pp. 185-203.

Djenane, D., Gómez, D., Yangüela, J., Roncalés, P., & Ariño, A. (2018). Olive leaves extract from Algerian oleaster (*Olea europaea* var. *Sylvestris*) on microbiological safety and shelf-life stability of raw halal minced beef during display. Foods., Vol. 8, No. 1 (December, 2018), pp. 1–17.

Elshafie, H. S., Camele, I., & Mohamed, A. A. (2023). A Comprehensive Review on the Biological, Agricultural and Pharmaceutical Properties of Secondary Metabolites Based-Plant Origin. Int. J. Mol. Sci., Vol. 24 (February, 2023), pp. 1-20.

El-Sohaimy, S. A., Mansour, H. M., Zeitoun, A. A., & Zeitoun, M. A. A. (2021). Antioxidant, antimicrobial and anti-inflammatory potential of olive leaves. Zagazig Journal of Agricultural Research, Vol. 48, No. 1 (December, 2020), pp. 161-173.

Emma, M. R., Augello, G., Di Stefano, V., Azzolina, A., Giannitrapani, L., Montalto, G., Cervello, M., & Cusimano, A. (2021). Potential Uses of Olive Oil Secoiridoids for the Prevention and Treatment of Cancer: A Narrative Review of Preclinical Studies. Int. J. Mol. Sci., Vol. 22, No. 3 (January), pp. 1-22.

Erbay, Z., & Icier, F. (2010). The importance and potential uses of olive leaves. Food Rev. Int., Vol. 26, No. 4 (October, 2010), pp. 319–334.

Ercelik, M., Tekin, C., Tezcan, G., Ak Aksoy, S., Bekar, A., Kocaeli, H., Taskapilioglu, M. O., Eser, P., & Tunca, B. (2023). *Olea europaea* Leaf Phenolics Oleuropein, Hydroxytyrosol, Tyrosol, and Rutin Induce Apoptosis and Additionally Affect Temozolomide against Glioblastoma: In Particular, Oleuropein

Inhibits Spheroid Growth by Attenuating Stem-like Cell Phenotype. Life, Vol. 13, No. 2 (February, 2023), pp. 1-28.

Esmailidehaj, M., Bajoovand, S., Rezvani, M. E., Sherifidehaj, M., Hafezimoghadam, Z., & Hafizibarjin, Z. (2016). Effect of oleuropein on myocardial dysfunction and oxidative stress induced by ischemic-reperfusion injury in isolated rat heart. Journal Ayurveda Integrative Medicine, Vol. 7, No. 4 (October-December, 2016), pp. 224–230.

Fakhraei, N., Abdolghaffari, A. H., Delfan, B., Abbasi, A., Rahimi, N., Khansari, A., Rahimian, R., & Dehpour, A. R. (2014). Protective effect of hydroalcoholic olive leaf extract on experimental model of colitis in rat: involvement of nitrergic and opioidergic systems. Phytotherapy Research, Vol. 28, No. 9 (September, 2014), pp. 1367–1373.

Fayez, N., Khalil, W., Abdel-Sattar, E., & Abdel-Fattah, A. M. (2023). In Vitro and In vivo Assessment of the Anti-Inflammatory Activity of Olive Leaf Extract in Rats. Inflammopharmacology, Vol. 31, No. 3 (April, 2023), pp. 1529–1538.

Fernández-Bolaños, J. G., López, O., Fernández-Bolaños, J., & Rodríguez-Gutiérrez, G. (2008). Hydroxytyrosol and derivatives: isolation, synthesis, and biological properties. Curr Org Chem., Vol. 12, No. 6, pp. 442–463.

Filardo, S., Roberto, M., Risola, D. D., Mosca, L., Pietro, M. D., & Sessa, R. (2024). *Olea europaea* L-derived secoiridoids: Beneficial health effects and potential therapeutic approaches. Pharmacology & Therapeutics, Vol. 254 (February, 2024), pp. 1-17.

Frumuzachi, O., Gavrilas, L. I., Vodnar, D. C., Rohn, S., & Mocan, A. (2024). Systemic Health Effects of Oleuropein and Hydroxytyrosol Supplementation: A Systematic Review of Randomized Controlled Trials. Antioxidants, Vol. 13 (August, 2024), pp. 1-26.

Fujiwara, Y., Tsukahara, C., Ikeda, N., Sone, Y., Ishikawa, T., Ichi, I., Koike, T., & Aoki, Y. (2017). Oleuropein improves insulin resistance in skeletal muscle by promoting the translocation of GLUT4. Journal of Clinical Biochemistry and Nutrition, Vol. 61, No. 3 (October, 2017), pp. 196–202.

García-Molina, G., Peters, E., Palmeri, R., Awoke, Y., Márquez-Álvarez, C., & Blanco, R. M. (2024). Enzymatic synthesis of Hydroxytyrosol from Oleuropein for valorization of an agricultural waste. Bioengineered, Vol. 15, No. 1 (September, 2024), pp. 1-17.

George, E. S., Marshall, S., Mayr, H. L., Trakman, G. L., Tatucu-Babet, O. A., Lassemillante, A.-C. M., Bramley, A., Reddy, A. J., Forsyth, A., Tierney, A. C., Thomas, C. J., Itsiopoulos, C., & Marx, W. (2019). The effect of high-polyphenol extra virgin olive oil on cardiovascular risk factors: a systematic review and meta-analysis. Crit. Rev. Food Sci. Nutr., Vol. 59, No. 17 (November, 2018), 2772–2795.

Gervasi, F. & Pojero, F. (2024). Use of Oleuropein and Hydroxytyrosol for Cancer Prevention and Treatment: Considerations about How Bioavailability and Metabolism Impact Their Adoption in Clinical Routine. Biomedicines, Vol. 12, No. 3 (February, 2024), pp. 1-36.

Geyikoğlu, F., Colak, S., Türkez, H., Bakır, M., Koç, K., Hosseinigouzdagani, M. K., Çeriğ, S., & Sönmez, M. (2017). Oleuropein ameliorates cisplatin-induced hematological damages via restraining oxidative stress and DNA injury. Indian Journal of Hematology and Blood Transfusion, Vol. 33, No. 3 (September, 2017), pp. 348–354.

Ghomari, O., Sounni, F., Massaoudi, Y., Ghanam, J., Drissi Kaitouni, L. B., Merzouki, M., & Benlemlih, M. (2019). Phenolic profile (HPLC-UV) of olive leaves according to extraction procedure and assessment of antibacterial activity. Biotechnology Reports, Vol. 23 (September, 2019), pp. 1-7.

Giner, E., Recio, M. C., Rios, J. L., Cerda-Nicolas, J. M., & Giner, R. M. (2016). Chemopreventive effect of oleuropein in colitis-associated colorectal cancer in c57bl/6 mice. Mol. Nutr. Food Res., Vol. 60, No. 2 (February, 2016), pp. 242–255.

Goncalves, M., Aiello, A., Rodríguez-Pérez, M., Accardi, G., Burgos-Ramos, E., & Silva, P. (2024). Olive Oil Components as Novel Antioxidants in Neuroblastoma Treatment: Exploring the Therapeutic Potential of Oleuropein and Hydroxytyrosol. Nutrients, Vol. 16, No. 6 (March, 2024), pp. 1-20.

Gökmen, M., Akkaya, L., Kara, R., Gök, V., Önen, A., & Ektik N. (2016). Zeytin yaprağı ekstraktı ilavesinin köftelerde *S. typhimurium, E. coli* O157 ve *S. aureus* gelişimi üzerine etkisi. Akademik Gıda, Vol. 14, No. 1 (March, 2016), pp. 28-32.

Grewal, R., Reutzel, M., Dilberger, B., Hein, H., Zotzel, J., Marx, S., Tretzel, J., Sarafeddinov, A., Fuchs, C., & Eckert, G. P. (2020). Purified oleocanthal and ligstroside protect against mitochondrial dysfunction in models of early Alzheimer's disease and brain ageing. Experiment Neurology, Vol. 328 (June, 2020), pp. 113-248.

Grossi, C., Rigacci, S., Ambrosini, S., Dami, T. E., Luccarini, I., Traini, C., Failli, P., Berti, A., Casamenti, F., & Stefani, M. (2013). The polyphenol oleuropein aglycone protects TgCRND8 mice against Aß plaque pathology. PloS One, Vol. 8, No. 8 (August, 2013), pp. 1-13.

Guasch-Ferré, M., Santos, J. L., Martínez-González, M. A., Clish, C. B., Razquin, C., Wang, D., Liang, L., Li, J., Dennis, C., Corella, D., Muňoz-Bravo, C., Romaguera, D., Estruch, R., Santos-Lozano, J. M., Castaňer, O., Alonso-Gómez, A., Serra-Majem, L., Ros, E., Canudas, S., Asensio, E. M., Fitó, M., Pierce, K., Martínez, J. A., Salas-Salvadó, J., Toledo, E., Hu, F. B., & Ruiz-Canela, M. (2020). Glycolysis/gluconeogenesis- and tricarboxylic acid cycle-related metabolites, Mediterranean diet, and type 2 diabetes. Am. J. Clin. Nutr., Vol. 111, No. 4 (April 2020), pp. 835–844.

Guclu, G., Kelebek, H., & Selli, S. (2021). Antioxidant activity in olive oils. In Olives and Olive Oil in Health and Disease Prevention, 2nd ed.; Preedy, V.R., Watson, R.R., Eds.; Elsevier Inc.: London, UK, 2021; pp. 313–325.

Guex, C. G., Reginato, F. Z., de Jesus, P. R., Brondani, J. C., Lopes, G. H. H., & Bauermann, L. d F (2019). Antidiabetic effects of *Olea* *europaea* L. leaves in diabetic rats induced by high-fat diet and low-dose streptozotocin. Journal of Ethnopharmacology, 235 (May, 2019), pp. 1–7.

Gyawali, R., & Ibrahim, S. A. (2014). Natural products as antimicrobial agents. Food Control, Vol. 46 (December, 2014), pp. 412-429.

Hadrich, F., Mahmoudi, A., Bouallagui, Z., Feki, I., Isoda, H., Feve, B., & Sayadi, S. (2016). Evaluation of hypocholesterolemic effect of oleuropein in cholesterol-fed rats. Chemico-Biological Interactions, Vol. 252 (May, 2016), pp. 54-60.

Hamed, M. M., Handoussa, H., Hussein, N. H., Eissa, R. A., Abdel-Aal, L. K., & El Tayebi, H. M. (2021). Oleuropin controls miR-194/XIST/PD-L1 loop in triple negative breast cancer: New role of nutri-epigenetics in immune-oncology. Life Sciences, Vol. 277 (March, 2021), pp. 1-12.

Hassan, M. M. S., Mohdaly, A. A. A., Elneairy, N. A. A., & Mahmoud, A. A. (2022). Using of olive leaves extract for increasing the stability of refined soybean oil. Fayoum Journal of Agricultural Research and Development, Vol. 36, No. 1 (January, 2022), pp. 12-20.

Hassen, I., Casabianca, H., & Hosni, K. (2015). Biological activities of the natural antioxidant oleuropein: Exceeding the expectation–A mini-review. Journal of Functional Foods, Vol. 18 (September, 2014), pp. 926-940.

Hu, T., He, X.-W., Jiang, J.-G., & Xu, X.-L. (2014). Hydroxytyrosol and its potential therapeutic effects. J. Agric. Food Chem., Vol. 62, No. 7 (February, 2014), pp. 1449–1455.

Hu, X., Zhao, N., Ranjbar, E., Foruozandeh, H., Nahal, A. S., Asadoola, Y., & Ahmadi, I. (2024). Protective effect of oleuropein on the brain tissue in D-Galactose-induced aging in rat model. Mol Biol Rep, Vol. 52, No. 1 (December, 2024), pp. 1-11.

Huang, C. L. & Sumpio, B. E. (2008). Olive oil, the mediterranean diet, and cardiovascular health. J Am Coll Surg., Vol. 207, No. 3 (May, 2008), pp. 407–416.

Iantomasi, M., Terzo, M. & Tsiani, E. (2024). Anti-Diabetic Effects of Oleuropein. Metabolites, Vol. 14, No. 11 (October, 2024), pp. 1-21.

Ilgaz, C., Casula, L., Sarais, G., Schlich, M., Dessì, D., Cardia, M. C., Sinico, C., Kadiroglu, P., & Lai, F. (2025). Proniosomal encapsulation of olive leaf extract for improved delivery of oleuropein: Towards the valorization of an agro-industrial byproduct. Food Chemistry, Vol. 479 (March, 2025), pp. 1-10.

Imran, M., Nadeem, M., Gilani, S. A., Khan, S., Sajid, M. W., & Amir, R. M. (2018). Antitumor perspectives of oleuropein and its metabolite hydroxytyrosol: recent updates. Journal of Food Science, Vol. 83, No. 7 (June 2018), pp. 1781–1791.

Issaoui, M., & Delgado, A. M. (2017). Chapter 4 - Olive Oil Properties from Technological Aspects to Dietary and Health Claims. In book: Chemistry of the Mediterranean Diet, (May, 2019), pp. 85-129.

Ivanov, M., Vajic, U. -J., Mihailovic-Stanojevic, N., Miloradovic, Z., Jovovic, D., GrujicMilanovic, J., Karanovic, D., & Dekanski, D. (2018). Highly potent antioxidant *Olea europaea* L. leaf extract affects carotid and renal haemodynamics in experimental hypertension: The role of oleuropein. EXCLI Journal, Vol. 17 (January, 2018), pp. 29–44.

Jahan, N., Mandal, M., Rakib, I. H., Hasan, S. A., Mia, E., Hossain, A., Yana, N. T., Ansari, S. A., Bappi, M. H., Hasan, A. M. W., Sayeed, A., and Islam, M. T. (2025). Assessment of Antidiarrheal Effect of Oleuropein Through μ-Oopioid Receptor Interaction Pathway: In Vivo and in Silico Studies. Vol. 86, No. 1 (February, 2025), e70064.

Jemai, H., Fki, I., Bouaziz, M., Bouallagui, Z., El Feki, A., Isoda, H., & Sayadi, S. (2008). Lipid-Lowering and Antioxidant Effects of Hydroxytyrosol and Its Triacetylated Derivative Recovered from Olive Tree Leaves in Cholesterol-Fed Rats. J. Agric. Food Chem., Vol. 56, No. 8 (April, 2008), pp. 2630–2636.

Kabach, I., Bouchmaa, N., Ben Mrid, R., Zouaoui, Z., Maadoudi, M. E., Kounnoun, A, Fadoua, A., Mansouri, F. E., Zyad, A., Cacciola, F., El Majdoub, Y. O., Mondello, L., & Nhiri, M. (2022). *Olea europaea* var. *Oleaster* a promising nutritional food with in vitro antioxidant, antiglycation, antidiabetic and antiproliferative effects. J Food Meas Charact., Vol. 17, No. 1 (November, 2022), pp. 882–894.

Kabera, J. N., Semana, E., Mussa, A. R., & He, X. (2014). Plant Secondary Metabolites: Biosynthesis, Classification, Function and Pharmacological Properties. Journal of Pharmacy and Pharmacology, Vol. 2, No. 7 (July, 2014), pp. 377-392.

Karković Marković, A., Torić, J., Barbarić, M., & Jakobušić Brala, C. (2019). Hydroxytyrosol, tyrosol and derivatives and their potential effects on human health. Molecules, Vol. 24, No. 10 (May, 2019), pp. 1-39.

Kerimi, A., Nyambe-Silavwe, H., Pyner, A., Oladele, E., Gauer, J. S., Stevens, Y., & Williamson, G. (2019). Nutritional implications of olives and sugar: Attenuation of post-prandial glucose spikes in healthy volunteers by inhibition of sucrose hydrolysis and glucose transport by oleuropein. European Journal of Nutrition, Vol. 58, No. 3 (April, 2019), pp. 1315–1330.

Keskin, D., Ceyhan, N., Uğur, A., & Dbeys, A. D. (2012). Antimicrobial activity and chemical constitutions of West Anatolian olive (*Olea europaea* L.) leaves. Journal of Food, Agriculture & Environment, Vol. 10, No. 2 (April, 2012), pp. 99-102.

Killeen, M. J., Linder, M., Pontoniere, P., & Crea, R. (2014). NF-κβ signaling and chronic inflammatory diseases: exploring the potential of natural products to drive new therapeutic opportunities. Drug Discovery Today, Vol. 19, No. 4 (April, 2014), pp. 373-378.

Kontogianni, V. G., & Gerothanassis, I. P. (2011). Phenolic compounds and antioxidant activity of olive leaf extracts. Nat. Prod. Res., Vol. 26, No. 2 (November, 2011), pp. 186–189.

Korukluoglu, M., Sahan, Y., & Yigit, A. (2008). Antifungal properties of olive leaf extracts and their phenolic compounds. Journal Food Safety, Vol. 28, No. 1 (February, 2008), pp. 76–87.

Kritikou, E., Kalogiouri, N. P., Kolyvira, L., & Thomaidis, N. S. (2020). Target and Suspect HRMS Metabolomics for the Determination of Functional Ingredients in 13 Varieties of Olive Leaves and Drupes from Greece. Molecules, Vol. 25, No. 21 (October, 2020), pp. 1-30.

Kumar, N., & Goel, N. (2019). Phenolic acids: Natural versatile molecules with promising therapeutic applications. Biotechnol. Rep., Vol. 24 (December, 2019), pp. 1-10.

Kyriazis, I. D., Koutsoni, O. S., Aligiannis, N., Karampetsou, K., Skaltsounis, A. L., & Dotsika, E. (2016). The leishmanicidal activity of oleuropein is selectively regulated through inflammationand oxidative stress-related genes. Parasites and Vectors, Vol. 9, No. 1 (August, 2016), pp. 1–16.

Lafka, T. I., Andriana, E., Lazou, V., Sinanoglou J, & Evangelos, S. L. (2013). Phenolic extracts from wild olive leaves and their potential as edible oils antioxidants. Foods, Vol. 2, No. 1 (January, 2013), pp. 18–31.

Lee-Huang, S., Huang, P. L., Zhang, D., Lee, J. W., Bao, J., Sun, Y., Chang, Y.-T., Zhang, J., & Huang, P. L. (2007). Discovery of small-molecule HIV-1 fusion and integrase inhibitors oleuropein and hydroxytyrosol: Part II. Integrase inhibition. Biochemical and Biophysical Research Communications, Vol. 354, No. 4 (March, 2007), pp. 879–884.

Lee, O., & Lee, B. (2010). Antioxidant and antimicrobial activities of individual and combined phenolics in *Olea europea* leaf extract. Bioresource Technology, Vol. 101, No. 10 (May, 2010), pp. 3751-3754.

Leri, M., & Bucciantini, M. (2016). Efficacy of Oleuropein Aglycone in the Treatment of Transthyretin-Amyloidosis. Biochemistry Molecular Biology Journal, Vol. 2, No. 1 (February, 2016), 1-6.

Leri, M., Natalello, A., Bruzzone, E., Stefani, M., & Bucciantini, M. (2019). Oleuropein aglycone and hydroxytyrosol interfere differently with toxic Aβ1-42 aggregation. Food and Chemical Toxicology, Vol. 129 (July, 2019), pp. 1-12.

Leri, M., Bertolini, A., Stefani, M., & Bucciantini, M. (2021). EVOO Polyphenols Relieve Synergistically Autophagy Dysregulation in a Cellular Model of Alzheimer's Disease. Int. J. Mol. Sci., Vol. 22, No. 13 (July, 2021), pp. 1-16.

Li, H., He, H., Liu, C., Akanji, T., Gutkowski, J., Li, R., Ma, H., Wan, Y., Wu, P., Li, D., Seeram, N. P., & Ma, H. (2022). Dietary polyphenol oleuropein and its metabolite hydroxytyrosol are moderate skin permeable elastase and collagenase inhibitors with synergistic cellular antioxidant effects in human skin fibroblasts. Int J Food Sci Nutr, Vol. 73, No. 4 (October, 2021), pp. 1-11.

Li H, Deng N, Yang J, Zhao Y, Jin X, Cai A, Seeram NP, Ma H, Li D, Yang H and Liu C (2025) Anti-inflammatory and antioxidant properties of oleuropein in human keratinocytes characterized by bottom-up proteomics. Front. Pharmacol. Vol. 15 (January, 2025), 1-13.

Liu, Y., McKeever, L. C., & Malik, N. S. A. (2017). Assessment of the antimicrobial activity of olive leaf extract against foodborne bacterial pathogens. Frontiers in Microbiology, Vol. 8 (February, 2017), pp. 1-8.

Lockyer, S., Rowland, I., Spencer, J. P. E., Yaqoob, P., & Stonehouse, W. (2017). Impact of phenolic-rich olive leaf extract on blood pressure, plasma lipids and inflammatory markers: A randomised controlled trial. European Journal of Nutrition, Vol. 56, No. 4 (June, 2017), pp. 1421–1432.

Longhi, R., Santos, A. S. E. A., López-Yerena, A., Rodrigues, A. P. S., de Oliveira, C., & Silveira, E. A. (2021). The effectiveness of extra virgin olive oil and the traditional Brazilian diet in reducing the inflammatory profile of individuals with severe obesity: a randomized clinical trial. Nutrients, Vol. 13, No. 11 (November, 2021), pp. 1-10.

Lozano-Castellón, J., López-Yerena, A., Rinaldi de Alvarenga, J. F., Romero del Castillo-Alba, J., Vallverdú-Queralt, A., Escribano-Ferrer, E., & Lamuela-Raventós, R. M. (2020). Health-promoting properties of oleocanthal and oleacein: Two secoiridoids from extra-virgin olive oil. Crit. Rev. Food, Vol. 60, No. 15 (August, 2019), pp. 2532–2548.

Magyari-Pavel, I. Z., Moacă, E.-A., Avram, S., Diaconeasa, Z., Haidu, D., Stefãnut, M. N., Rostas, A. M., Muntean, D., Bora, L., Badescu, B., et al. (2024) Antioxidant Extracts from Greek and Spanish Olive Leaves: Antimicrobial, Anticancer and Antiangiogenic Effects. Antioxidants, Vol. 13, No. 7 (June, 2024), pp. 1-30.

Makowska-Wąs J, Galanty A, Gdula-Argasińska J, Tyszka-Czochara M, Szewczyk A, Nunes R, Carvalho, I. S., Michalik, M., & Paśko, P. (2017). Identification of predominant phytochemical compounds and cytotoxic activity of wild olive leaves (*Olea europaea* L. ssp. *sylvestris*) harvested in south Portugal. Chem Biodivers., Vol. 14, No. 3 (March, 2017), pp. 1–10.

Malliou, F., Andreadou, I., Gonzalez, F. J., Lazou, A., Xepapadaki, E., Vallianou, I., Lambrinidis, G., Mikros, E., Marselos, M., Skaltsounis, A.-L., & Konstandi, M. (2018). The olive constituent oleuropein, as a PPARαagonist, markedly reduces serum triglycerides. The Journal of nutritional biochemistry, Vol. 59 (June, 2018), pp. 17-28.

Manna, C., Migliardi, V., Golino, P., Scognamiglio, A., Galletti, P. Chiariello, M., & Zappia, V. (2004). Oleuropein prevents oxidative myocardial injury induced by ischemia and reperfusion. Journal Nutrition Biochemistry, Vol. 15, No. 8 (August, 2004), pp. 461–466.

Mansour, H. M. M., Zeitoun, A. A., Abd-Rabou, H. S., El Enshasy, H. A., Dailin, D. J., Zeitoun, M. A. A., & El-Sohaimy, S. A. (2023). Antioxidant and Anti-Diabetic Properties of Olive (*Olea europaea*) Leaf Extracts: In Vitro and In Vivo Evaluation. Antioxidants, Vol. 12, No. 6 (June, 2023), pp. 1-21.

Markin, D., Duek, L., & Berdicevsky, I. (2003). In vitro antimicrobial activity of olive leaves. Mycoses, Vol. 46, No. 3-4 (March, 2003), pp. 132–136.

Marrone, G., Urciuoli, S., Candi, E., Bernini, R., Vanni, G., Masci, C., Guerriero, C., Mancini, M., De Lorenzo, A., Vignolini, P., & Noce, A. (2023). Biological Activities of Molecules Derived from *Olea europaea* L. Tested In Vitro. Life, Vol. 14, No. 1 (December, 2023), pp. 1-10.

Marrero, A. D., Quesada, A. R., Martínez-Poveda, B., & Medina, M. Á. (2024). Anti-Cancer, Anti-Angiogenic, and Anti-Atherogenic Potential of Key Phenolic Compounds from Virgin Olive Oil. Nutrients, Vol. 16, No. 9 (April, 2024), pp. 1-22.

Mattioli, L. B., Frosini, M., Amoroso, R., Maccallini, C., Chiano, E., Aldini, R., ... Budriesi, R. (2022). *Olea europea* L. leaves and *Hibiscus sabdariffa* L. petals extracts: Herbal mix from cardiovascular network target to gut motility dysfunction application. Nutrients, Vol. 14, No. 3 (January, 2022), pp. 1-26.

Medfai, W., Contreras, M. D. M., Lama-Muñoz, A., Mhamdi, R., Oueslati, I., & Castro, E. (2020). How Cultivar and Extraction Conditions Affect Antioxidants Type and Extractability for Olive Leaves Valorization. ACS Sustain. Chem. Eng., Vol. 8, No. 13 (February, 2020), pp. 5107–5118.

Messa, F., Giotta, L., Troisi, L., Perrone, S., & Salomone, A. (2024). Sustainable Extraction of Hydroxytyrosol from Olive Leaves Based on a Nature-Inspired Deep Eutectic Solvent (NADES). ChemistrySelect, Vol. 9, No. 37 (September, 2024), pp. 1-12.

Micol, V., Caturla, N., Perez-Fons, L., Mas, V. Perez, L., & Estepa, A. (2005). The olive leaf extract exhibits antiviral activity against viral haemorrhagic septicaemia rhabdovirus (VHSV). Antiviral Research, Vol. 66, No. 2-3 (June, 2005), pp. 129–136.

Miho, H., Moral, J., Barranco, D., Ledesma-Escobar, C. A., Priego-Capote, F., & Díez, C. M. (2021). Influence of genetic and interannual factors on the phenolic profiles of virgin olive oils. Food Chem., Vol. 16, No. 342 (April, 2021), 128357.

Monache, S. D., Pulcini, F. Frosini, R. Mattei, V. Talesa, V. N., & Antognelli, C. (2021). Methylglyoxal-dependent glycative stress is prevented by the natural antioxidant oleuropein in human dental pulp stem cells through nrf2/glo1 pathway. Antioxidants, Vol. 10, No. 5 (May, 2021), pp. 1-19.

Moraes, J. P., Pereira, D. S., Matos, A. S., Santana, D. G., Santos, C. A., Estevam, C. S., Fakhouri, R., de Lucca Junior, W., Camargo, E. A. & Camargo, E. A. (2013). The ethanol extract of the inner bark of *Caesalpinia pyramidalis* (Tul.) reduces urinary bladder damage during cyclophosphamide-induced cystitis in rats. The Scientific World Journal, Vol. 2013 (September, 2013), pp. 1-8.

Morana, J. M., Leal-Hernande, O., Canal-Macias, M. L., Roncero-Martin, R., Guerrero-Bonmatty, R., Aliaga, I., & Zamorano, J. D. (2016). Antiproliferative Properties of Oleuropein in Human Osteosarcoma Cells. Nat. Prod. Commun., Vol. 11, No. 4 (April, 2016), pp. 491–492.

Mousavi, S., de la Rosa, R., Moukhli, A., El Riachy, M., Mariotti, R., Torres, M., Pierantozzi, P., Stanzione, V., Mastio, V., Zaher, H., et al. (2019). Plasticity of fruit and oil traits in olive among different environments. Sci. Rep., Vol. 9 (November, 2019), 16968.

Mousavi, S., Stanzione, V., Mariotti, R., Mastio, V., Azariadis, A., Passeri, V., Valeri, M. C., Baldoni, L., & Bufacchi, M. (2022). Bioactive Compound Profiling of Olive Fruit: The Contribution of Genotype. Antioxidants, Vol. 11, No. 4 (March, 2022), pp. 1-19.

Mumcu, A. (2023). Olive Leaf: Antimicrobial and Antioxidant Properties, Food Applications, and Current Studies. Eurasian Journal of Food Science and Technology, Vol. 7, No. 1 (June, 2023), pp. 23-43.

Munekata, P. E. S., Nieto, G., Pateiro, M., & Lorenzo, J. M. (2020). Phenolic compounds obtained from *Olea europaea* by-products and their use to improve the quality and shelf life of meat and meat products - A review. Antioxidants, Vol. 9, No. 11 (October, 2020), pp. 1-24.

Murotomi, K., Umeno, A., Yasunaga, M., Shichiri, M., Ishida, N., Koike, T., ... Nakajima, Y. (2015). Oleuropein-rich diet attenuates hyperglycemia and impaired glucose tolerance in type 2 diabetes model mouse. Journal of Agricultural and Food Chemistry, Vol. 63, No. 30 (July, 2015), pp. 6715–6722.

Muzzalupo, I., Badolati, G. Chiappetta, A. Picci, N., & Muzzalupo, R. (2020). In vitro Antifungal Activity of Olive (*Olea europaea*) Leaf Extracts Loaded in Chitosan Nanoparticles. Frontier Bioeng Biotechnology, Vol. 8, No. 151 (March, 2020), pp. 1–10.

Nasrollahi, Z., & Abolhasannezhad, M. (2015). Evaluation of the antifungal activity of olive leaf aqueous extracts against *Candida albicans* PTCC-5027. Current Medical Mycology, Vol. 1, No. 4 (March, 2015), pp. 37-39.

Nediani, C., Ruzzolini, J., Romani, A., & Calorini, L. (2019). Oleuropein, a bioactive compound from *Olea europaea* L., as a potential preventive and therapeutic agent in noncommunicable diseases. Antioxidants, Vol. 8, No. 12 (November, 2019), pp. 1-26.

Nekooeian, A. A., Khalili, A., & Khosravi, M. B. (2014). Oleuropein offers cardioprotection in rats with simultaneous type 2 diabetes and renal hypertension. Indian J Pharmacol., Vol. 46, No. 4 (July, 2014), pp. 398-403.

Nicolì, F., Negro, C., Vergine, M., Aprile, A., Nutricati, E., Sabella, E., Miceli, A., Luvisi, A., & De Bellis, L. (2019). Evaluation of phytochemical and antioxidant properties of 15 Italian *Olea europaea* L. Cultivar Leaves. Molecules, Vol. 24, No. 10, pp. 1-12.

Noce, A., Marrone, G., Di Lauro, M., Mitterhofer, A. P., Ceravolo, M. J., Di Daniele, N., Manenti, G., & De Lorenzo, A. (2023). The Onco-Nephrology Field: The Role of Personalized Chemotherapy to Prevent Kidney Damage. Cancers, Vol. 15, No. 8 (April, 2023), pp. 1-22.

Nocella, C., Cammisotto, V., Fianchini, L., D'Amico, A., Novo, M., Castellani, V., Stefanini, L., Violi, F., & Carnevale, R. (2017). Extra virgin olive oil and cardiovascular diseases: benefits for human health. Endocr., Metab. Immune Disord.: Drug Targets, Vol. 18, No. 1 (November, 2017), pp. 4–13.

Nunes, M. A., Pimentel, F. B., Costa, A. S. G., Alves, R. C., Beatriz, M., & Oliveira, P. P. (2016). Olive by-products for functional and food applications: Challenging opportunities to face environmental constraints. Innovative Food Science & Emerging Technologies, Vol. 35, No. 4 (April, 2016), pp. 139-148.

Oi-Kano, Y., Iwasaki, Y., Nakamura, T., Watanabe, T., Goto, T., Kawada, T., Watanabe, K., & Iwai, K. (2017). Oleuropein aglycone enhances UCP1 expression in Brown adipose tissue in high-fat-diet-induced obese rats by activating β-adrenergic signaling. J. Nutr. Biochem., Vol. 40 (February, 2017), pp. 209–218.

Omar, S. H. (2010). Oleuropein in Olive and its Pharmacological Effects. Sci. Pharm., Vol. 78, No. 2 (April-June, 2010), pp. 133–154.

Otero, D. M., Lorini, A., Oliveira, F. M., da Fonseca Antunes, B., Oliveira, R. M., & Zambiazi, R. C. (2021). Leaves of *Olea europaea* L. as a source of oleuropein: characteristics and biological aspects. Research, Society and Development, Vol. 10, No. 13 (October, 2021), pp. 1-17.

Papachristodoulou, A., Tsoukala, M., Benaki, D., Kostidis, S., Gioti, K., Aligiannis, N., Pratsinis, H., Kletsas, D., Skaltsounis, A. L., Mikros, E., et al. (2016). Oleuropein is a Powerful Sensitizer of Doxorubicin-mediated Killing of Prostate Cancer Cells and Exerts Its Action via Induction of Autophagy. J. Cancer Res. Treat., Vol. 4, No. 4 (January, 2016), pp. 61–68.

Pasban-Aliabadi, H., Esmaeili-Mahani, S., Sheibani, V., Abbasnejad, M., Mehdizadeh, A., & Yaghoobi, M. M. (2013). Inhibition of 6-hydroxydopamineinduced PC12 cell apoptosis by olive (*Olea europaea* L.) leaf extract is performed by its main component oleuropein. Rejuvenation Research, Vol. 16, No. 2 (January, 2013), pp. 134-142.

Pennisi, R., Ben Amor, I., Gargouri, B., Attia, H., Zaabi, R., Chira, A. B., Saoudi, M., Piperno, A., Trischitta, P., Tamburello, M. P., & Sciortino, M. T. (2023). Analysis of Antioxidant and Antiviral Effects of Olive (*Olea europaea* L.) Leaf Extracts and Pure Compound Using Cancer Cell Model. Biomolecules, Vol. 13, No. 2 (January, 2023), pp. 1-17.

Plastina, P., Benincasa, C., Perri, E., Fazio, A., Augimeri, G., Poland, M., Witkamp, R., & Meijerink, J. (2019). Identification of hydroxytyrosyl oleate, a derivative of hydroxytyrosol with anti-inflammatory properties, in olive oil by-products. Food Chemistry, Vol. 279 (May, 2019), pp. 105-113.

Pojero, F., Aiello, A., Gervasi, F., Caruso, C., Ligotti, M. E., Calabr., A., Procopio, A., Candore, G., Accardi, G., & Allegra, M. (2022). Effects of Oleuropein and Hydroxytyrosol on Inflammatory Mediators: Consequences on Inflammaging. Int. J. Mol. Sci., Vol. 24, No. 1 (December, 2022), pp. 1-23.

Pojero, F., Gervasi, F., Fiore, S. D., Aiello, A., Bonacci, S., Caldarella, R., Attanzio, A., Candore, G., Caruso, C., Ligotti, M. E., Procopio, A., Restivo, I., Tesoriere, L., Allegra, M., & Accardi, G. (2023). Anti-Inflammatory Effects of Nutritionally Relevant Concentrations of Oleuropein and Hydroxytyrosol on Peripheral Blood Mononuclear Cells: An Age-Related Analysis. Int. J. Mol. Sci., Vol. 24, No. 13 (July, 2023), pp. 1-23.

Qadir, N. M., Ali, K. A., & Qader, S. W. (2016). Antidiabetic Effect of Oleuropein from Olea europaea Leaf against Alloxan Induced Type 1 Diabetic in Rats. Brazilian Archives of Biology and Technology, Vol. 59 (January-December, 2016), pp. 1-10.

Özcan, M. M. & Matthäus, B. (2017). A review: benefit and bioactive properties of olive (*Olea europaea* L.) leaves. European Food Research and Technology, Vol. 243 (June, 2016), pp. 89-99.

Ramírez, E., Brenes, M., García, P., Medina, E., & Romero, C. (2016). Oleuropein hydrolysis in natural green olives: Importance of the endogenous enzymes. Food Chem., Vol. 206 (March, 2016), pp. 204–209.

Ramírez-Expósito, M. J., Carrera-González, M. P., Mayas, M. D., & Martínez-Martos, J. M. (2021). Gender differences in the antioxidant response of oral administration of hydroxytyrosol and oleuropein against N-ethyl-N-nitrosourea (ENU)-induced glioma. Food Research International, Vol. 140, No. 1 (December, 2020), 110023.

Riolo, R., De Rosa, R., Simonetta, I., & Tuttolomondo, A. (2022). Olive Oil in the Mediterranean Diet and Its Biochemical and Molecular Effects on Cardiovascular Health through an Analysis of Genetics and Epigenetics. Int. J. Mol. Sci., Vol. 23, No. 24 (December, 2022), pp. 1-26.

Rishmawi, S., Haddad, F., Dokmak, G., & Karaman, R. (2022). A comprehensive review on the anti-cancer e4ects of oleuropein. Life, Vol. 12, No. 8 (July, 2022), pp. 1-18.

Romani, A., Ieri, F., Urciuoli, S., Noce, A., Marrone, G., Nediani, C., & Bernini, R. (2019). Health effects of phenolic compounds found in extra-virgin olive oil, by-products, and leaf of *Olea europaea* L. Nutrients, Vol. 11, No. 8 (August, 2019), 1776.

Romani, A., Bernini, R., Noce, A., Urciuoli, S., Di Lauro, M., Pietroboni Zaitseva, A., Marrone, G., & Di Daniele, N. (2020). Potential Beneficial Effects of Extra Virgin Olive Oils Characterized by High Content in Minor Polar Compounds in Nephropathic Patients: A Pilot Study. Molecules, Vol. 25, No. 20 (October, 2020), pp. 1-13.

Romero, M., Toral, M., Gómez-Guzmán, M., Jiménez, R., Galindo, P., Sánchez, M., Olivares, M., Gálvez, J., & Duarte, J. (2016). Antihypertensive effects of oleuropein-enriched olive leaf extract in spontaneously hypertensive rats. Food & Function, Vol. 7, No. 1 (January, 2016), pp. 584–593.

Ruzzolini, J., Peppicelli, S., Andreucci, E., Bianchini, F., Scardigli, A., Romani, A., la Marca, G., Nediani, C., & Calorini, L. (2018). Oleuropein, the Main Polyphenol of Olea europaea Leaf Extract, Has an Anti-Cancer Effect on Human BRAF Melanoma Cells and Potentiates the Cytotoxicity of Current Chemotherapies. Nutrients, Vol. 10, No. 12 (December, 2018), 1950–1967.

Saad, B. (2023). A Review of the Anti-Obesity Effects of Wild Edible Plants in the Mediterranean Diet and Their Active Compounds: From Traditional Uses to Action Mechanisms and Therapeutic Targets. Int. J. Mol. Sci., Vol. 24 (August, 2023), pp. 1-24.

Salamanca, A., Almodovar, P. Jarama, I. Gonzalez-Hedstrom, D. Prodanov, M., & Inarejos-Garcia, A. M. (2021). Antiinfluenza virus activity of the elenolic acid rich olive leaf (*Olea europaea* L.) extract Isenolic®. Antiviral Chemistry and Chemotherapy, Vol. 29 (November, 2021), pp. 1-9.

Salta, F. N., Mylona, A., Chiou, A., Boskou, G., & Andrikopoulos, N. K. (2007). Oxidative stability of edible vegetable oils enriched in polyphenols with olive leaf extract. Food Science and Technology International, Vol. 13, No. 6 (December, 2007), pp. 413-421.

Salvo, A. & Tuttolomondo, A. (2025). The Role of Olive Oil in Cardiometabolic Risk. Metabolites 2025, Vol. 15 (March, 2025), pp. 1-27.

Sanchez, J. C., Alsina, M. A., Herrlein, M. K., & Mestres, C. (2007). Interaction between the antibacterial compound, oleuropein, and model membranes. Colloid and Polymer Science, Vol. 285, No. 12 (January, 2007), pp. 1351–1360.

Sánchez-Gutiérrez, M., Bascón-Villegas, I., Rodríguez, A., Pérez-Rodríguez, F., Fernández-Prior, Á., Rosal A., & Carrasco E. (2021). Valorisation of Olea europaea L. olive leaves through the evaluation of their extracts: Antioxidant and antimicrobial activity. Foods, Vol. 10, No. 5 (April, 2021), pp. 1-19.

Sangi, S. M. A., Sulaiman, M. I., Abd El-wahab, M. F., Ahmedani, E. I., & Ali, S. S. (2015). Antihyperglycemic effect of thymoquinone and oleuropein, on streptozotocin-induced diabetes mellitus in experimental animals. Pharmacognosy Magazine, Vol. 11, No. Suppl 2 (October, 2015), pp. S251-S257.

Santos, M. M., Piccirillo, C., Castro, P. M. L., Kalogerakis, N., & Pintado, M. E. (2012). Bioconversion of oleuropein to hydroxytyrosol by lactic acid bacteria. World J. Microbiol. Biotechnol., Vol. 28, No. 6 (June, 2012), pp. 2435–2440.

Sarapis, K., George, E. S., Marx, W., Mayr, H. L., Willcox, J., Esmaili, T., Powell, K. L., Folasire, O. S., Lohning, A. E., Garg, M., Thomas, C. J., Itsiopoulos, C., & Moschonis, G. (2022). Extra virgin olive oil high in polyphenols improves antioxidant status in adults: a double-blind, randomized, controlled, cross-over study (OLIVAUS). Eur. J. Nutr., Vol. 61, No. 1 (March, 2022), pp. 1073–1086.

Sarbishegi, M., Mehraein, F., & Soleimani, M. (2014). Antioxidant role of oleuropein on midbrain and dopaminergic neurons of substantia nigra in aged rats. Iranian Biomedical Journal, Vol. 18, No. 1 (January, 2014), pp. 16-23.

Sato, H., Genet, C., Strehle, A., Thomas, C., Lobstein, A., Wagner, A., Mioskowski, C., Auwerx, J., & Saladin, R. (2007). Anti-hyperglycemic activity of a TGR5 agonist isolated from *Olea europaea*. Biochemical and Biophysical Research Communications, Vol. 362, No. 4 (November, 2007), pp. 793–798.

Sayadi, S., & Manel, H. (2016). The Possibility of Recovering of Hydroxytyrosol from Olive The Possibility of Recovering of Hydroxytyrosol from Milling Wastewater by Enzymatic Bioconversion Olive Milling Wastewater by Enzymatic Bioconversion Wastewater by Enzymatic Bioconversion Olive M. Products from Olive Tree. Intech Open Science Open Minds, pp. 263-281.

Shaibani, Z., & Rafieirad, M. (2024). Protective Effect of Oleuropein on Memory Impairment and Oxidative Stress in Streptozotocin - Induced Diabetes Rats via Modulation of NF -kB and Nrf-2 Pathways. Journal of Advanced Biomedical Sciences, Vol. 14, No. 2 (May, 2024), pp. 115-127.

Shamshoum, H., Vlavcheski, F., & Tsiani, E. (2017). Anticancer effects of oleuropein. Biofactors, Vol. 43, No. 4 (July, 2017), pp. 517–528.

Sherif, I. O., Nakshabandi, Z. M., Mohamed, M. A., & Sarhan, O. M. (2016). Uroprotective effect of oleuropein in a rat model of hemorrhagic cystitis. The International Journal of Biochemistry & Cell Biology, Vol. 74 (May, 2016), pp. 12-17.

Shi, J., Wu, G., Zou, X., & Jiang, K. (2017). Oleuropein protects intracerebral hemorrhage-induced disruption of blood-brain barrier through alleviation of oxidative stress. Pharmacological Reports, Vol. 69, No. 6 (December, 2017), pp. 1206-1212.

Shialy, Z., Zarrin, M., Nejad, B. S., & Naanaie, S. Y. (2015). In vitro antifungal properties of Pistacia atlantica and olive extracts on different fungal species. Current Medical Mycology, Vol. 1, No. 4 (March, 2015), pp. 40-45.

Silvestrini, A., Giordani, C., Bonacci, S., Giuliani, A., Ramini, D., Matacchione, G., Sabbatinelli, J., Di Valerio, S., Pacetti, D., Procopio, A. D., et al. (2023). Anti-Inflammatory Effects of Olive Leaf Extract and Its Bioactive Compounds Oleacin and Oleuropein-Aglycone on Senescent Endothelial and Small Airway Epithelial Cells. Antioxidants, Vol. 12, No. 8 (1-17), pp. 1-17.

Sinanoglu, O., Yener, A. N., Ekici, S., Midi, A., & Aksungar, F. B. (2012). The protective effects of spirulina in cyclophosphamide induced nephrotoxicity and urotoxicity in rats. Urology, Vol. 80, No. 6 (December, 2012), 1392.e1-1392.e6.

Soldo, B., Bilušić, T., Giacometti, J., Ljubenkov, I., Čikeš Čulić, V., Bratanić, A., Bošković, P., Šola, I., & Ilić, K. (2024). A Comparative Study of Oleuropein Extraction from Wild Olive Leaves (*Olea europea* subsp. *oleaster*, Hoffmanns. & Link), Its Gastrointestinal Stability, and Biological Potential. Appl. Sci., Vol. 14, No. 2 (January, 2024), pp. 1-14.

Sudjana, A. N., D'Orazio, C., Ryan, V., Rasool, N., Ng, J., Islam, N., Riley, T. V., & Hammer, K. A. (2009). Antimicrobial activity of commercial *Olea europaea* (olive) leaf extract. International Journal of Antimicrobial Agents, Vol. 33, No. 5 (February, 2009), pp. 461-463.

Sun, W., Wang, X., Hou, C., Yang, L., Li, H., Guo, J., Huo, C., Wang, M., Miao, Y., Liu, J., & Kang, Y. (2017a). Oleuropein improves mitochondrial function to attenuate oxidative stress by activating the Nrf2 pathway in the hypothalamic paraventricular nucleus of spontaneously hypertensive rats. Neuropharmacology, Vol. 113, No. Pt A (February, 2017), pp. 556-566.

Sun, W., Frost, B., & Liu, J. (2017b). Oleuropein, unexpected benefits! Oncotarget, Vol. 8, No. 11 (March, 2017), pp. 17409-17409.

Sun, X., Shi, Y., Shi, D., Tu, Y., & Liu, L. (2024). Biological Activities of Secondary Metabolites from the Edible-Medicinal Macrofungi. J. Fungi, Vol. 10, No. 2 (February, 2024), pp. 1-24.

Şahin, S., Şahin, E., Esenülkü, G., Renda, G., Gürgen, S. G., Alver, A., Abidin, İ., & Cansu, A. (2024). Oleuropein Has Modulatory Effects on Systemic Lipopolysaccharide-Induced

Neuroinflammation in Male Rats. The Journal of Nutrition, Vol. 154, No. 4 (April, 2024), pp. 1282-1297.

Şenol, H., Tulay, P., Ergören, M. Ç., Hanoğlu, A., Çaliş, İ., & Mocan, G. (2021). Cytotoxic effects of verbascoside on MCF-7 and MDA-MB-231. Turk J Pharm Sci., Vol. 18, No. 5 (February, 2021), pp. 637–651.

Talhaoui, N., Gómez-Caravaca, A. M., León, L., de la Rosa, R., Fernández-Gutiérrez, A., & Segura-Carretero, A. (2015). Pattern of Variation of Fruit Traits and Phenol Content in Olive Fruits from Six Different Cultivars. J. Agric. Food Chem., Vol. 63, No. 48 (October, 2015), pp. 10466–10476.

Tarabanis, C., Long, C., Scolaro, B., & Heffron, S. P. (2023). Reviewing the cardiovascular and other health effects of olive oil: Limitations and future directions of current supplement formulations. Nutr. Metab. Cardiovasc. Dis., Vol. 33, No. 12 (December, 2023), pp. 2326–2333.

Tasioula-Margari, M., & Tsabolatidou, E. (2015). Extraction, separation, and identification of phenolic compounds in virgin olive oil by HPLC-DAD and HPLC-MS. Antioxidants, Vol 4, No. 3 (August, 2015), pp. 548–562.

Tiedje, C., Holtmann, H., & Gaestel, M. (2014). The role of mammalian MAPK signaling in regulation of cytokine mRNA stability and translation. Journal of Interferon & Cytokine Research, Vol. 34, No. 4 (April, 2014), pp. 220-232.

Tong, T., Kim, N., & Park, T. (2015). Topical application of oleuropein induces anagen hair growth in telogen mouse skin. PloS one, Vol. 10, No. 6 (June, 2015), pp. 129-578.

Topuz, S., & Bayram, M. (2022). Oleuropein extraction from leaves of three olive varieties (*Olea europaea* L.): Antioxidant and antimicrobial properties of purified oleuropein and oleuropein extracts. Journal of Food Processing and Preservation, Vol. 46, No. 6 (June, 2022), pp. 15697-15728.

Torić, J., Karković Marković, A., Jakobušić Brala, C., & Barbarić, M. (2019). Anticancer effects of olive oil polyphenols and their combinations with anticancer drugs. Acta Pharmaceutica, Vol. 69, No. 4 (December, 2019), pp. 461-482.

Tsoumani, M., Georgoulis, A., Nikolaou, P. E., Kostopoulos, I. V., Dermintzoglou, T., Papatheodorou, I., Zoga, A., Efentakis, P., Konstantinou, M., Gikas, E., Kostomitsopoulos, N., Papapetropoulos, A., Lazou, A., Skaltsounis, A. L., Hausenloy, D. J., Tsitsilonis, O., Tseti, I., Lisa, F. D., Iliodromitis, E. K., & Andreadou, I. (2021). Acute administration of the olive constituent, oleuropein, combined with ischemic postconditioning increases myocardial protection by modulating oxidative defense. Free Radical Biology and Medicine, Vol. 166 (April, 2021), pp. 18-32.

Tuccinardi, D., Di Mauro, A., Lattanzi, G., Rossini, G., Monte, L., Beato, I., Spiezia, C., Bravo, M., Watanabe, M., Soare, A., Kyanvash, S., Armirotti, A., Bertozzi, S. M., Gastaldelli, A., Pedone, C., Khazrai, Y. M., Pozzilli, P., & Manfrini, S. (2022). An extra virgin olive oil-enriched chocolate spread positively modulates insulin-resistance markers compared with a palm oil-enriched one in healthy young adults: a double-blind, cross-over, randomised controlled trial. Diabetes Metab. Res. Rev., Vol. 38, No. 2 (February, 2022), pp. 1-10.

Xu, F., Li, Y., Zheng, M., Xi, X., Zhang, X., & Han, C. (2018). Structure Properties, Acquisition Protocols, and Biological Activities of Oleuropein Aglycone. Front. Chem., Vol. 6, No. 239 (August, 2018), pp. 1-10.

Vanni, G., Pellicciaro, M., Materazzo, M., Pedini, D., Portarena, I., Buonomo, C., Perretta, T., Rizza, S., Pistolese, C. A., & Buonomo, O. C. (2021). Advanced Stages and Increased Need for Adjuvant Treatments in Breast Cancer Patients: The Effect of the One-year COVID-19 Pandemic. Anticancer Res., Vol. 41, Vol. 5 (May, 2021), pp. 2689–2696.

Velasco, L., Fernández-Cuesta, Á., De la Rosa, R., Ruiz-Méndez, M. V., & León, L. (2014). Selection for some olive oil quality components through the analysis of fruit flesh. J. Am. Oil Chem. Soc., Vol. 91 (August, 2014), pp. 1731–1736.

Venturini, D., Sim˜ao, A.N.C., Urbano, M. R., & Dichi, I. (2015). Effects of extra virgin olive oil and fish oil on lipid profile and oxidative stress in patients with metabolic syndrome. Nutr. Burbank Los Angel, Cty. Calif, Vol. 31, No.6 (June, 2015), pp. 834–840.

Vezza, T., Algieri, F., Rodriguez-Nogales, A., Garrido-Mesa, J., Utrilla, M. P., Talhaoui, N., Gomez-Caravaca, A. M., Segura-Carretero, A., Rodriguez-Cabezas, M. E., Monteleone, G., & Gálvez, J. (2017). Immunomodulatory properties of *Olea europaea* leaf extract in intestinal inflammation. Molecular Nutrition & Food Research, Vol. 61, No. 10 (October, 2017), 1601066.

Vijakumaran, U., Goh, N.-Y., Razali, R. A., Abdullah, N. A. H., Yazid, M. D., & Sulaiman, N. (2023). Role of Olive Bioactive Compounds in Respiratory Diseases. Antioxidants, Vol. 12, No. 6 (May, 2023), pp. 1-24.

Vogel, P., Machado, I. K., Garavaglia, J., Zani, V. T., de Souza, D., & Bosco, S. M. D. (2015). Polyphenols benefits of olive leaf (*Olea europaea* L) to human health. Nutr Hosp., Vol. 31, No. n13 (October, 2014), pp. 1427-1433.

Wan, Y., Liang, Y. X., Zou, B., Fu, G. M., & Xie, M. Y. (2018). The possible mechanism of hydroxytyrosol on reducing uric acid levels. Journal of Functional Foods, Vol. 42 (March, 2018), pp. 319-326.

Wanitphakdeedecha, R., Ng, J. N. C., Junsuwan, N., Phaitoonwattanakij, S., Phothong, W., Eimpunth, S., & Manuskiatti, W. (2020). Efficacy of olive leaf extract–containing cream for facial rejuvenation: A pilot study. Journal Cosmetic Dermatology, Vol. 19, No. 7 (July, 2020), pp. 1662–1666.

Yubero-Serrano, E. M., Lopez-Moreno, J., Gomez-Delgado, F., & Lopez-Miranda, J. (2019). Extra virgin olive oil: More than a healthy fat. Eur. J. Clin. Nutr., Vol. 72, No. Suppl 1 (November, 2018), pp. 8–17.

Zhang, J. Y., Yang, Z., Fang, K., Shi, Z. L., Ren, D. H., & Sun, J. (2017). Oleuropein prevents the development of experimental autoimmune myocarditis in rats. International Immunopharmacology, Vol. 48 (May, 2017), pp. 187-195.

Zhang, W., Liu, X., & Li, Q. (2018). Protective Effects of Oleuropein Against Cerebral Ischemia/Reperfusion by Inhibiting Neuronal Apoptosis. Med Sci Monit, Vol. 24 (September, 2018), pp. 6587-6598.

Zhang, Y., Cai, P., Cheng, G., & Zhang, Y. (2022). A Brief Review of Phenolic Compounds Identified from Plants: Their Extraction, Analysis, and Biological Activity, Natural Product Communications, Vol. 17, No. 1 (January, 2022), 1934578X2110697.

Zhao, G., Yin, Z., & Dong, J. (2009). Antiviral efficacy against hepatitis B virus replication of oleuropein isolated from *Jasminum officinale* L. var. *grandiflorum*. Journal of Ethnopharmacology, Vol. 125, No. 2 (August, 2009), pp. 265-268.

Zhao, M., Yuan, S., Li, Z., Liu, C., & Zhang, R. (2024). Review of the Structural Characteristics and Biological Activities of Tricholoma Secondary Metabolites (2018–2023). Molecules, Vol. 29, No. 19 (October, 2024), pp. 1-16.

Zheng, S., Huang, K. & Tong, T. (2021). Efficacy and mechanisms of oleuropein in mitigating diabetes and diabetes complications. J. Agric. Food Chem., Vol. 69, No. 22 (June, 2021), pp. 6145–6155.

Zheng, S., Geng, R., Guo, J., Kang, S.-G., Huang, K., & Tong, T. (2024). Oleuropein Supplementation Ameliorates Long-Course Diabetic Nephropathy and Diabetic Cardiomyopathy Induced by Advanced Stage of Type 2 Diabetes in db/db Mice. Nutrients, Vol. 16, No. 6 (March, 2024), pp. 1-15.

Zighed, A., Derradji, L., & Hadef, Y. (2022). Determination of polyphenolic components by high performance liquid chromatography (HPLC) and evaluation of the antioxidant activity of leaves of *Olea europaea* L. var. *sylvestris* (Miller) Lehr. GSC Biol Pharm Sci., Vol 20, No. 1 (July, 2022), pp. 95–99.

Zorić, N., Kopjar, N., Kraljić, K., Oršolić, N., Tomić, S., & Kosalec, I. (2016). Olive leaf extract activity against *Candida albicans* and *C. dubliniensis*—The in vitro viability study. Acta Pharmaceutica, Vol. 66, No. 3 (Febrary, 2016), pp. 411–421.

CHAPTER 4

BETA GLUCAN AS A FUNCTIONAL COMPONENT: MOLECULAR STRUCTURE AND HEALTH EFFECTS

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INTRODUCTION

Various polysaccharides of natural origin have attracted attention due to their properties to regulate the functions of the immune system. These compounds are pharmacologically classified as Biological Response Modifiers (BRMs) due to their immunostimulating or stabilizing effects. The immunomodulatory properties of these polysaccharides make them potential biotherapeutics, especially in the prevention and supportive treatment of immune-related diseases. β-glucans are considered to be among the most effective of these compounds (Bohn and BeMiller, 1995).

β-glucans are natural polysaccharides composed of D-glucose monomers and these glucose units are linked together by β-glycosidic bonds (specifically β-(1→3), β-(1→4), and/or β-(1→6) bonds). They are found in yeast, fungi, some cereals (such as oats and barley), some bacteria and seaweeds (Du et al., 2019).

As an important dietary fiber, β-glucans are notable for their anti-cancer, anti-inflammatory, antioxidant, anti-hypertensive and anti-obesity effects as well as their strong immunomodulatory properties. They also possess antiviral, anti-bacterial and anti-fungal activities. They lower cholesterol and blood lipid levels, reduce insulin resistance and help stabilize body weight (Şirinyıldız and Bulut, 2022; Singla et al., 2024).

Glucans have a wide range of applications from health to food, cosmetics to pharmacology. Since β-glucan can increase viscosity thanks to its gelling structure in aqueous solutions, it is preferred as a thickener in sauces and desserts in the food industry. It is also preferred in low-calorie food production as a fat mimetic. In addition, due to their health benefits, they are subject to various applications in functional food production, cosmetic products, pharmaceutical preparations and other industrial fields (Du et al., 2019; Yang and Huang, 2021)

Classification and Structure of β-glucans

Glucans are divided into two main groups, α-glucans and β-glucans, according to the configuration of glycosidic bonds between monosaccharide units. α-glucans are generally amorphous, soluble in hot water and serve as building blocks for energy storage in biological systems. Examples of this group include starch found in plants and algae and glycogen found in fungal and animal cells (Edo et al., 2024). There are water-soluble and insoluble varieties of β-glucans. These properties enable them to take part in structural functions. For example, plant cellulose and β-(1→3)-D-glucans found in yeast and fungal cell walls are among the important compounds included in the β-glucan group (Xin et al., 2022; Edo et al., 2024).

β-glucans are classified into seven main groups according to their structural properties. This classification is based on the way glucose units bind and their branching structure:

1. Unbranched β-(1→3)-glucans: Glucans with a linear structure containing only β-(1→3) glycosidic bonds.

2. Less branched β-(1→3)-glucans: Structures whose main chain is composed of β-(1→3) bonds, showing a limited number of branches.

3. β-(1→6)-glucans: Glucans in which glucose units are largely linked by β-(1→6) bonds.

4. β-glucans contain D-glucose fragments linked by β-(1→3) and β-(1→4) bonds: Structures commonly found in cereals (e.g. oats, barley) that affect properties such as solubility and viscosity.

5. β-glucans are composed of D-glucose fragments containing β-(1→3), β-(1→4) and β-(1→6) bonds: They are more complex types of glucans and may exhibit different biological activities.

6. Phosphorylated β-(1→3)-D-glucans: Forms of glucans with phosphate groups in their structure and enhanced biological activity.

7. β-glucans composed predominantly of β-(1→6)-D-glucose units: Glucans with a distinct structural difference, synthesized especially by some microorganisms (Ruiz-Herrera and Ortiz-Castellanos, 2019).

The classification of β-glucans is based on the type of glycosidic bond between the glucose monomers that form their chain structure. Unbranched β-(1→3)-glucans represent the structurally simplest form; these glucans consist of long, linear D-glucose chains linked only by β-(1→3) bonds. Other types of β-glucans exhibit more complex structures. For example, less branched β-(1→3)-glucans contain a large proportion of β-(1→3) linkages in the main chain, while branching with β-(1→6) linkages at certain positions. These structural variations significantly affect the physicochemical properties of β-glucans such as water solubility, viscosity and gel-forming capacity (Edo et al., 2024).

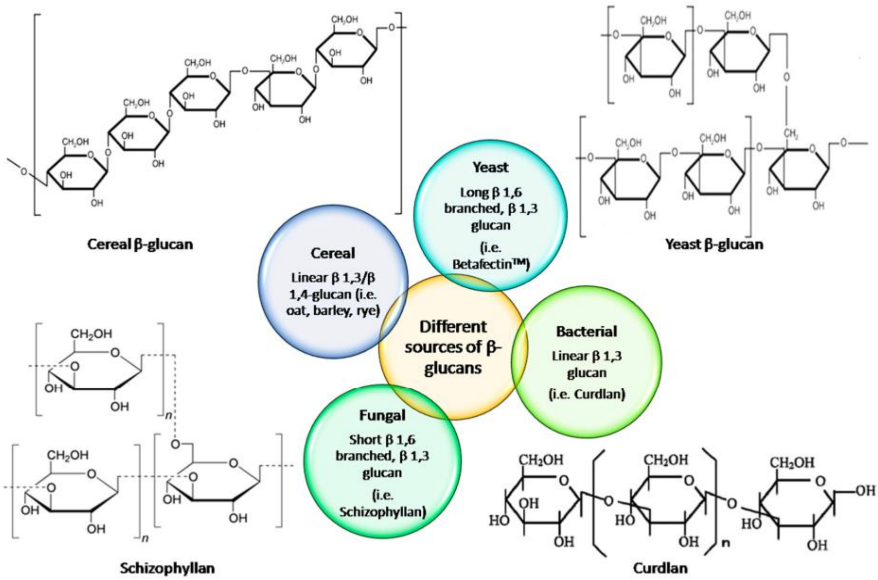

Figure 1. Structure and branching degree of β-glucan from different recourses (Du et al., 2019)

Non-cellulosic β-glucans generally have a β-(1→3) linked glucose backbone and varying proportions of β-(1→6) side chain substitutions. In some cases, such as bacterial β-glucan curdlan, no side chain substitution is observed. Among the β-glucans of fungal origin, schizophyllan from *Schizophyllum commune*, scleroglucan from *Sclerotium glucanicum*, lentinan from *Lentinus edodes*, epiglucan from *Epicoccum nigrum* and pestalotan from *Pestalotia* sp. are notable examples exhibiting regular β-(1→6) branching motifs on the β-(1→3) backbone (Figure 1). The frequency of branching of these structures varies from species to species and the detailed structural features of many fungal β-glucans are still not fully elucidated (Chen and Seviour, 2007; Schmid et al., 2001; McIntosh et al., 2005; Johnson et al., 1963; Kikumoto, 1971; Sasaki and Takasuka, 1976; Misaki et al., 1984; Demleitner et al., 1992).

The composition and structural properties of β-glucans can be assessed using various analytical techniques. Liquid chromatography/mass spectrometry (LC/MS) and high-performance liquid chromatography (HPLC) are among the most widely used methods. Less frequently, advanced techniques such as X-ray crystallography and atomic force microscopy are also used for structural analysis of β-glucans. Other analytical methods for β-glucan quantification include phenol-sulfuric acid carbohydrate assay, aniline blue staining method and enzyme-linked immunosorbent assay (ELISA). These methods provide researchers with important data for both qualitative and quantitative analysis of β-glucans (Chan et al., 2009).

When β-glucans are considered in terms of molecular size, it has been reported that the molecular weights of rye, barley, oat and wheat-derived β-glucans vary between 21-1100×10^3, 31-2700×10^3, 65-3100×10^3 and 209-487×10^3 g/mol, respectively (Du et al., 2019).

The biological activity of β-glucan varies according to different properties such as molecular weight, degree of branching, solubility and capacity to form intermolecular interactions. Accordingly, β-glucans have various physiological functions (Cui et al., 2023; Zhong et al., 2023; Synytsya and Novák, 2013).

Sources of β-glucan

β-glucan is found as a cell wall component in various natural sources including bacteria; yeasts such as Saccharomyces cerevisiae; fungi such as *Aspergillus* and *Agaricus* species; algae; edible mushroom species *Reishi* and *Ganoderma applanatum*, and cereal grains such as oats, barley, wheat and rye (Maheshwari et al., 2017). The cell wall of *Saccharomyces cerevisiae* consists of three layers: the inner layer is composed of insoluble β-glucans (30-35%), the middle layer is composed of soluble β-glucans (20-22%) and the outer layer is predominantly glycoproteins (30%) (Zhong et al., 2023). Among cereals, especially oats and barley contain higher levels of β-glucans compared to other species. Among the cereal grains, the highest β-glucan content is found in barley (2-11%) and oat (2-7.5%) grains, whereas in other cereals such as wheat and rye, this ratio is lower and can vary between 0.5-1% and 1.4-2.6%, respectively. It has been observed that the amount and quality of β-glucan in these cereals varies according to the cereal type, genotype, geographical region where it is grown, and extraction method (Ahmad et al., 2012a).

Purification

Various extraction and purification methods such as hot water extraction (Smiderle et al., 2006; Ahmad et al., 2009), solvent extraction (Bhatty, 1993), enzymatic extraction (Irakli et al., 2004; Ahmad et al., 2010) and alkaline extraction (Li et al., 2006) have been developed for the isolation of β-glucan (Ahmad et al., 2012b). In addition to the traditional extraction methods mentioned above, some innovative extraction techniques such as ultrasound-assisted extraction (UAE), response surface method (RSM), microwave-assisted extraction (MAE) and accelerated solvent extraction (ASE) have also been reported in the literature. In all the mentioned methods, parameters such as pH, temperature, extraction time, centrifugal force, preferred method, selected species will create differences in the amount and quality of the product to be obtained (Maheshwari et al., 2017).

Health Effects of β-glucans

The use of natural products for therapeutic purposes dates back to the earliest periods of human history. Throughout history, people have used substances obtained from nature in the treatment of various diseases. The oldest known written sources on herbal treatment practices are found in clay tablets of the Sumerian civilization dating back to 4000 BC. Similarly, the earliest records of the use of medicinal mushrooms are found in Indian documents dating back about 5000 years. Ancient medical practices, such as traditional Chinese medicine and the Ayurvedic system, represent important approaches to healing that have been shaped by centuries of observation and experience, systematically evaluating the effects of natural resources on health (Vetvicka etal., 2021).

Found in the cell walls of yeast, fungi and many cereals such as oats and barley, β-glucan has long been favored both as a food product and for its health effects. Studies have reported immune-enhancing, anti-inflammatory, antimicrobial, anti-diabetic, cholesterol-lowering, anti-allergic, anti-cancer and antioxidant effects of β-glucans (Kidd, 2000; Xin et al., 2022; Şirinyıldız and Bulut, 2022).

The first line of defense in the body's immune system is innate immunity. In the early stages, this immune system recognizes, ingests and destroys pathogens that enter the body, primarily using phagocytic cells such as macrophages and neutrophils. It also contributes to the activation of the adaptive (acquired) immune system through the secretion of cytokines and chemokines. β-glucan has been shown to modulate the activity of a variety of immune cells, including macrophages, natural killer cells (NK cells) and neutrophils, thereby producing numerous immune effects. For these reasons, β-glucan is considered a natural immunomodulator and is widely used in tumor immunotherapy (Zhong et al., 2023).

It has been shown that immune responses to β-glucans in vertebrates are mediated mainly by receptors on the cell surface. Although the process of opsonization contributes to the recognition of particulate β-glucans, no plasma-derived molecule that specifically recognizes these polysaccharides has yet been identified. β-glucan receptor activity has been found in both immune and non-immune cells such as monocytes, macrophages, neutrophils, Langerhans cells, eosinophils, natural killer (NK) cells, endothelial cells, alveolar epithelial cells and fibroblasts (Figure 2) (Brown and Gordon, 2005). In this context, β-glucans can activate immune pathways by interacting with specific receptors or proteins such as Dectin-1, Toll-like receptors (TLR), complement receptor 3 (CR3), scavenger receptors (SR) and lactosylceramide (LacCer) (Figure 3) (Noorbakhsh Varnosfaderani et al., 2024). This interaction triggers cytokine secretion, which in turn activates tumor-responsive immune cells such as macrophages, neutrophils and monocytes. These cells increase phagocytosis capacity and stimulate the production of pro-inflammatory cytokines, leading to a strengthening of the immune response, which may explain the mechanism of anticancer action (Noorbakhsh Varnosfaderani et al., 2024; Setyawan et al., 2024) However, only Dectin-1 has been clearly demonstrated to be directly involved in the generation of cellular responses specific to β-glucans (Brown and Gordon, 2005).

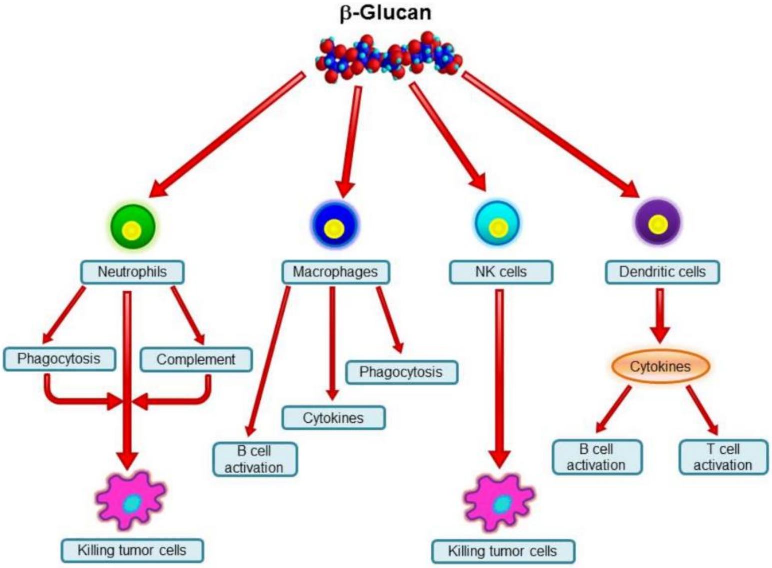

Figure 2. Major effects of beta-glucan on immune cells (Vetvicka et al., 2021).

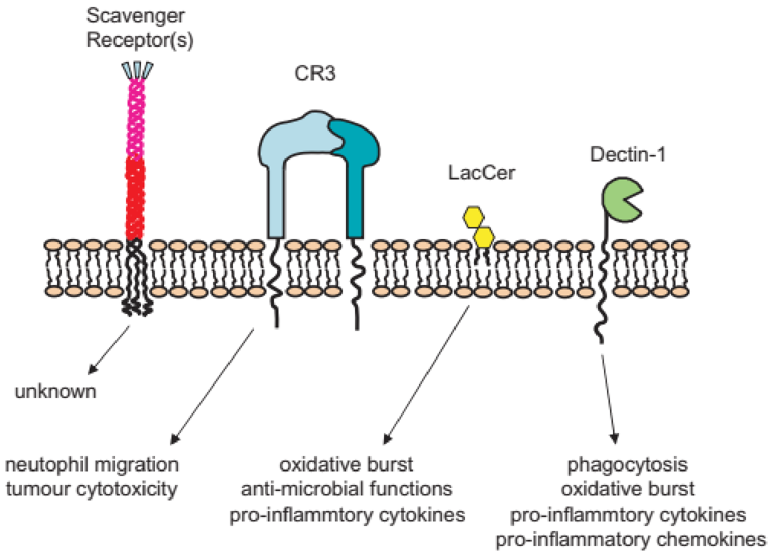

Figure 3 Receptors with which β-glucans interact (Brown and Gordon, 2005).

One of the important properties of β-glucan that allows it to be included as a functional ingredient in various food products is its positive effects on the gastrointestinal system. According to studies, β-glucan may have protective effects against the development of colorectal cancer, increase the feeling of satiety by suppressing appetite and support overall intestinal health. It also facilitates the excretion of toxic substances from the body by increasing stool volume and plays a preventive role against constipation. Thus, it also provides protection against metabolic diseases (Ahmad et al., 2012b).

Oat β-glucan shows positive effects on gastrointestinal health because it cannot be digested by enzymes such as salivary amylase. Thanks to this feature, it prevents the proliferation of pathogenic bacteria and supports the proliferation of beneficial microorganisms such as lactic acid bacteria and *Bifidobacteria*, thus supporting the formation of a healthy microbiota. In the large intestine, especially in the cecum, β-glucan is fermented by commensal microorganisms to produce short-chain fatty acids (SCFAs). SCFAs play an important role in maintaining intestinal health by affecting many mechanisms such as regulation of gene expression, epithelial morphology, mucus production, mucosal immune responses. They also exert protective effects against the overgrowth of opportunistic pathogens. Studies on animal models show that oat and barley β-glucans promote colonic mucosa development, reduce the microorganism load on harmful bacteria (e.g. *Escherichia coli*) by increasing SCFA production. These findings suggest that β-glucan functions as a prebiotic substance (Hu et al., 2015).

The hypoglycemic effect of carbohydrate-containing foods is usually assessed by the glycemic index (GI). The GI is calculated by comparing the area of the blood glucose response curve after consumption of the tested food with that of a reference food (e.g. glucose solution or white bread). Clinical studies have shown that diets enriched with oat and barley β-glucans resulted in significant reductions in both glycemic index (GI) and glycemic insulin index (GII). These effects were observed in different groups of individuals, including individuals with type 2 diabetes, non-diabetic individuals, and moderately hypercholesterolemic or overweight individuals (Lazaridou et al., 2007). At the metabolic level, it offers important effects such as lowering the glycemic index, stabilizing postprandial glucose levels and reducing serum cholesterol levels. These effects support the protective potential of β-glucan on cardiovascular health and in particular contribute to reducing the risk of coronary heart disease (Ahmad et al., 2012b; Lante et al., 2023) (Figure 4). The U.S. Food and Drug Administration (FDA) approved the use of health claims on product labels in 1997 and 2005 that consumption of whole grain barley, oats and products containing them may reduce the risk of coronary heart disease (Hu et al., 2015).

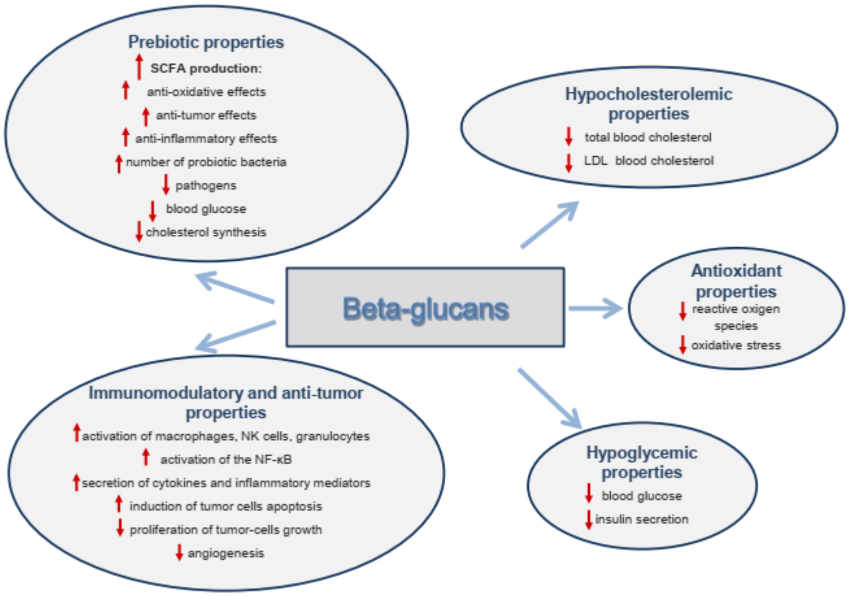

Figure 4. Health effects of β-glucans (Ciecierska et al., 2019)

Ikekawa et al. (1969) published the first scientific findings that extracts from fruiting bodies of fungi belonging to the family Polyporaceae (Aphyllophoromycetideae) and some other families showed host-mediated antitumor activity on tumors transplanted into animal models (Ikekawa et al., 1982; 1992; Ikekawa, 2001). This study is among the pioneering researches that revealed the potential biological effects of medicinal mushrooms for cancer treatment.

Following these developments, the first three important antitumor agents derived from medicinal mushrooms were developed. All of these compounds are polysaccharides, specifically classified as β-glucans. These include: Krestin, from the cultured mycelial biomass of *Trametes versicolor* (Turkey Tail); Lentinan, from the fruiting body of *Lentinula edodes* (shiitake); and Schizophyll, from the liquid culture medium of *Schizophyllum commune* (Split Gill) (Mizuno, 1996; 1999; Wasser and Weis, 1999; Ikekawa, 2001; Wasser, 2002). Subsequently, the pharmacological effects of medicinal mushrooms in in vivo and in vitro model systems have been studied in detail; as a result of these studies, many new antitumor and immunomodulatory polysaccharides have been identified and put into practical use (Wasser, 2002). Today, lentinan is mainly used in the treatment of stomach cancer in medical applications. However, it has also been evaluated in experimental studies on various cancer types such as sarcoma, colon, lung, liver, bladder and pancreatic cancer. In gastric cancer patients, concurrent administration of lentinan with chemotherapy agents significantly increased anticancer efficacy (Vetvicka et al., 2021).

β-glucans as Functional Foods and Their Use in the Food Industry

Functional foods are products containing specific nutrients or bioactive components and play important roles in supporting basic nutritional needs, regulating physiological and metabolic functions, reducing disease risk and protecting general health. Worldwide, interest in functional foods is increasing day by day in order to prolong life, improve quality of life and prevent diseases. In this respect, β-glucan is frequently preferred in the food sector both as an important dietary fiber that has been found to be highly beneficial for health and due to its physicochemical properties (Şengül and Ufuk, 2022).

β-glucan also has thickening, stabilizing, emulsifying and gel-forming properties. These properties increase the usability of β-glucan in different food products such as soups, sauces and beverages. Barley-derived β-glucan, in particular, improves sensory properties through its ability to impart a soft mouthfeel to beverage products, while also acting as a good source of soluble dietary fiber. Thus, β-glucan is considered as an alternative to traditional thickening agents such as gum arabic, alginates, pectin, xanthan gum and carboxymethyl cellulose. It is also used as a fat substitute in reduced-calorie dietary products such as low-fat cheese, pickled fresh cheeses and low-fat sausages. In addition, since beta glucan is known to lower the glycemic index, it is used as an additive to breakfast cereals, breads and pastas (Ahmad et al., 2012a, 2012b).

CONCLUSION

β-glucans, as polysaccharides of natural origin, are of great importance for their various health benefits and immunomodulatory properties. With their immunomodulatory, anti-cancer, anti-inflammatory, antioxidant and antimicrobial properties, these compounds find a wide range of applications as functional ingredients in pharmacology and food industry.

In particular, the structure and biological activities of β-(1→3)-glucans make them potential therapeutic strategies for the treatment of various diseases. Furthermore, β-glucans may be useful in the management of metabolic diseases such as diabetes, obesity and cardiovascular diseases.

In the food industry, β-glucans obtained from cereals such as oats and barley are widely used in food products with their thickening, emulsifying and gel-forming properties. In addition, the health benefits of β-glucans have led to an increased demand for functional foods and further deepened research in this field.

Research is ongoing to fully understand the biological activities of β-glucans. Differences in their structural properties and their relationship with biological effects should be investigated in more detail so that the health effects of β-glucans can be used more effectively. Overall, it can be safely said that β-glucans have a wide potential in the health and food industries.

Authors' Contribution

The authors contributed equally to the article.

Declaration of Conflict of Interest

There is no conflict of interest between the authors.

Declaration of Research and Publication Ethics

Research and publication ethics were complied with in the study.

REFERENCES

Ahmad, A., Anjum, F. M., Zahoor, T., Nawaz, H., & Ahmed, Z. (2010). Extraction and characterization of β-d-glucan from oat for industrial utilization. International journal of biological macromolecules, 46(3), 304-309.

Ahmad, A., Anjum, F. M., Zahoor, T., Nawaz, H., & Dilshad, S. M. R. (2012b). Beta glucan: a valuable functional ingredient in foods. Critical reviews in food science and nutrition, 52(3), 201-212.

Ahmad, A., Anjum, F. M., Zahoor, T., Nawaz, H., & Din, A. (2009). Physicochemical and functional properties of barley β-glucan as affected by different extraction procedures. International journal of food science & technology, 44(1), 181-187.

Ahmad, A., Munir, B., Abrar, M., Bashir, S., Adnan, M., & Tabassum, T. (2012a). Perspective of β-glucan as functional ingredient for food industry. J. Nutr. Food Sci, 2(2), 133-139.

Bhatty, R. S. (1993). β-glucan content and viscosities of barleys and their roller milled flour and bran products. Cereal Chem. 69: 469–471

Bohn, J. A., & BeMiller, J. N. (1995). (1→ 3)-β-d-Glucans as biological response modifiers: a review of structure-functional activity relationships. Carbohydrate polymers, 28(1), 3-14.

Brown, G. D., & Gordon, S. (2005). Immune recognition of fungal β-glucans. Cellular microbiology, 7(4), 471-479.

Chan, G. C. F., Chan, W. K., & Sze, D. M. Y. (2009). The effects of β-glucan on human immune and cancer cells. Journal of hematology & oncology, 2, 1-11.

Chen, J., & Seviour, R. (2007). Medicinal importance of fungal β-(1→ 3),(1→ 6)-glucans. Mycological research, 111(6), 635-652.

Ciecierska, A., Drywien, M., Hamulka, J., & Sadkowski, T. (2019). Nutraceutical functions of beta-glucans in human nutrition. Roczniki Państwowego Zakładu Higieny, 70(4).

Cui, Y., Han, X., Huang, X., Xie, W., Zhang, X., Zhang, Z., ... & Li, S. (2023). Effects of different sources of β-glucan on pasting, gelation, and digestive properties of pea starch. Food Hydrocolloids, 135, 108172.

Demleitner, S., Kraus, J., & Franz, G. (1992). Synthesis and antitumour activity of sulfoalkyl derivatives of curdlan and lichenan. Carbohydrate research, 226(2), 247-252.

Du, B., Meenu, M., Liu, H., & Xu, B. (2019). A concise review on the molecular structure and function relationship of β-glucan. International journal of molecular sciences, 20(16), 4032.

Edo, G. I., Ndudi, W., Makia, R. S., Ainyanbhor, I. E., Yousif, E., Gaaz, T. S., ... & Umar, H. (2024). Beta-glucan: An overview in biological activities, derivatives, properties, modifications and current advancements in food, health and industrial applications. Process Biochemistry. 147, 347-370.

Hu, X., Zhao, J., Zhao, Q., & Zheng, J. (2015). Structure and characteristic of β-glucan in cereal: A review. Journal of food processing and preservation, 39(6), 3145-3153.

Ikekawa T (2001) Beneficial effects of edible and medicinal mushrooms in health care. Int J Med Mushrooms 3:291–298

Ikekawa T, Ikeda Y, Yoshioka Y, Nakanishi K, Yokoyama E, Yamazaki E (1982) Antitumor polysaccharides of *Flammulina velutipes* 2. The structure of EA-3 and further purification of EA-5. J Pharmacobiol Dyn 5:576–581

Ikekawa T, Saitoh H, Feng W, Zhang H, Li L, Matsuzawa T (1992) Antitumor activity of extracts and polysaccharides. Chem Pharm Bull (Tokyo) 40:1954–1957

Ikekawa T, Uehara N, Maeda Y, Nakanishi M, Fukuoka F (1969) Antitumor activity of aqueous extracts of edible mushrooms. Cancer Res 29:734–735

Irakli, M., Biliaderis, C. G., Izydorczyk, M. S., & Papadoyannis, I. N. (2004). Isolation, structural features and rheological properties of water-extractable β-glucans from different Greek barley cultivars. Journal of the Science of Food and Agriculture, 84(10), 1170-1178.

Johnson, J., Kirkwood, S., Misaki, A., Nelson, T. E., Scaletti, J. V., & Smith, F. (1963). Structure of a new glucan. Chem. Ind, 41, 820-822.

Kidd, P. M. (2000). The use of mushroom glucans and proteoglycans in cancer treatment. Alternative medicine review, 5(1), 4-27.

Kikumoto, S. (1971). Polysaccharide produced by Schizophyllum commune. Pt. II. Chemical structure of an extracellular polysaccharide. Nippon Nougeikagaku Kaishi, 45, 162-168.

Lante, A., Canazza, E., & Tessari, P. (2023). Beta-glucans of cereals: Functional and technological properties. Nutrients, 15(9), 2124.

Lazaridou, A., Biliaderis, C. G., & Izydorczyk, M. S. (2007). Cereal beta-glucans: structures, physical properties, and physiological functions. Functional food carbohydrates, 1-72.

Li, W., Cui, S. W., & Kakuda, Y. (2006). Extraction, fractionation, structural and physical characterization of wheat β-D-glucans. Carbohydrate Polymers, 63(3), 408-416.

Maheshwari, G., Sowrirajan, S., & Joseph, B. (2017). Extraction and isolation of β-glucan from grain sources—A review. Journal of food science, 82(7), 1535-1545.

McIntosh, M., Stone, B. A., & Stanisich, V. A. (2005). Curdlan and other bacterial (1→ 3)-β-D-glucans. Applied microbiology and biotechnology, 68, 163-173.

Misaki, A., Kawaguchi, K., Miyaji, H., Nagae, H., Hokkoku, S., Kakuta, M., & Sasaki, T. (1984). Structure of pestalotan, a highly branched (1→ 3)-β-D-glucan elaborated by *Pestalotia* sp. 815, and the enhancement of its antitumor activity by polyol modification of the side chains. Carbohydrate research, 129, 209-227.

Mizuno T, Yeohlui P, Kinoshita T, Zhuang C, Ito H, Mayuzumi Y (1996) Antitumor activity and chemical modification of polysaccharides from Niohshimeji mushroom, *Tricholoma giganteum*. Biosci Biotechnol Biochem 60:30–33

Mizuno T, Zhuang C, Abe K, Okamoto H, Kiho T, Ukai S, Leclerc S, Meijer L (1999) Antitumor and hypoglycemic activities of polysaccharides from the sclerotia and mycelia of *Inonotus obliquus* (Pers.: Fr.) Pil. (Aphyllophoromycetideae). Int J Med Mushrooms 1:301–316

Noorbakhsh Varnosfaderani, S. M., Ebrahimzadeh, F., Akbari Oryani, M., Khalili, S., Almasi, F., Mosaddeghi Heris, R., ... & Alagheband Bahrami, A. (2024). Potential promising anticancer applications of β-glucans: a review. Bioscience Reports, *44*(1).

Ruiz-Herrera, J., & Ortiz-Castellanos, L. (2019). Cell wall glucans of fungi. A review. The Cell Surface, *5*, 100022.

Sasaki, T., & Takasuka, N. (1976). Further study of the structure of lentinan, an anti-tumor polysaccharide from *Lentinus edodes*. Carbohydrate Research, 47(1), 99-104.

Schmid, F., Stone, B. A., McDougall, B. M., Bacic, A., Martin, K. L., Brownlee, R. T., ... & Seviour, R. J. (2001). Structure of epiglucan, a highly side-chain/branched (1→ 3; 1→ 6)-β-glucan from the micro fungus *Epicoccum nigrum* Ehrenb. ex Schlecht. Carbohydrate Research, 331(2), 163-171.

Şengül, M., & Ufuk, S. (2022). Therapeutic and functional properties of beta-glucan, and its effects on health. Eurasian Journal of Food Science and Technology, 6(1), 29-41.

Setyawan, R. H., Ardiansyah, A., Solihat, N. N., Elfirta, R. R., Saskiawan, I., Ningrum, R. S., ... & Ermawar, R. A. (2024). Chemical structure characterization of edible mushroom-extracted beta-glucan and its bioactivity. Bioactive Carbohydrates and Dietary Fibre, 31, 100411.

Singla, A., Gupta, O. P., Sagwal, V., Kumar, A., Patwa, N., Mohan, N., ... & Singh, G. (2024). Beta-glucan as a soluble dietary fiber source: Origins, biosynthesis, extraction, purification, structural characteristics, bioavailability, biofunctional attributes, industrial utilization, and global trade. Nutrients, 16(6), 900.

Şirinyıldız, F., & Bulut, A. M. (2022). Effects of beta glucans on immunity: Current approaches. Izmir Katip Çelebi University Faculty of Health Sciences Journal, 7(1), 173-178.

Smiderle, F. R., Carbonero, E. R., Mellinger, C. G., Sassaki, G. L., Gorin, P. A., & Iacomini, M. (2006). Structural characterization of a polysaccharide and a β-glucan isolated from the edible mushroom *Flammulina velutipes*. Phytochemistry, 67(19), 2189-2196.

Synytsya, A., & Novák, M. (2013). Structural diversity of fungal glucans. Carbohydrate polymers, 92(1), 792-809.

Vetvicka, V., Teplyakova, T. V., Shintyapina, A. B., & Korolenko, T. A. (2021). Effects of medicinal fungi-derived β-glucan on tumor progression. Journal of Fungi, 7(4), 250.

Wasser SP, Weis AL (1999) Medicinal properties of substances occurring in Higher Basidiomycetes mushrooms: current perspectives. Int J Med Mushrooms 1:31–62

Wasser, S. J. A. M. B. (2002). Medicinal mushrooms as a source of antitumor and immunomodulating polysaccharides. Applied microbiology and biotechnology, 60, 258-274.

Xin, Y., Ji, H., Cho, E., Roh, K. B., You, J., Park, D., & Jung, E. (2022). Immune-enhancing effect of water-soluble beta-glucan derived from enzymatic hydrolysis of yeast glucan. Biochemistry and Biophysics Reports, 30, 101256.

Yang, W., & Huang, G. (2021). Extraction methods and activities of natural glucans. Trends in Food Science & Technology, 112, 50-57.

Zhong, X., Wang, G., Li, F., Fang, S., Zhou, S., Ishiwata, A., ... & Ding, F. (2023). Immunomodulatory effect and biological significance of β-glucans. Pharmaceutics, 15(6), 1615.

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