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Chemical components, antidiabetic and anticancer effects of *Origanum* species

Origanum türlerinin kimyasal bileşenleri, antidiyabetik ve antikanser etkileri

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ABSTRACT

Cancer and diabetes are two of the most common chronic diseases in people worldwide. Developing countries in particular, still rely on herbs as supportive or complementary therapies in the treatment of these diseases. The aim of this study is to review the phytochemical content and studies on the antidiabetic and anticancer effects of *Origanum* genus, which is safely used as spice and tea and is one of the important genera for Türkiye, and to reveal the importance of this species in terms of health. For this purpose, important databases such as ScienceDirect, Springer, Web of Science, Wiley Online Library, Taylor & Francis, Google Scholar were searched. As a result of these researches, it was seen that intensive researches were carried out especially on the essential oils of *Origanum* species and when the essential oil was evaluated phytochemically, it was seen that it contains especially carvacrol and thymol compounds as the main components. In addition, it was revealed that both the essential oil and extracts of this species have significant antidiabetic and anticancer effects when used both directly and in nanoparticles. *Origanum* species, which people are quite familiar with due to its safe use as a spice and tea by the public for many years, has shown that it can be promisingly effective on human health, including diabetes and cancer, with recent studies on it.

Keywords: *Origanum* species, phytochemicals, antidiabetic activity, anticancer activity

ÖZET

Kanser ve diyabet, dünya genelinde insanlarda en sık görülen kronik hastalıklardan ikisidir. Özellikle gelişmekte olan ülkeler, bu hastalıkların tedavisinde destekleyici veya tamamlayıcı tedavi olarak bitkilere güvenmeye devam etmektedir. Bu çalışmanın amacı, baharat ve çay olarak güvenle kullanılan ve Türkiye için önemli cinslerden biri olan *Origanum* cinsinin fitokimyasal içeriği ile antidiyabetik ve antikanser etkileri üzerine yapılan çalışmaları derlemek ve bu türün sağlık açısından önemini ortaya koymaktır. Bu amaçla ScienceDirect, Springer, Wiley Online Library, Web of Science, Taylor & Francis, Google Scholar gibi önemli veri tabanları taranmıştır. Bu araştırmalar sonucunda özellikle *Origanum* türlerinin uçucu yağları üzerinde yoğun araştırmalar yapıldığı görülmüş ve uçucu yağ fitokimyasal olarak değerlendirildiğinde ana bileşen olarak özellikle karvakrol ve timol bileşiklerini içerdiği görülmüştür. Ayrıca bu türün hem uçucu yağının hem de ekstraktlarının, hem doğrudan hem de nanopartiküller içinde kullanıldığında önemli antidiyabetik ve antikanser etkilere sahip olduğu ortaya konmuştur. Uzun yıllardır halk tarafından baharat ve çay olarak güvenli bir şekilde kullanılması nedeniyle insanların oldukça aşina olduğu *Origanum* türleri üzerinde yapılan son çalışmalar, bu türlerin diyabet ve kanser de dahil olmak üzere insan sağlığı üzerinde umut verici bir şekilde etkili olabileceğini göstermiştir.

Anahtar Kelimeler: *Origanum* türleri, fitokimyasallar, antidiyabetik aktivite, antikanser aktivite

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Introduction

The first interest of man in plants began by the need for food, shelter and protection, but later on, attention in this regard turned to seeking remedies for injuries and diseases.

Lamiaceae is one of the families containing the most important plant species used for medicinal purposes from ancient times to the present day. This family is the sixth largest Angiosperm with more than 245 genera and 7886 species and is spread all over the world. Many species of this family are very important in economic and medical terms (Selvi et al., 2022).

One of the most economically important of the Lamiaceae family is the genus *Origanum*. This plant can be annual, perennial and shrubby. It is quite widespread worldwide. It is used as a flavoring, ornamental and spice (Zhou et al., 2021). *Origanum* species has been described by a wide range of chemical and morphological and diversity (Padulosi et al., 1997).

Each species in the genus *Origanum* have an erect, medium-thick stem and spotted glands, ±ovate leaves, are annual or perennial semi-bushy. Flowers on vertical laster (semi) sessile. Verticillaster in dense spikes with distinct, colored bracts. Slightly paniculate and inflorescences, Calyxes straight and very variable: Regularly 5-toothed, 2 or 1-lipped for 9/10 to 1/5; tubular, campanulate or flat; throats may or may not be hairy. Corollas variable: 2-lipped for 2/5 to 1/7, may or may not be humped (vesicular), sometimes flattened; straight tubular or slightly curved. Stamens equal or unequal in length; ascending, straight or separated, widely ridged (Ietswaart et al., 1980).

The current survey of the genus *Origanum* has been identified 10 sections so far: Prolaticorolla Amaracus, Campanulaticalyx, Brevifilamentum, Longitubus, Chilocalyx, Majorana, Elongatispica, Origanum and Anatolicon. There are 38 known species, one by 6 subspecies and the other with 3 species. Also, 17 taxa of hybrid origin have been identified (Ietswaart et al., 1980). Most of this genus is very locally distributed around the Mediterranean (Padulosi et al., 1997).

Metabolites (primary and secondary) formed by plants have a wide range of functions. Secondary metabolites have been used for beneficial roles in humans. At the same time, essential oils and their components are also used for potential multipurpose functions (Chishti et al., 2013).

Volatile oils are abundant in plants belonging to the genus *Origanum* (Zhou et al., 2021). *Origanum* essential oils consist of a number of main components that play a role in the various plant scents (Padulosi et al., 1997). Terpenoids such as carvacrol, thymol, carbamen and terpirenol are the main components of the essential oil of this genus. 92 compounds such as monoterpenes, sesquiterpenoids and other derivatives are the compounds found in these essential oils to date. The non-volatile components of genus *Origanum* such as flavonoids, triterpenes and organic acids have rarely been studied (Zhou et al., 2021). The essential oils of members of the *Origanum* genus vary in both the total quantity and the qualitative composition produced by the plants. Even a single *Origanum* species, such as *O. vulgare*, which is quite common and widely used, contains a wide chemical diversity (Padulosi et al., 1997). Different parts of plants and roots of plants change the composition and content of essential oils (Zhou et al., 2021). The geographical distribution or the time of collection of the plant determines the qualitative and quantitative variation of essential oils in species (Padulosi et al., 1997).

1. Traditional uses of the genus *Origanum*

Medicinal and aromatic plants are important for biological processes because some populations can achieve their primary health care from these plants (Chishti et al., 2013). *Origanum* species have a curative value in hypoglycemic treatments and have been used for a long time as local medicines in traditional medicine and spices and in purification rituals (Kintzios et al., 2002). Antispasmodic, antitumoral and analgesic are the reported activities of *Origanu*m spp., and its activities also include antifungal, antimicrobial, insecticidal and antioxidant activities. *Origanum* species are used in Turkish folk medicine for expectorant, antiparasitic, antihemontic and gastrointestinal complaints. The Genus *Origanum* is beneficial in the healing process of stomach ulcers. Some of the uses of *Origanum* spp. are as a carminative, sudorific, stimulant and tonic. It is also used as a folk remedy against colic, cough, toothache and irregular menstrual cycles. *Origanum* spp. is also a very effective disinfectant. It is used as a spice in all cuisines of the world to add flavor to foods. It is used in long-term treatments to prevent diabetes complications. It has an anti-inflammatory effect and its potential is promising (Chishti et al., 2013)

Iranian Medicine uses *O. vulgare* ssp. *viride* (Boiss.) as a stomachic, antitussive, antineuralgic, expectorant and diuretic,. *O. dubium* Boiss. is widespread in Southern Türkiye, Greece, and Cyprus. It is used externally as an antirheumatic by the public in Cyprus. *Origanum hypericifolium* O. Schwarz and P.H. Davis is an species endemic to Türkiye and is used as a medicinal herbal tea in Türkiye for stomach complaints, colds and weakness.

Origanum sipyleum L. has traditional use for the treatment of gastrointestinal disorders and cough. Origani vulgaris herba has been used as an expectorant and spasmolytic agent in respiratory diseases, gastrointestinal diseases (such as bile expectorant, digestive, spasmolytic), oral antiseptic, diuretic and antiseptic, and in dermatological disorders.

2. Phytochemical constituents of the genus *Origanum*

Identification of *O. compactum* volatile components was performed using GC-MS analysis. The essential oil of *O. compactum* is mainly represented by oxygenated monoterpenes with 80.7%, while monoterpene hydrocarbons with 8.24%, oxygenated sesquiterpenes with 5.34% and sesquiterpene hydrocarbons with 3.37% occur in the lowest percentage. The major components identified were 54.6% thymol, 23.18% carvacrol and 7.12% *p*-cymene (Assaggaf et al., 2023).

LC-MS/MS results showed the presence of 12 polyphenolic compounds in *O. majorana* and 6 in *O. vulgare*. *O. majorana* contains caffeic acid, carnosic acid, cinnamic acid, chlorogenic acid, eugenol, ferulic acid, gallic acid, p-coumaric acid, pyrogallol, resorcinol, rosmarinic acid and syringic acid. Chicoric acid, chlorogenic acid, ferulic acid, gentic acid, rosmarinic acid and salvianolic acid B were found in *O. vulgare* (Perez Gutierrez et al., 2022).

A study indicated that the main component of *Origanum onites* L. essential oil was carvacrol (CV, phenolic monoterpene) with 72% and the other components were 7.6% thymol (phenolic monoterpene), 7.3% *p*-cymene (monocyclic monoterpene), 3.8% linalool (acyclic monoterpene), 2.0% *β*-bisabolene (sesquiterpene), 1.8% terpinen-4-ol (monocyclic monoterpene), 1.1% borneol (bicyclic monoterpene), 0.7% *β*-caryophyllene (sesquiterpene), 0.7% γ-terpinene (monocyclic monoterpene), 0.6% α-terpinene (monocyclic monoterpene) and 0.5% α-terpineol (monocyclic monoterpene) (Tomsuk et al., 2024).

Sökmen et al. evaluated the essential oil obtained by hydrodistillation from the leaves of the *Origanum minutiflorum* in terms of yield and chemical components (by GC-MS and GC-FID analyses); and revealed that the yield was 3.1% (v/w), the volatile oil contained 64 compounds, carvacrol was the predominant compound with a rate of 64.29%, followed by *p*-cymene with a rate of 9.56% (Sökmen et al., 2020).

Yusuf et al. analyzed the aqueous extract of *O. vulgare* (OV) using gas chromatography-mass spectrometry (GC-MS) and revealed the presence of 13 bioactive compounds. The main compounds among these compounds were determined to be hexadecanoic acid, methyl ester with 24.71%, 9-octadecenoic acid (Z)-, methyl ester with 22.52%, methyl stearate with 15.40% and 9-octadecenoic acid (Z)-methyl ester with 11.56% (Yusuf et al., 2023).

Erenler et al. identified the compounds of *O. vulgare* essential oil (OVEO) were by GC-MS analysis, and OVEO was found to contain carvacrol (90.4%) as the major compound (Erenler et al., 2021).

3. Biological activity

3.1. Antidiabetic activity

Chronic Diabetes occurs when the pancreas does not produce enough insulin or when the body cannot use the insulin it produces effectively. The function of the insulin hormone is to regulate blood sugar. High blood sugar or increased blood sugar is hyperglycemia and is a prominent and common effect of uncontrolled diabetes. Over time, diabetes causes serious damage to many systems in the body, primarily nerve cells and blood vessels (WHO, 2023). Increased glucose concentrations in venous plasma or increased A1C in the blood are indicators of the presence of diabetes. Diabetes is typically divided into several clinical categories, but these are tested repeatedly based on metabolomics, genetics, and other criteria and pathophysiology. Diabetes is generally classified as follows: 1. Type 1 diabetes; 2. Type 2 diabetes; 3. Gestational diabetes mellitus; 4. There are also specific types of diabetes due to other causes, such as monogenic diabetes syndromes, exocrine pancreas diseases, and drug or chemical-induced diabetes (ElSayed et al., 2024).

Insulin injection and hypoglycemic agents are basic and effective drugs for the treatment of diabetes mellitus, but they have some side effects and do not affect diabetes complications in the long term. Effective compounds by fewer side effects are absolutely necessary for the treatment of diabetes. Medicinal plants have long been used as alternative or complementary treatments for these and other diseases. Herbal medicines are widely prescribed to patients all over the world due to their availability, low cost, low side effects, and also their effectiveness. (Bahmani et al., 2014). Effects on glucose uptake and glucose transporters, inhibition of α-glucosidase and α-amylase, inhibition of protein tyrosine phosphatase 1B activity, enhancement of insulin secretion and pancreatic β-cell proliferation and antioxidant activity are possible mechanisms of action of natural products in diabetes (Governa et al., 2018).

In a study, the inhibitory effects of *Origanum compactum* and *Origanum elongatum* extracts on α-glucosidase and α-amylase activity were evaluated under controlled

conditions. As a result of the evaluation, they showed significant dose-dependent inhibition. According to the results, aqueous extracts showed significant inhibitory effects against both enzymes, even outperforming the reference inhibitor acarbose. *O. compactum* and *O. elongatum* extracts exhibited effective inhibitory activity against α-amylase with an EC_{50} value of 128.13 and 162.81 µg/mL, respectively. As the concentration of acarbose used as standard, a gradual increase in inhibitory activity was observed. The EC_{50} values of *O. compactum* and *O. elongatum* extracts for inhibition of α-glucosidase secretion were found to be 14.28 and 14.70 µg/mL, respectively, which were equivalent and comparable to standard acarbose (EC_{50} value: 17.27 µg/mL). Moreover, in healthy rats, *ex vivo* oral glucose tolerance test (OGTT) was carried out and the capacity of the extract to reduce elevated blood glucose levels after high glucose load was evaluated. Rats receiving *Origanum compactum* and *Origanum longatum* extracts and oral antidiabetic drug glibenclamide showed significant positive antihyperglycemic responses compared to rats in the control group, which were given pre-distilled water. The extracts administered orally at a dose of 400 mg/kg successfully reduced postprandial hyperglycemia when taken 30 minutes before glucose overload. On the other hand, glibenclamide effectively suppressed the increase in postprandial blood glucose levels during the first hour (60 minutes) after glucose consumption, and the blood glucose levels were significantly reduced. The results indicate that the boiled extracts of the tested oregano species possess remarkable antihyperglycemic effects comparable to glibenclamide, a widely used antidiabetic drug in clinical practice (Al Kamaly et al., 2024).

In another study, the antidiabetic potential of *Origanum compacta* essential oil (OCEO) was evaluated using α-glucosidase and α-amylase enzymes. The results show that OCEO exhibits significant ability to inhibit pancreatic α-glucosidase and α-amylase *in vitro*. Experimental evaluations revealed higher IC_{50} values (120 µg/mL for α-glucosidase; 150 µg/mL for α-amylase) of OCEO compared to the control drug acarbose. It can be said that the antidiabetic activity of essential oils is based on various bioactive compounds. Numerous studies have reported that carvacrol and thymol exhibited antidiabetic properties in both *in vivo* and *in vitro* experiments. In an *in silico* study investigating the effect of essential oil components (carvacrol and thymol) on human NADPH oxidase, it was found that the essential oil components showed good binding affinity, and carvacrol and thymol also showed good binding affinity towards lysosomal acid alpha-glucosidase and salivary amylase. The researchers suggested that these results indicate that *O. compactum* essential oil-based diabetes treatment may have translational potential (Assaggaf et al., 2023).

In another experimentation, evaluated streptozotocin (STZ) induced diabetics rats and aimed to reveal the protective effect of *Origanum onites* L. against possible changes in these parameters. *Origanum onites* L. extract was administered intraperitoneally to these sera at a dose of 50 mg/kg per day for 6 weeks and serum creatinine, ALT, AST and inflammatory cytokine levels were measured biochemically. Malondialdehyde (MDA) and glutathione (GSH) levels were also measured in liver tissues. ALT, AST, creatinine and MDA levels increased in the DM group, whereas a significant decrease was observed in the treatment group. GSH levels decreased in the DM group, whereas there was a significant increase in the opposite direction in the *Origanum onites* group. When plasma cytokine levels were analyzed, an increase was observed in the DM group, while a significant decrease was observed in the *Origanum onites* group. These results revealed that *Origanum onites* L. has a protective effect against the complications that may occur in DM by preventing inflammation and oxidative damage. At the end of the study, the diabetic rats had lost 40% of their body weight, while the *Origanum onites*-treated diabetics lost only 12%. After 3 weeks, a 6% decrease in blood glucose levels was observed in the *Origanum onites*-treated group, while there was no change in blood glucose levels in the untreated group (Aydemir et al., 2022).

In another experiment, according to the glucose tolerance test, *Origanum grosii* extract at a dose of 150 mg/kg significantly suppressed the level of postprandial hyperglycemia compared to the normal control group. This species has an antihyperglycemic effect. This may be due to the presence of a large family of hypoglycemic chemicals such as flavonoids, terpenes, and tannins found in *Origanum grosii*. These components improve the functioning of pancreatic tissue by increasing insulin secretion or reducing glucose absorption from the intestine. In addition, the antihyperglycemic effect of this herb may be partly explained by the inhibition of α-amylase or other enzymes. The antienzymatic activity of this species is likely due to its phenolic content. It showed that the leaves had high concentrations of trace elements (Ca, Mg and K) and a complete absence of heavy metals (Cr, Ni and B), which were present in small quantities. The chemical families of the oregano plant may act individually or synergistically to cause the hypoglycemic effect of this genus (El Hassouni et al., 2021).

In another study, it has been established that exposure to chronic immobilization stress promotes an increase in fasting glucose levels and the development of hyperglycemia. Immobilization stress leads to impaired

stomatal functions of the endocrine, cardiovascular and immune systems characterized by hyperlipidemia and hyperglycemia, as well as impairment of some biochemical parameters such as total creatinine, protein and urea. The hypoglycemic effect of *O. vulgare* aqueous extract was evaluated in rabbits with hyperglycemia model for 21 days. During the treatment, an oral glucose tolerance test (OGTT) was performed. Oral administration of aqueous extracts showed a significant effect on improving glucose tolerance and hyperglycemia. In addition, *O. vulgare* extract decreased LDL cholesterol and total cholesterol, conversely, increased HDL cholesterol, and also decreased liver enzymes (ALT and AST) compared to the untreated group (Aghajanyan et al., 2022).

In different study, the ultrasonic extraction options of polyphenolic compounds from the combination of *Cinnamomum verum* (CV), *Origanum majora* (OM) and *Origanum vulgare* (OV) and their potential antidiabetic activities against glucose-induced diabetes activity were investigated. Diabetic zebrafish were studied. Hyperglycemic fish showed elevated triglyceride and cholesterol levels, while the extracts completely blocked these metabolic changes. The combination of the three herbs showed a higher antidiabetic effect than CV, OM and OV, suggesting a synergistic effect between them. Extracts of CV, CM, OV and COV (a mixture of three extracts) showed antidiabetic effects probably due to their phenolic compounds. The results indicate that supplementation by a combination of three herbs can reduce diabetic complications. The ability to suppress glycemia and lipid profile after treatment with the polyherbal formulation was confirmed in our zebrafish model of T2DM. (Perez Gutierrez et al., 2022)

In another experiment, the development of inhibitors of advanced glycation end products (AGEs) is considered to have therapeutic potential in diabetic patients. *Origanum majorana* (OM) and glibenclamide were administered to streptozotocin-induced diabetic mice for 28 days and were found to have beneficial effects on glucose levels and renal metabolic abnormalities including AGE formation. OM also had a significant effect on AGE formation *in vitro*, and its glycation inhibitory activity was found to be more effective than that obtained using aminoguanidine as a standard antiglycation agent. The antiglycation activity of OM is partly attributed to its antioxidant activity and its ability to scavenge reactive carbonyls. OM alleviated oxidative stress in diabetic conditions by inhibiting lipid peroxidation, preventing and/or delaying the onset of renal injury. OM treatment improved diabetes control and these parameters compared to glibenclamide. These results suggest that OM may prevent or alleviate AGE-related chronic diseases (Perez Gutierrez et al., 2012).

In a study investigating the protective role of *Origanum majorana* L. on biochemical parameters of STZ-induced rats, diabetic rats were divided into two groups; the first group received no treatment, while the second group was administered *Origanum majorana* L. extract (200 mg/kg) for 6 weeks, and serum alanine aminotransferase (ALT), creatinine, and aminotransferase (AST) values were measured. In addition, GSH and MDA levels were measured in liver and kidney tissues. It was found that creatinine, ALT and AST values increased in diabetic rats and decreased significantly in the treatment group administered *Origanum majorana* extract. While GSH values decreased in diabetic rats, conversely, MDA levels increased. It was observed that treatment with *Origanum majorana* extract reduced lipid peroxidation and caused a significant increase in GSH levels. As a result, the researchers concluded that treatment with *Origanum majorana* extract has a protective effect against diabetic nephropathy by preventing oxidative damage. STZ-induced DM is known to be associated with significant weight loss and increased blood sugar levels. At the end of the study, it was determined that the body weight of the rats in the OM treatment group increased significantly compared to the DM group. It was also observed that the blood glucose levels in the OM-treated rats decreased significantly compared to the DM group (Çakar et al., 2023).

In another experiment, medicinal plants and green silver nanoparticle production (AgNP) are effective treatments for diabetes. Evaluation of antidiabetic and liver-protective effects of *Origanum majorana* leaf extract (OMLE) and nanoparticles (OMLENP) in STZ-induced diabetes in rats. The rats were divided into 5 groups: Group I: non-diabetic control, Group II: streptozotoSTZ administered; Group III: Diabetic rats were administered with glibenclamide, Group IV: Diabetic rats were administered with OMLE, Group V: Diabetic rats were administered with OMLENP. Various parameters were evaluated. Both OMLE and OMLENP significantly reduced blood glucose levels compared to the untreated diabetic group. Diabetics treated with glibenclamide and diabetics treated with OMLE or OMLENP had lower TG and TC levels compared to the diabetic group showed a significant decrease in the levels. Compared with the extract, OMLENP treatment showed superior effect in improving insulin sensitivity, lipid profile, antioxidant functions and liver functions. Histopathological examination showed that OMLE and OMLENP alleviated STZ-induced liver tissue injury with significant reduction in inflammatory infiltrates and cellular degeneration. OMLE and OMLENP exhibit potential antidiabetic and liver protective effects with enhanced efficacy possibly due to improved bioavailability (Rateb et al., 2024).

Elghazaly et al. evaluated the ameliorative and antihyperglycemic effects of *O. majora*na leaf extract (OMLE) on the spleen tissue of diabetic rats. Blood glucose and insulin levels, catalase (CAT) and superoxide dismutase (SOD) activities, GSH and MDA levels, and white blood cell (WBC) counts were measured. Spleen tissues were examined histologically. In diabetic patients, there was a significant increase in blood glucose and MDA levels, and a significant decrease in plasma insulin levels, SOD and CAT activities, white blood cell counts, and GSH levels. Treatment of diabetic rats with OMLE improved glucose, insulin, and white blood cell counts. There was a significant increase in antioxidant enzyme activities when diabetic rats were treated with OMLE. The results showed that there were many histological changes in the spleen tissues of diabetic rats. The biochemical indices and histological structure were significantly improved when diabetic rats were treated with OMLE. OMLE can have a protective effect on spleen problems in diabetic rats and reduce the complications of diabetes (Elghazaly et al., 2023).

Oregano majorana extract (OME) was incorporated into nanoscale systems to enhance its biological effects at low doses. Optimal nano-cubosomal (NC) systems were selected and evaluated *in vivo* to compare their effects with conventional OME in streptozotocin-induced diabetic patients. The results showed that OME was effective in reducing blood glucose levels and attenuating molecular and histopathological changes in the submandibular salivary glands in diabetes due to its antihyperglycemic, anti-inflammatory and antioxidant effects. Furthermore, the biological activity of the extract was shown to be enhanced when incorporated into NC systems even at lower doses. Therefore, it is possible that cubosomal nanosystems can be considered as potential carriers to achieve the best result with OME (Farag et al., 2022).

In another experiment has evaluated the antidiabetic activity of the oral aqueous extract of *Origanum floribundum* daily for 28 days using alloxan as a diabetes inducing agent. Blood glucose levels were significantly elevated in untreated alloxan-induced diabetics compared to untreated normal rats. The aqueous extract of the leaves at doses of 200 and 400 mg/kg exhibited significant antihyperglycemic activity and caused a decrease in blood glucose levels. The findings showed that various secondary metabolites such as flavonoids, alkaloids, saponins, terpenoids, polyphenols, tannins, sterols, and coumarins were found in the extract. The hypoglycemic effect of the aqueous extract is due to its components: polyphenols from these secondary metabolites, especially flavonoids, have been proposed as the best therapeutic agents in the treatment of diabetes mellitus and its chronic complications. Moreover, natural ingredients may act individually or synergistically to produce a hypoglycemic effect (M'hamed Nasri et al., 2020).

3.2. Anticancer activity

Cancer is a large group of diseases that can begin in virtually any organ or tissue of the body in which abnormal cells grow uncontrollably, expand beyond their normal boundaries, penetrate into adjacent areas of the body and spread into other organs. The latter process is called metastasis and is one of the leading causes of cancer-related deaths. Neoplasm and malignancy are other common names for cancer (WHO, Cancer).

Cancer is the result of genetic and epigenetic changes in the stem cells (progenitors) of certain cell types. Two distinct categories of genes are involved in carcinogenesis. Oncogenes are activated proto-oncogenes, whereas tumor suppressor genes are globally inactivated by mutations, point mutations, deletions, rearrangements, and duplications. Both types of genes are required for normal cell proliferation and differentiation, and abnormal expression leads to abnormal cell proliferation. When this situation is systematically disrupted, cancer occurs (Spandidos, 2007).

In addition, cancer is one of the most feared diseases of the 20th century and continues to spread more and more in the 21st century. The situation is so alarming that every fourth person is at risk of developing cancer during their lifetime (Roy et al., 2016).

The most common cancers in men are colorectal, liver, lung, prostate and stomach cancers; and in women breast, cervical, colorectal, lung and thyroid cancers (WHO, Cancer).

Although effective cancer treatments are still awaiting, some unconventional treatments such as surgery, radiotherapy and chemotherapy and some advanced technologies such as stem cell therapy, gene therapy, natural antioxidants, nanoparticles, photodynamic therapy, targeted therapy and precision medicine are used to diagnose cancer and are available for treatment (Kaur et al., 2023).

Today, the active ingredients of many drugs used in cancer treatment are derived from natural sources. A large part of these natural resources are plants, which are capable of synthesizing a wide variety of chemicals. Plant chemicals exert their anticancer effects through mechanisms such as inactivation of carcinogens, antiproliferation, cell cycle arrest, induction of apoptosis and differentiation, suppression of angiogenesis, antioxidant effects, and reduction of multidrug resistance. In recent years, the

number of studies on cancer treatment with medicinal herbs has increased worldwide. In this case, ethnobotanical knowledge, passed down from the depths of centuries to the present day, comes to the fore, and the use of medicinal plants becomes important (Bozyel et al., 2019).

In a study, the DNA synthesis inhibitory and antiproliferative effects of *Origanum onites* L. essential oil (EOOO) and carvacrol (CV), one of the most important components in its essential oil, were demonstrated on the hepatocellular carcinoma cell line HepG2. HepG2 cells were treated with EOOO and CV for 48 hours and then the DNA synthesis level was evaluated by BrdU incorporation test. As a result, a decline in DNA damage in HepG2 cancer cell lines was observed as EOOO and CV increased. DNA synthesis was significantly decreased in cells by EOOO applied at a concentration of 0.06 µg/mL compared to vehicle-treated control cells. It was found that EOOO applied at a concentration of 0.08 µg/ml had an inhibition rate of DNA synthesis of approximately 50%. Compared to solvent-treated control cells, DNA synthesis in cells was significantly decreased in a concentration-dependent manner at CV at a concentration of 60 µg/mL. EOOO and CV were found to inhibit HepG2 cell proliferation. Cell viability was determined using trypan blue exclusion (TB) test after incubation with EOOO and CV. The number of viable cells decreased in a time- and concentration-dependent manner, similar to the results obtained using the BrdU test. After 48 h, the number of viable cells decreased to 65% and 51% with EOOO applied at concentrations of 0.08 and 0.09 µg/mL, respectively. In addition, the number of viable cells was significantly reduced to 39% after 72 h with EOOO applied at a concentration of 0.09 µg/mL. The IC_{50} value of EOOO at 24 and 48 h was calculated as 0.09 µg/mL. CV was also found to be cytotoxic to HepG2 cells, similar to the effect of EOOO. Compared to vehicle-treated control cells, the number of cells was significantly decreased with CV applied at a concentration of 45 and 75 µg/mL. When applied at a concentration of 75 µg/ml, CV reduced cell viability to 64% and 45% at 24 and 48 hours, respectively, and when applied at a concentration of 45 µg/ml, it reduced cell viability to 54% at 72 hours and 50% at 96 hours. The CV IC_{50} values were revealed to be 75 µg/mL for the 48th hour and 45 µg/mL for the 72nd and 96th hours (Tomsuk et al., 2024).

Carvacrol has been reported to be the main component of essential oils of aromatic medicinal plants belonging to the Lamiaceae family, such as *Origanum vulgare* and *Thymus vulgaris*. Chemically, it is a phenolic monoterpenoid known as 5-isopropyl-2-methylphenol. The researchers proposed that the current research is directed towards identifying carvacrol, a potent compound with various pharmacological activities such as antioxidant, anticancer and anti-inflammatory. Carvacrol has been found to exhibit potent cytotoxic activities against various carcinoma cell lines by inducing apoptosis through the action of numerous proteins related to the apoptotic pathway, the PI3K/Akt pathway, and the MAPK pathway. In addition to the apoptotic pathway, carvacrol has also been shown to exhibit cytotoxic activity against some cancer cells. Carvacrol has been shown to exhibit potent anticancer activity against various carcinoma cell lines by inhibiting cell proliferation through the apoptotic pathway triggered by activation of caspases and increased DNA fragmentation. It also showed protective activity against H_2O_2-induced DNA damage (Mondal et al., 2020).

In another study, the cytotoxic effects of essential oils obtained from wild and cultivated forms of *Origanum acutidens* against A549 and H1299 lung cancer cells were investigated using MTT and CellTiter-Blue® Cell Viability assays. In the MTT experiment, the IC_{50} values of the essential oil obtained from the wild form of *O. acutidens* species against H1299 cells were calculated as 179, 157 and 132 µg/mL after 24, 48 and 72 hours, respectively. With rezazurin-based analysis, the IC_{50} values of *O. acutidens* wild form essential oil on H1299 cells after 24, 48 and 72 hours were determined as 150, 131 and 110 µg/mL. Using the MTT test, the IC_{50} values of the essential oil obtained from the wild form of *O. acutidens* against A549 cells after 24, 48 and 72 hours were found to be 118, 99 and 69 µg/mL, respectively. The cytotoxic effect of the essential oil obtained from the wild form of *O. acutidens* against A549 cells was evaluated using rezazurin-based assay and the essential oil was calculated to have 98, 83 and 57 µg/mL IC_{50} values after 24, 48 and 72 hours. It was observed that essential oils obtained from cultured and wild *O. acutidens* increased malondialdehyde levels in both A549 and H1299 cells. It was revealed that the highest membrane damage was seen in A549 cells treated with wild *O. acutidens* essential oil (Gökhan et al., 2021).

In another experiment, researchers tested the *in vitro* anticancer effects of ethanol extract obtained from *O. syriacum* (OSEE) against MDA-MB-231 cell line, an aggressive and highly metastatic human triple negative BC (TNBC) cell line, and the possible underlying mechanisms of action were investigated. The results showed that *O. syriacum* ethanol extract (OSEE) exerted potent anticancer and antimetastatic effects on aggressive TNBC phenotype by regulating cell adhesion, migration, invasion and angiogenesis processes via inhibition of STAT3 signaling as well as activation of p38 MAPK signaling pathways. OSEE not only induced cell cycle arrest in MDA-MB-231 cells, but also inhibited angiogenesis as well as activated apoptosis.

Origanum syriacum contains multiple primary and secondary bioactive metabolites. The study confirmed the presence of different classes of phytochemical compounds in *O. syriacum* ethanol extract (OSEE). OSEE contains cardiac glycosides, essential oils, flavonoids, phenols, quinones, steroids, tannins and terpenoids. Many of the bioactive compounds found in *O. syriacum* have been reported to have potent anti-breast cancer activities. Carvacrol, thymol, apigenin, naringenin, rosmarinic acid and thymoquinone have been reported to reduce the malignant phenotype of breast cancer (Mesmar et al., 2022).

The anticancer activity of different concentrations of *Origanum minutiflorum* essential oil was proven on A-549 (human lung cancer cell line), MCF-7 (human breastcancer cell line) and HepG2 (human hepatocellular carcinoma cell line). All the tested concentrations of the oil showed significant scolicidal activity against protoscolecium hydatid cysts. The results showed a concentration-dependent decrease in the viability of A-549, HepG2 and MCF-7 cells after exposure to *Origanum minutiflorum* oil for 24 hours. IC_{50} for HepG2, A-549 and MCF-7 cells were 0.028457%, 0.028682% and 0.0349235%, respectively. It was found that the anticancer activity of *O. minutiflorum* essential oil was more in HepG2 cells followed by MCF-7 and A-549 cells (Sökmen et al., 2020).

In a different study, it was investigated the anticancer potential of *Origanum majorana* leaf acetone extract (OMAE) against human colon cancer cells HT-29. The cytotoxic effect of OMAE, which was investigated by MTT test, was revealed by the researchers to have a significant inhibitory effect on the growth of HT-29 cells from a concentration of 1000 µg/mL to 62.5 µg/mL. It was observed that these inhibitory effects continued slightly up to a concentration of 31.25 µg/mL, and the IC_{50} of OMAE was stated to be at a concentration of 90 µg/mL. After the IC_{50} of OMAE was found, real-time RT-PCR was used to quantitatively analyze p53 expression after *in vitro* treatment of HT-29 cells with this IC_{50} dose. The results showed that the expression of p53 mRNA increased by 5.44-fold compared to the control cells. The apoptotic effect of OMAE was evaluated using annexin V staining. The extract induced cell apoptosis, with the number of apoptotic cells significantly increased (11.74%) in treated cells compared to untreated cells (0.73%). This increase in the percentage of apoptotic cells (treated) was almost the same in the early (5.92%) and late (5.82%) stages. Therefore, it was inferred that OMAE had an apoptotic effect rather than a necrotic effect (Ibrahim et al., 2022).

Since 2004, the World Health Organization has endorsed the use of alternative therapies as adjuvant therapies based on evidence of their benefits. Since then, some natural alternatives for treatment of cancer have been examined, including Oregano (Ov) and one of its main compound, carvacrol (Crv). Rojo-Ruvalcaba et al. also evaluated the cytotoxic effect of Ov and Crv on TN BC cell line (HCC-70). The lethal dose 50 was determined on the control HaCaT cell line using MTT assay with stimulation of Ov and Crv at different doses and concentrations. The found dose was used on the HCC-70 cell line. It was found that Ov reduced proliferation by 94.05 ± 0.11% and Crv by 93.43 ± 0.21%. This showed that Ov and Crv have strong cytotoxic effect to the HCC-70 cell line (Rojo-Ruvalcaba et al., 2020).

In another study, MTT assay was performed to determine the effect of *Origanum vulgare* extract on the viability of Molt-4 cells showed that *O. vulgare* extract reduced the viability of Molt-4 cells in a time- and dose-dependent manner. MTT assay showed that *O. vulgare* extract eliminated half of the Molt-4 cells after 72 hours at a concentration of 457 µg/mL. Expression of apoptotic pathway genes after treatment with *O. vulgare* extract, Bax and Bcl-2 gene expression were assessed after Molt-4 cells were treated with 1/5 IC_{50} of *O. vulgare* extract for 72 hours. *O. vulgare* extract induced the expression of the apoptotic gene Bax, while the expression of the anti-apoptotic gene Bcl-2 was decreased. Moreover, the expression of the gene Nrf2 was increased by *O. vulgare* extract. *O. vulgare* extract not only induced early or late apoptosis, but also increased necrosis in Molt-4 cells (Solouki et al., 2021).

Yusuf et al. investigated the cytotoxic potential of *O. vulgare* (OV) was evaluated as a potential source of natural products in the treatment of cervical cancer. Crude extracts and fractions were exposed to a cervical cancer cell line (HeLa) using the MTT assay. The potentials of the OV fractions, n-hexane, DCM, ethyl acetate and aqueous solutions were 57.95, 61.63, 172.4 and 176 µg/mL, respectively. These results were compared to vincristine (standard) with a CC_{50} of 0.75 µg/mL. The n-hexane fraction of *O. vulgare* showed the highest anticervical effect (57.95 µg/mL), followed by the DCM fraction (61.63 µg/mL). Also, the results obtained have showed that the crude extract of *O. vulgare* had an IC_{50} value of 170.2 ± 0.11 µg/mL (Yusuf et al., 2023).

Gîrd et al. investigated the cytotoxic activity of freeze-dried extracts of *Origanum vul*gare (OV) against human osteosarcoma cell line MG-63. The effects of the analyzed dried extracts on, cell survival, cell morphology and cell proliferation were measured. The antiproliferative effect of OV dried extract was performed against osteosarcoma bone cell line MG-63 by MTT assay. The results of the MTT assay showed that osteosarcoma cells were sensitive to OV dried extract and the effect was prominent at concentrations of 500 µg/mL and 700 µg/mL compared to

the control group. Cytotoxicity was evaluated using Live & Dead and lactate dehydrogenase assays. Treatment of osteosarcoma cells with *Origanum vul*gare dried extracts presented a dose-dependent increase in LDH release. After treating MG-63 cancer cells with 700 µg/mL OV dried extract for 24 h, a significant release of LDH into the medium was observed compared to the control. However, no significant differences were found at other OV dried extract concentrations (100, 300, and 500 µg/mL) compared to untreated cells. Microscopic observations using Calcein-AM and EthD-1 confirmed the cytotoxic effect of the tested dried extracts at various concentrations. To further investigate the potential anticancer effects, it has been investigated the effect of the dried extracts on cells using caspase-3/7 and proliferating cell nuclear antigen (PCNA) expression assays. Cells were incubated with extracts in a range of concentrations (100-700 µg/mL) for 24 h. Concerning the effect of the analyzed dried extracts on caspase-3/7 activation, it has been observed a dose-dependent effect at an extract concentration of 300 µg/mL. PCNA expression in osteoblasts treated with OV dried extracts at all analyzed concentrations was similar to that in untreated cells. According to the results, apoptosis is one of the main mechanisms involved in the cytotoxic properties of the tested extracts. As the extracts were standardized for phenolic compounds (rich in phenolic carboxylic acids and flavones), it is likely that these are the major components involved in the cytotoxic effect (Gird et al., 2021).

The cytotoxic effects of *O. majorana* volatile oils against A-431 and A-549 cancer cell lines were tested by MTT and CellTiter-Blue® cell viability assays. In both assays, the cytotoxic effect was observed to increase in parallel with the concentration and incubation time in both A-549 and A-431 cells. According to the results of MTT, the IC_{50} values after 24, 48 and 72 hours of incubation of the oil, were 218, 187 and 140 µg/mL in A-431 cells and 266, 222 and 182 µg/mL in A-549 cancer cell lines, respectively. Moreover, the IC_{50} values of oil after 24, 48, and 72 hours of incubation with the oil were 243, 203, and 167 µg/mL in A-549 in the CellTiter-Blue® Cell Viability assay. In A-431 cells, after incubation of oil at similar time intervals, 182, 145 and 111 µg/mL IC_{50} values were detected, respectively. It was found that the volatile oil was more effective on A-431 cancer cell lines, (mutant p53) than on A-549 cancer cell lines (wild-type p53). To assess the effect of *O. majorana* essential oil on the cell membrane, lactate dehydrogenase (LDH) activity was measured; it is released from the cells into the medium and is an early indicator of apoptosis. The LDH activity in A-431 cells increased more than that in A-549 cells, and the activity of LDH in both A-549 and A-431 cancer cell lines was higher than that in the control group. The apoptosis-inducing potential of *O. majorana* oil was observed after treating A-549 and A-431 cancer cell lines, cells with *O. majorana* volatile oil for 24 hours. It was observed that the apoptotic effect of volatile oil in terms of increasing caspase-3/7 activity in A-549 cells was twice as high as the apoptotic effect of *O. majorana* volatile oil in A-431 cells (Gökhan et al., 2022).

The inhibitory effects of *O. majorana* essential oil and extract on cell proliferation were investigated in one normal cell line and four cancer cell lines. The anticancer effects of extract, essential oil, 5-fluorouracil (5-FU) and cisplatin were evaluated on the cancer cell lines Hep3B (hepatocellular carcinoma), A549 (human lung carcinoma), MCF7 (human breast adenocarcinoma), HT29 (human colon carcinoma), and normal cell lines FL (human amniotic cells). The cytotoxic effect and antiproliferative activity of the extract and essential oil were examined by MTT and LDH (lactate dehydrogenase) methods, respectively. The essential oil showed significant activity against the cancer cell lines MCF-7 (IC_{50}, 7.1 µg/mL), Hep3B (IC_{50}, 7.4 µg/mL) and A549 (IC_{50}, 27.2 µg/mL) compared with the standards. In addition, the extract showed significant activity against MCF-7 (IC_{50}, 10.8 µg/mL) and Hep3B (IC_{50}, 27.2 µg/mL) cell lines. When comparing the essential oil and the extract, it was found that the essential oil had a higher antiproliferative effect than the extract on Hep3B, A549 and MCF7 cell lines. In this study, the cytotoxic activity of the essential oil and extract on cell lines was measured using an LDH cytotoxicity kit, which is based on measuring the amount of cytoplasmic LDH, an indicator of membrane integrity. The extract and essential oil (17%) were not cytotoxic to FL cells, but were toxic to cancer cells. However, the essential oil has therapeutic efficacy since it is safe for FL cells only at IC_{50} concentrations and below. The results showed that the essential oil has a cytostatic effect on cells. The cytotoxic effect of the extract was found to be higher than that of the essential oil. It has been suggested that the activity of the essential oil may be due to the synergistic effect of other compounds as well as the high content of carvacrol (90.4%) in the essential oil (Erenler et al., 2021).

Silver nanoparticles are recognized as smart magnetic particles due to their small size and large adsorption surface area. Silver nanoparticles have revolutionized cancer treatment, with silver nanoparticles playing an important role in this field due to advances in nanotechnology. In a study conducted by Chao Qian et al., AgNPs derived from *Origanum majorana* (*Thymus majorana*) caused a decrease in the viability of human breast cancer cells (MCF-7). MTT assay revealed the anti-breast cancer properties of silver nanoparticles in MCF-7, T-47D, and SkBr3 cells. The results indicated that the viability of cancer cells decreased within 3 days as the

concentration of nanoparticles increased. The activities of AgNPs against MCF-7, T-47D and SkBr3 cell lines were calculated as IC_{50} values and these values were found to be 97, 186 and 180 µg/mL, respectively. It was revealed that these nanoparticles induced apoptosis through signal transducer and transcription pathway 3 and P53 activator. The presence of silver NPs was found to induce cell apoptosis through activation of the pro-apoptotic markers Bax and cleaved caspase-8, while down-regulating the anti-apoptotic marker Bcl-2. In addition, silver NPs both inhibited colony formation and showed high sensitivity in the electrochemical detection of hydrazine, a potential carcinogen, with a detection limit of 0.25 µM (Chao Qian et al., 2024).

Conclusions

Cancer and diabetes are among the most important chronic diseases. In the treatment of these diseases, in addition to conventional medicines, products of natural origin are used as supportive or complementary. The fact that *Origanum* species are used both as spices and herbal teas in the world and in our country under the name of thyme suggests that the use of these species may be safe. In this review study, it was observed that intensive studies have been carried out on the essential oils of *Origanum* species, and the major components of the oil are carvacrol and thymol. Antidiabetic and anticancer studies on *Origanum* species show that these species have the potential to be promising naturally derived agents as supportive or complementary therapies in the treatment of diabetes and cancer. In addition, with the nanotechnology developed in recent years, the increase in the number of studies investigating the effects of nanoparticles developed from the essential oil or extract of *Origanum* species against these diseases has shown that *Origanum* species are important.

Author contributions

Merve Nur Bay, Ali Şen: Collection and compilation of data, writing of the manuscript. Ali Şen, Leyla Bitiş: Review and editing of the manuscript. Ali Şen, Leyla Bitiş: Correction and analysis of chemical compounds. Merve Nur Bay, Ali Şen, Leyla Bitiş: Designing, supervising and editing of the manuscript. Merve Nur Bay, Ali Şen, Leyla Bitiş: All authors read and approved the final manuscript.

Declaration of interests

The authors declare that there is no conflict of interest.

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