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Antimicrobial Activity of *Pimpinella* – an Overview

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Abstract

Pimpinella species that are classified under *Apiaceae* (*Lindl*.) family are utilized in many fields of industry as spice, fruit, vegetable, and beverage and have especially been used in traditional medicine as a remedy in various countries. Essential oils of various species including *Pimpinella cypria, Pimpinella kotshchyana, Pimpinella saxifraga, and Pimpinella anisum* were reported to have antibacterial, antiviral, and antifungal activities. Along with its antimicrobial activity, *Pimpinella* species were found to have antioxidant, anti-inflammatory, anticonvulsant, antispasmodic, estrogenic, cytotoxic, insecticidal, and repellent properties. This review aims to provide an enhanced understanding on the morphology, chemical constituent, industrial and medicinal use, and antimicrobial activities of some important *Pimpinella* species against bacteria, fungi, and viruses.

Keywords

Antibacterial, antiviral, antifungal, essential oil, *Pimpinella*.

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INTRODUCTION

Numerous health problems that were experienced throughout the hiory were solved out by humankind using natural products. As human-being has steadily been in touch with the nature during their daily lives, medicinal benefits of various plants have been experienced and passed from one generation to another. The increase in the use of natural products as complementary and alternative medicine for a variety of health problems has attracted the attention of scientists to investigate the beneficial effects of medicinal plants. *Pimpinella* that belongs to *Apiaceae* (*Lindl*.) family was used as a herbal remedy for treating various disorders in several countries including Turkey (Tepe Sihoglu and Tepe, 2015; Tas *et al.*, 2006; Kuruuzum-Uz *et al.*, 2010; Demirezer *et al.*, 2012; Tetik *et al.*, 2013), China (Kang *et al.*, 2012; Kang *et al.*, 2013), Iran (Fard and Shojaii, 2013), Korea (Lee *et al.*, 2012), Palestine (Sawalha *et al.*, 2008), Lebanon (Kreydiyyeh *et al.*, 2003) and the United Kingdom (Yoney *et al.*, 2010). In addition to their conventional medicinal properties, *Pimpinella* species have economically of great importance because they are used as a spice, fruit and vegetable especially in the Mediterranean countries. *Pimpinella anisum* is frequently encountered in the beverage industry as “raki” in Turkey, “pastis” in France, “anesone” in Spain and “arak” in Syria (Anli and Bayram, 2010; Jurado *et al.*, 2007).

The genus *Pimpinella* includes around 150 species, the most perennial and permanent of which are full and needle-like, with graceful, star-shaped flowers carrying umbrella-like heads. They have small, oval-shaped fruits (Tepe *et al.*, 2005).

Pimpinella species contain monoterpene and sesquiterpene hydrocarbons, trinorsquiterpenes, phenylpropanoids, and 2-hydroxy-5-methoxy-1- (E) - propenylbenzene skeleton (pseudoisougenol) as the main essential oils (Tabanca *et al.*, 2003; Tabanca *et al.*, 2005; Tabanca *et al.*, 2006; Joshi, 2013; Tabanca *et al.*, 2016). Pharmacological and biological studies have shown that various *Pimpinella* species have antimicrobial, antifungal, antioxidant, anti-inflammatory, anticonvulsant, antispasmodic, estrogenic, cytotoxic, insecticidal, and repellent properties (Tepe Sihoglu A and Tepe B, 2015). Especially, *P. anisum* has been used as a remedy for asthma, bronchitis, cancer, diarrhea, cough, and nausea (Tabanca *et al.*, 2004; Baser *et al.*, 2007).

In this review, it was aimed to revise the plant morphology, chemical constituents, traditional and industrial uses, and antibacterial/antiviral activities of *Pimpinella* species.

Morphology

Pimpinella is one of the largest genus (170–180 species) classified under the family of *Umbelliferae/Apiaceae*. *Pimpinella* species that are found primarily in the subtropical/temperate locations of northern hemisphere and the Mediterranean region are biennial, permanent and grow yearly in the rocky cracks, fields, wilderness, hill pastures and meadows on dry rocky areas. They comprise mostly long-term herbs with slight and laterally compressed fruits that are cordate or oblong-ovoid, each with five filiform ribs constricted at its commissures. On the commissural side, the fruit generally has two vittae. The fruit is recognized on the commissural side with two major vittae. In the transverse section, mericarps are two and have elliptical, semi-round, or pentagonal shapes. Epidermal surface is pubescent, papillate or tubercuate. The seeds contain a thick-walled testa and an endosperm that includes a plenty of oils and proteins (Akalin *et al.,* 2016). The aerial and fluorescent parts of *Pimpinella cypria* are shown in Figure 1.

Figure 1: *P. cypria* and its florescence in the natural habitat (Muti and Ozhatay, 2020).

Chemical constituents

Biological activities of *Pimpinella* species are primarily due to the phenylpropanoid derivatives. The structural moiety of these compounds, 2-hydroxy-5-methoxy-1-(E)-propenylbenzene, that is known as pseudoisoeugenol has only been discovered in the *Pimpinella* genus. Previous studies on the *Pimpinella* identified antigermination, insecticidal, acaricidal, and poor antitumor activities of phenylpropanoids (Tabanca *et al.,* 2003). Monoterpenes, sesquiterpenes, trinorsesquiterpenes and phenylpropanoids (propenylphenols, pseudoisoeugenols) were reported to be the main volatile compounds (Tabanca *et al.*, 2006). Table 1 shows the chemical constituents and their biological effects. Some important essential oil components and their biological activities are given Table 2.

Table 1: Chemical constiutents of *Pimpinella* species and their effects (Muti S and Ozhatay FN, 2020).

Constituents	Effect
Flavonoids (e.g. falcarinol)	Cytotoxic against acute lymphoblastic leukemia cells Antioxidant Antispasmodic Anti-inflammatory
Caumarin	Vascular effect Hepatoprotective Anticancer Antispasmodic Hormonal Immune enhancement
Umbelliferone	Antiproliferative effect on vascular smooth muscles Anti-hyperlipidaemic Anticancer Antiviral

Table 2: Essential oil components of *Pimpinella* and their biological effects (Tabanca *et al.,* 2005).

Essential Oil	Antimicrobial Effect
Pseudoisoeugenol 2-methylbutanoate	Potent activity against fungi species Potent activity against *Mycobacterium intracellulare*
Traginone	Negligible antifungal activity
Dictamnol	Negligible antifungal activity
2- methoxy-4-(1-propenyl) phenyl tiglate	Potent activity against *M. intracellulare*
Epoxyisoeugenol	Antimycobacterial activity

Traditional and industrial use of *Pimpinella s*pecies

Various *Pimpinella* species have been used in both traditional medicine and industry. Anise seeds have been utilized in traditional Iranian medicine to treat epilepsy. Seeds of *P. anisum* are also used as a diuretic, carminative, fragrant, antiseptic, and analgesic for migraines in traditional medicine (Sun *et al.,* 2019). To increase milk secretion, essential oil of anise seed is used in lactating women whereas that of *Pimpinella isaurica*, *Pimpinella aurea*, and *Pimpinella corymbosa* are used as animal feed (Mahboubi, 2021; Tabanca *et al.,* 2003, Baser *et al.,* 2007). The roots of *Pimpinella saxifraga* are used as a demulcent, stomachic, expectorant, and tonic (Baser *et al.,* 2007). Fruits and seeds of anise are used in the food industry such as making bread, cookies and sugar, as well as in the production of alcoholic beverages such as raki, ouzo, pastis, pernod, anisette, ricard, and granier (Boztas and Bayram, 2020; Baser *et al.,* 2007). Additionally, anise is used in the cosmetic industry in the production of toothpastes, soaps, lotions, and dermal creams (Boztas and Bayram, 2020).

Antimicrobial Activity of the Essential Oils of *Pimpinella*: Action of Mechanism

The chemical composition and functional attachments that target various bacterial pathways play a major role in the antibacterial efficacy and mode of action of crude or individual essential oils. The essential oils of *Pimpinella* results in the loss of vital processes such ion homeostasis and the electron transport chain by disrupting the permeability of the outer membrane of Gram negative bacteria and damaging bacterial cell membrane of both Gram positive and Gram negative bacteria. The hydrophobic nature of the essential oils is the key chemical characteristic for cell membrane disruption (Tang *et al.*, 2020). Additionally, the essential oils may stop bacterial cell division and inhibit bacterial protein synthesis. The deficiency in ATP synthesis is among other fundamental mechanisms of antimicrobial and antifungal activities (Turgis *et al.*, 2009). In general, it is difficult to attract an antibacterial activity to one specific mechanism due to the numerous essential oil components and two or more mechanisms are thought to be responsible for antimicrobial activity.

A review of Literature: Antimicrobial Activity

In the study conducted by Tabanca *et al.* (2016), aerial parts of *P. cypria*, which is an endemic plant specific to Cyprus, were subjected to hydrodistillation for 3 hours after which yellowish essential oil was obtained. The essential oil was subjected to gas chromatography-mass spectrometry (GC-MS) and gas chromatography-flame ionisation detector (GC-FID). As a result, oxygenated sesquiterpenes, sesquiterpenes and monoterpens were found to be the most prevalent compounds (33.9%, 22% and 11.4%, respectively). The main components were (Z)-β-farnesene (6.0%), spathulenol (5.9%), ar-curcumene (4.3%), and 1,5-epoxy-salvial(4)14-ene (3.8%). Although the essential oil was found to be less effective than l N,N-diethyl-3-methylbenzamide (DEET), a commonly used insect repellent, it was reported to act as a repellent against *Aedes aegypti* (a vector for yellow fever) and star tick, *Amblyomma americanum*. Moreover, moderate antibacterial activity was detected against various Gram positive and Gram negative bacteria including *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis, Enterococcus faecium,* and Salmonella *Typhimurium.* On the other hand, the essential oil was found to have similar antifungal activity against *Candida albicans* compared to flucytosine.

In another research conducted by Askari *et al.* (2010), essental oils were isolated from different parts (including aerial parts, stem/leaf, flowers, unripe and ripe seeds) of *Pimpinella barbata* collected from the south of Iran. The highest yield of oil was extracted from unripe and ripe seeds followed by inflorescence, aerial parts and stem/leaf, in order. Sixteen, 22, 28, 22 and 12 components were detected in the aerial parts, stem/leaf, inflorescence, unripe seed and ripe seed essential oils, respectively. The major components were pregeijerene that comprised 32.7% of the essential oil extracted from aerial parts, g-muurolene that made up 28.2% of stem/leaf oil and methyl eugenol (18.7% in unripe seed oil). Although the antibacterial activities of the essential oils detected by disk diffusion method were much weaker than tetracycline and gentamycin, the oil showed higher activity against Gram positive bacteria (*Bacillus subtilis, Bacillus cereus, Micrococcus luteus and S. aureus*) than Gram negative bacteria (*Yersinia enterocolitica, Klebsiella oxytoca, Klebsiella pneumoniae, Serratia marcescens, E. coli* and *Pseudomonas aeruginosa*). On the other hand, unriped and ripe seeds revealed high antifungal activity against *C. albicans*. The essential oils extracted from the inflorescence and seeds of *P. kotschyana,* a species that is spread in Iran and north of Iraq, were reported to be rich in β-caryophyllene, germacrene D and langipinanol. Essential oils extracted from seeds that were collected after their colors changed to brown were effective against *B. subtilis*, *P. aeruginosa,* and *E. coli* and that extracted from inflorescence against *E. coli* (Asgari *et al*., 2011).

In a study carried out by Ksouda *et al.* (2019), the main components of the essential oil of *P. saxifraga* were found to be anethole, pseudoisoeugenol and p-anisaldehyde by gas chromatography-high resolution mass spectrometry (GC–HRMS) analysis. Along with strong total antioxidant and radical scavenging activity, β-carotene bleaching inhibition, ferric reducing power and potential DNA protection, the essential oil was shown to have potent antibacterial activity against Gram negative bacteria such as *E. coli*, *P. aeruginosa*, S. *Typhimurium* and Gram positive bacteria including *Listeria monocytogenes*, *M. luteus* and *B. cereus*. MICs and MBCs ranged from 0.78 to 3.125 mg/ml and 3.125 to 6.25 mg/ml against Gram negative bacteria whereas they were 1.56-3.125 mg/ml and 3.125-12.5 mg/ml against Gram positive bacteria, respectively. Considering MBC/MIC ratio (eg., MBC/MIC <4 bactericidal; MBC/MIC >4 bacteriostatic effect), the essential oil was reported to exert bactericidal activity against S. *Typhimurium*, *B. cereus* and *M. luteus* whereas it had bacteriostatic effect against *E. coli*, *P. aeruginosa* and *L. monocytogenes.* Antibacterial activity was attributed to anethole. Similar to the findings of Ksauda *et al.* (2019), Tepe *et al.* (2006) reported that the main components of the essential oil of *P. anisetum* were (E)-anethole (82.8%) and methyl chavicol and that of *P. flabellifoli* were limonene (47.0%), (E)-anethole (37.9%) and α-pinene (6.0%). The essential oils of both species had moderate antibacterial and antifungal activities.

Pimpinella anisetum essential oils had stronger antimicrobial activity than *Pimpinella flabellifolia* essential oil. *Clostridium perfringens* was the most sensitive bacterium to both of the essential oils followed by *Streptococcus pneumoniae* by microdilution method. *Anethole, as the highest* component of the essential oils, was thought to play a fundemental role in the antimicrobial activity.

The composition and antimicrobial activity of essential oils of air-dried and grained *P. anisum* ripe seeds were investigated by Abdel-Reheem and Oraby (2015). Propanoids and monoterpens were the major consituents of the essential oil. The major compounds were determined by ultra performance liquid chromatography (UPLC) coupled with tandem mass spectrometry (MS/MS) as trans-anethole (82.1%) followed by cis-anethole (5.8%), estragole (2.5%), linalool (2.3%), aterpineol (1.5%), and methyl eugenol (1.3%). A strong antibacterial acitivity was observed against Salmonella *Typhi* (zone of inhibition: 17 mm) and *E. faecalis* zone of inhibition: 16 mm) by disk diffusion method. Zones of inhibition of the essential oil were greater than corn oil against *E. coli* and *M. luteus*. MIC of the essential oil was found to be 2 µg/ml against S. Typhi, *E. faecalis* and *M. luteus.* Similar to the findings by disk diffusion method, the essential oil revealed stronger effect with MICs of the essential oil smaller than that of corn oil against *E. coli* and *M. luteus*.

In contrast to antibacterial and antifungal activities, studies investigating the antiviral activities of antimicrobial activities of various *Pimpinella* species are limited. Lee *et al.* (2011), isolated three antiviral and immuno-stimulating complexes identified as lignin-carbohydrate-protein complexes (LC1, LC2 and LC3) from the hot water extracts of *P. anisum* seeds using combination of anion-exchange, gel filtration and hydrophobic interaction column chromatography. The lignin-carbohydrate complexes included neutral sugars and uronic acids. All three LCs exerted antiviral activities against Herpes simplex type 1 and 2, cytomegalovirus and measles viruses. Additionally, respective selective toxicity was found for LC1 and LC3 against human coronaviruses and Coxsackie viruses. The antiviral activity was most probably due to interference with the adhesion of the virus to host cell and decrease in the infectivity of viruses which are two early phases of virus replication. The immunomodulatory effect of LCs were attributed to enhanced nitric oxide production, IL-1β and IL-10 production.

In a recent in silico study carried out in 2021, isovitexine, a flavone, of *P. anisum* was reported as the most potent ligands against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike proteins and main proteases which are potential target for treatment or vaccine discovery because they have indispensable role during SARS-CoV-2 replication (Kumar *et al.*, 2021).

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