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The Review on the Antimicrobial Potential of Maidenhair Fern, *Adiantum capillus-veneris* L.

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Abstract

Adiantum capillus-veneris L. or Maidenhair fern is a perennial fern that belongs to the family Pteridaceae. It is widespread in temperate and tropical regions with high humidity. *A. capillus-veneris* has a long history of medicinal use, and recent investigations suggest the presence of many bioactive compounds in this plant. This review debates the antimicrobial potential of *Adiantum capillus-veneris* in a comprehensive manner that includes data about the antibacterial, antifungal, and antiviral activity. Data regarding the antimicrobial potential of *A. capillus-veneris* were collected from scientific databases Web of Science, Scopus, PubMed, and Google Scholar. The largest number of reviewed studies were related to the antibacterial activity of extracts made from *A. capillus-veneris* plant. Mainly, leaves, stems, roots, and rhizomes were tested, while water, methanol, ethanol, ethyl acetate, and hexane were used as solvents. For the testing of antimicrobial susceptibility, standard tests were implemented, such as the disk-diffusion method, agar dilution method, and determination of MIC and MBC values. There are also studies testing the antibiofilm effects of the investigated plant. Our review showed that *A. capillus-veneris* exhibits large antibacterial potential, with the capacity to inhibit the growth of different bacteria, including multidrug-resistant strains. The antifungal and antiviral activity of the investigated plant was also recorded. This review summarized data regarding the antimicrobial potential of *A. capillus-veneris* and suggests that future phytochemical investigations of ferns may lead to the discovery of new therapeutic agents.

Keywords: *Adiantum capillus-veneris* L., antibacterial, antifungal, antiviral, plant antimicrobials.

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1. Introduction

Ferns are a plant group with worldwide distribution in different habitats, and the floristic wealth of pteridophytes is estimated to be 12.000 species, globally (Johnson et al, 2017). According to Kumar & Kumari (2023) pteridophytes are represented by 48 families with 587 genera in the world. The genus name *Adiantum* has etymological origin in the ancient Greek word "Adiantos", which could be translated as "unwetted" (Kumar & Kumari, 2023). Prado et al (2007) state that around 200 species were reported in the large and diverse genus *Adiantum*.

Adiantum capillus-veneris L. or Maidenhair fern is a delicate, perennial fern of ca. 35 centimeters in height, with a creeping rhizome (Sallam et al, 2019). Taxonomically, it belongs to the family Pteridaceae, subfamily Vittarioideae (Singh et al, 2020). The plant is widespread in regions with warm or tropical temperatures with high humidity (Kashkooe et al, 2021). Therefore, it could be found in different areas in southern Europe, the Atlantic coast of Ireland, and northern Africa (Boukada et al, 2022). Typical habitats are limestone cliffs away from direct insolation (Al-Snafi, 2015). Furthermore, the plant prefers well-drained, neutral, and alkaline soils, and it can grow in the semi-shade (Ansari & Ekhlasi-Kazaj, 2012).

Pteridophytes are indeed one of the oldest and most primitive vascular plant groups on earth, possessing leaves, roots, and erect stems (Kumar & Kumari, 2023). Interestingly, there are observations that pteridophytes are not infected with microbial pathogens, which could be related to their evolutionary success and the fact that they survived more than 350 million years (Johnson et al, 2017).

Historically, ferns have been known in folk medicine for more than 2000 years, and they are an indispensable part of many traditional medical practices and remedies due to the exploration and utilization of different species because of their beneficial properties (Baskaran et al, 2018). Numerous species of the genus

Adiantum are used in traditional medicine, such as *Adiantum philippense* L. (syn. *A. lunulatum* Burm), *A. caudatum* Klotzsch, *A. flabellulatum* L., *A. pedatum* L., *A. venustum* D. Don, *A. aethiopicum* L., *A. tenerum* Sw. (Brahmachari et al, 2003).

A. capillus-veneris is characterized by a long history of medicinal use. The medicinal parts of the plant are the leafy fronds, rhizomes, and roots (Boukada et al, 2022). The fresh and dried leaves are used as antidandruff, antitussive, astringent, demulcent, depurative, diuretic, emetic, emmenagogue, emollient, expectorant, galactagogue, laxative, pectoral, refrigerant, stimulant, sudorific and tonic. A tea or syrup of this plant is used to treat cough and bronchitis (Ansari & Ekhlasi-Kazaj, 2012), as well as for fever, pneumonia, mucous formation, diabetes, erysipelas, urinary insufficiency, and hepatitis (Yumkham et al, 2018; Kumar & Kumari, 2023). In general, the fresh plant is more effective, but it could be collected in the summer and dried for later use (Nazim et al, 2018).

1.1. Antimicrobial resistance (AMR)

According to Hernando-Amado et al (2019), antimicrobial resistance (AMR) is one of the major challenges to global health. It is estimated that around 750.000 annual deaths worldwide are caused by AMR (Chassagne et al, 2021) and this number is likely to reach 10 million annually by the year 2050 (O'Neill, 2016). AMR is a consequence of the microorganisms' ability to survive in the presence of drugs that would usually inhibit their growth (Founou et al, 2017).

The development of multidrug-resistant (MDR) microbial strains is related to the accumulation of various resistance mechanisms inside the same strain (Harbottle et al, 2006), and despite the production of new antibiotics, resistance to drugs increased (Hussain et al, 2014). Therefore, new anti-infective agents are needed to overcome the abovementioned issues (Thabit et al, 2015).

The acronym ESKAPE refers to bacteria recognized by The Infectious Disease Society of America and the American Society of Microbiology as very compelling in terms of the resistance exhibiting, and defined as a high priority for drug discovery. ESKAPE stands for *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanni*, *Pseudomonas aeruginosa*, and *Enterobacter* species (Boucher et al, 2009). Besides bacteria, other microbial pathogens such as fungi and viruses exhibit multidrug-resistance patterns and there is an emphasized need for adequate antimicrobial treatment. Due to the described reasons, recent studies are directed toward plant products, in order to identify and develop new antimicrobial agents with antifungal, antibacterial, and antiviral activities (Maiyo et al, 2010).

From ancient times plants and their products have been used in the promotion of human health, and modern findings recognize them as a valuable source of compounds with various biological potentials. There is also evidence that herbal medicines were used throughout history against different infectious diseases, in the form of crude plant extracts as well as pure compounds (Parekh & Chanda, 2007). The World Health Organization (WHO) states that 88% of the global population relies on traditional medicine (WHO, 2023) since that represents an easily available treatment method. The usage of plants in traditional medicinal practices is based on their capacity to inhibit the growth and virulence of numerous microbes (Khan et al, 2018), but at the same time, they have fewer side effects and decreased toxicity (Chai et al, 2013).

Secondary metabolites *per se* are synthesized by plants in order to overcome evolutionary challenges, for self-defense reasons, as well as for communication with other organisms in the ecosystems (Khan et al, 2018). Nevertheless, these compounds are involved in the development of new antimicrobial drugs of natural origin, since they are generally bioactive and even exhibit synergy with other secondary metabolites as a part of the plant's multicomponent defense system (Harvey et al, 2015). Novel studies showed that plants have a wide bioactive potential, particularly antimicrobial (Zhang et al, 2019).

This review debates the antimicrobial potential of *Adiantum capillus-veneris* in a comprehensive manner that includes data regarding antibacterial, antifungal, and antiviral activity, as well as the potential phytochemicals related to described effects.

2. Material and Methods

2.1. Literature search

The available data regarding the antimicrobial potential of *Adiantum capillus-veneris* L. were collected from scientific databases such as Web of Science, Scopus, PubMed, and Google Scholar. The search terms used for this review included: "*Adiantum capillus-veneris*", "antimicrobial activity", "antimicrobial resistance", "plant antimicrobials", "phytochemical composition", and "traditional use". This article represents an overview of the current state of knowledge about the antimicrobial properties of *Adiantum capillus-veneris* L.

3. Results

3.1. Antimicrobial potential of Adiantum capillus-veneris

According to Chassagne et al. (2021) who systematically examined plants with antibacterial activity, only four families of ferns: Polypodiaceae, Pteridaceae, Salviniaceae, and Lygodiaceae were noted with antibacterial effects. Additionally, in each of these families, a single species was studied. Recently, there has been increased interest in the antimicrobial properties of ferns, because available data confirms large potential in that sense, especially when compared to the higher plants, which could be related to the presence of numerous defensive biochemical constituents (Rani et al, 2010). Although the genus *Adiantum* comprises many species, only a few are studied in terms of biological activity, while others are still unexplored (Brahmachari et al, 2003).

3.2. Antibacterial activity

The study of Mahmoud et al (1989) investigated the antibacterial effects of aqueous and methanolic extracts made from *A. capillus-veneris* aerial parts and obtained results showed inhibition of *Bacillus subtilis*, *Proteus vulgaris*, and *Staphylococcus aureus* by crude extracts obtained from organic solvents, while water extract did not cause inhibition. Gram-negative species included in the investigation, *Pseudomonas aeruginosa* and *Escherichia coli* were resistant to the tested substances.

The antibacterial activity of the active oils from the *A. capillus-veneris* leaves is proven against *Klebsiella pneumoniae*, *Pseudomonas* sp., *Salmonella typhi*, *S. aureus*, and *Streptococcus pyogenes* (Victor et al, 2003). There are also data regarding the antibacterial activity of particular *A. capillus-veneris* compounds: adiantone, 22,29ξ-Epoxy-30-norhopane-13β-ol, fern-9(11)-en-28-ol, fern-9(11)-en-25-oic acid, fern-9(11)-en-6α-ol, fern-9(11)-ene, filicenol B, and 6-oxofern-9(11)-ene against Gram-negative bacteria *E. coli*, *P. aeruginosa*, *S. typhi,* and Gram-positive bacteria *Bacillus sphaericus*, B. subtilis, and *S. aureus* (Reddy et al, 2001).

Essential oil of the *A. capillus-veneris* is also investigated by Nasrollahi et al (2022) in terms of antibacterial activity, and inhibition is proven against *S. aureus*, *S. pyogenes*, and Diphteroid. Observed effects are probably related to the detected chemical constituents: carvone, carvacrol, hexadecanoic acid, hexahydrofarnesyl acetone, and n-nonanal. These findings are in accordance with the previous study of Khodaie et al (2015) that identified several phytochemicals in the volatile oil of

A. capillus-veneris: carvone, carvacrol, hexadecanoic acid, thymol, hexahydrofarnesyl acetone, and n-nonanal related to its antioxidant capacity.

Guha et al (2004) observed inhibition of *E. coli*, *S. aureus*, *Agrobacterium tumefaciens*, *Salmonella arizonae*, and *S. typhi* by the aqueous and alcoholic leaves extract of *A. capillus-veneris*. Results of Parihar et al (2010) confirmed that the aqueous and alcoholic leaves extract of *A. capillus-veneris* are effective against *A. tumefaciens*, *E. coli*, *S. arizonae*, *S. typhi,* and *S. aureus*.

The broad antibacterial activity of *A. capillus-veneris* methanolic extract is noted by Singh et al (2008), who also determined values of the minimum inhibitory (MIC) and minimum bactericidal concentrations (MBC). Low MIC values are given against *Streptococcus pneumoniae* (7.81 µg/ml), and *E. coli* (0.48 µg/ml). Similar findings are presented in the work of Pan et al (2011), where the MIC of *A. capillus-veneris* sample against *E. coli* was very low, 0.97 µg/ml. Besides the already mentioned bacteria, Shirazi et al (2011) observed the antibacterial activity of *A. capillus-veneris* methanolic extract against *Helicobacter pylori*. Ethanolic extracts of *A. capillus-veneris* were investigated by Nyarko et al (2012) and antibacterial activity is noted against *Proteus mirabilis*, *K. pneumoniae*, and *S. aureus*. Further phytochemical investigation revealed the presence of sugars, flavonoids, triterpenoids, and steroids in the tested sample.

Ishaq et al (2014) presented a study of the antibacterial potential of different *A. capillus-veneris*, namely aqueous, methanolic, ethanolic, ethyl acetate, and hexane extracts derived from leaves, stems, and roots of the plant. The investigation included MDR strain and gave a comparative illustration of the activity of the following commercial antibiotics against tested strains: amoxicillin, ampicillin, cefaclor, ciprofloxacin, cephradine, cefotaxime, cefoperazone-sulbactam, ceftriaxone, gentamicin, moxifloxacin, nalidixic acid, tetracycline, norfloxacin, and trimethoprim-sulfamethoxazole. Bacteria included were: *Citrobacter freundii*, *E. coli*, *Providencia* sp., *K. pneumoniae*, *P. vulgaris*, *S. typhi*, *Shigella* sp., *Vibrio cholerae*, *P. aeruginosa*, and *S. aureus*. Overall results suggested higher growth inhibition of bacteria caused by the leaves extracts, excluding the hexane leaves extract, that achieved inhibition only of *E. coli*, *P. aeruginosa*, and *Shigella* sp. From all stem extracts, methanolic and ethanolic extracts had the broadest activity, while hexane root extract was inactive against tested strains. This study detected the presence of the following phytochemicals: alkaloids, flavonoids, tannins, saponins, terpenoids, steroids, glycosides, and reducing sugar.

In a similar study by Hussain et al (2014), leaves and stem extracts of *A. capillus-veneris* achieved antibacterial activity against the following MDR strains: *C. freundii*, *E. coli*, *Providencia* sp., *P. aeruginosa*, *S. aureus*, *K. pneumoniae*, *P. vulgaris*, *S. typhi*, *Shigella* sp., and *V. cholerae*. Medrar et al (2014) demonstrated that the aqueous and methanolic extracts of *A. capillus-veneris* showed comparatively higher competence against *P. aeruginosa* in comparison to the drug amoxicillin.

Antibacterial activity of the methanolic extract of *A. capillus-veneris* is described against clinical pathogens in the investigation of Hussein et al (2016), more precisely against *B. subtilis*, *P. aeruginosa*, *Streptococcus faecalis*, *S. typhi*, and S*. aureus*, with *S. faecalis* being the most sensitive species to the tested substance. Major phytochemical compounds identified in the investigated extract that possess antibacterial activity were: d-Mannose, imidazole-4-carboxylic acid, 2-fluoro-1-methoxymethyl-ethyl ester, D-Carvone, Pyrrolizin-1,7-dione-6-carboxylic acid, methyl (ester), phenol,2-methyl-5-(1-methylethyl)-, tetraacetyl-d-xylonic nitrile, curan-17-oic acid, 2,16-didehydro-20-hydroxy-19-oxo, methyl ester, tributyl acetylcitrate, 10,13-dioxatricyclo[7.3.1.0(4,9)]tridecan-5-ol-2-carboxylic acid, 9-Octadecenamide,(Z)-.

Additionally, other studies confirmed the antibacterial potential of different *A. capillus-veneris* extracts against *B. subtilis*, *P. vulgaris*, *S. aureus*, *A. tumefaciens*, *E. coli*, *S. arizonae*, and *S. typhi*, *S. enterica*, with various patterns of solvent-dependent and species-specific activity (Moradi et al, 2018; Nermin & Sadik, 2018; Parihar et al, 2018; Rautray et al, 2018). Moradi et al (2018) observed the high flavonoid content in the investigated sample (57.2 mg/ml). Additionally, other secondary metabolites are also described such as triterpenes, flavonoids, phenylpropanoids, carotenoids, quercetin, rutin, shikimic acid, violaxanthin, and zeaxanthin (Rautray et al, 2018).

In the comprehensive study of Khan et al (2018) it was shown that ethanolic and aqueous extracts of *A. capillus veneris* exhibited growth inhibition ≥50% (IC_{50}) against ESKAPE pathogens *E. faecium* and *S. aureus* when screened at 256 µg/ml of extract. Furthermore, regarding the antibiofilm activity, statistically significant *quorum sensing* inhibition was observed in the case of *S. aureus*.

Boukada et al (2022) investigated the antibacterial properties of A*. capillus-veneris* hydro-methanolic extract and noted growth inhibition of *E. coli*, *S. pneumoniae*, and *S. aureus*. In this case, antibacterial effects are in relation to the presence of phenolic compounds that use different mechanisms to kill bacteria, including the inhibition of nucleic acid synthesis, disruption of the plasma membrane, as well as the enzymatic and energy metabolism of the bacterial cell. In the investigated sample, the most abundant compounds were flavonoids: quercetin 3-O-glucoside and kaempferol 3-O-glucoside; and phenolic acids: 3,5-Di-O-caffeoylquinic acid and hydroxycinnamic derivative. This is in accordance with the previous results (Yuan et al, 2012; Al-Hallaq et al, 2015; Zeb & Ullah, 2017).

Yazdani & Kashi (2021) performed an investigation on the antibacterial potential of different *A. capillus-veneris* extracts, including water, methanolic, and hexane extracts of the leaves. The antibacterial potential is confirmed for *B. subtilis*, *Staphylococcus epidermidis*, *S. aureus*, *E. coli*, *Shigella dysenteriae*, *P. vulgaris*, *P. aeruginosa*, with different diameters of the inhibition zones, and MIC values ranging from 125 to 500 µg/ml of the extract. The high total phenolic content and considerable amounts of phenols and flavonoids are detected in the sample. The plant extracts have contained saponins, triterpenes, alkaloids, glycosides, tannins, and flavonoids.

Since the selection of the active compounds in medicinal plants is of great interest and may serve as a promising source of new prototype antibiotics and have great therapeutic potential against infectious diseases (Boukada et al, 2022), many investigations are performed in order to identify bioactive compounds of *A. capillus veneris*. Al-Snafi (2015) highlighted the importance of flavonoids, triterpenoids, oleananes, phenylpropanoids, carbohydrates, and carotenoids in this plant species. Many triterpenoids were isolated from the leaves, such as 21-hydroxyadiantone, adiantoxide, isoadiantone, isoglaucanone, isoadiantol, hydroxyadiantone, olean-12-en-3-one, olean-18-en-3-one, fern-9(11)-ene, fern-α-7,9(11)-diene, 7-fernene, hop- 22(29)-ene, filic-3-ene, neohop-12-ene, pteron-14-en-7α-ol, fern-9(11)-en-3α-ol, fern-7-en-3α-ol, adian-5(10)-en-3α-ol, adian5-en-3α-ol, fern-9(11)-en-28-O, fern-9(11)-en-12-β-ol, and 4-α-hydroxyfilican-3-one (Berti et al, 1969; Marino et al, 1989; Shiojima et al, 1992; Shiojima et al, 1993; Ageta et al, 1994; Shiojima et al, 1995; Nakane et al, 1999; Abdel-Halim et al, 2002; Nakane et al, 2002; Shinozaki et al, 2008). The leaves also contain flavonoids such as rutin, quercetin, quercetin-3-O-glucuronide, isoquercetin, nicotiflorin, naringin, astragalin, populnin, procyanidin, prodelphinidin, and kaempferol-3-sulfate (Akabori & Hasagava, 1969; Cooper-Driver & Swain, 1977; Imperato, 1982; Ibraheim et al, 2011).

Although the chemical composition of plant extracts could be influenced by the cultivation method, the phenological stage, the nature of the soil, the climate at the time of sampling, as well as the constitution of the sample (Boukada et al, 2022), it is possible to establish major bioactive phytochemical compounds of some species. According to Singh et al (2020) in *A. capillus-veneris*, these are 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, Acetic acid, 3,7,11,15-tetramethyl-hexadecyl ester, Docosane, 1,2-Benzenedicarboxylic acid, butyloctyl ester, phthalic acid, butyl octyl ester, Hexadecanoic acid, ethyl ester, 9-Octadecenoic acid, Di-n-octyl phthalate, and Tetracontane.

3.3. Antifungal activity

So far, antifungal activity of *A. capillus-veneris* preparations is confirmed against different fungal species, starting with one of the oldest available records in Mahmoud et al (1989), who described antifungal effects of the methanolic extract against *Candida albicans*. Singh et al (2008) also recorded antifungal activity against *C. albicans*, with a MIC value of 3.90 µg/ml, as well as the activity toward *Cryptococcus albidus*, *Trichophyton rubrum*, *Aspergillus niger*, *A. flavus*, *A. terreus*, *A. spinulosus*, and *A. nidulans*. Preliminary phytochemical screening showed the presence of flavonoids and tannins.

Together with *C. albicans*, *A. flavus*, and *A. niger*, Ishaq et al (2014) presented the study with the described antifungal activity of various *A. capillus-veneris* extracts against *Pythium* sp. and *Trichoderma* sp. Inhibition is achieved with all tested extracts, but nevertheless, hexane extract exhibited very low antifungal action.

Similarly, Yazdani & Kashi (2021) conducted results regarding the antifungal effects of aquatic, methanolic, acetate, and hexane extracts of the leaves and stems of *A. capillus-veneris* against *C. albicans*. Their results suggested broader activity of the leaves extracts in comparison to those made from stems, as well as that hexane extracts performed relatively low activity.

The aqueous extracts and phenols extracted from gametophytes of *A. capillus-veneris* performed antifungal activity against *A. niger* and *Rhizopus stolonifer* (Piyali et al, 2005).

An investigation by Hussein et al (2016) described the antifungal potential of the methanolic extract against the following subjects: *A. niger*, *A. terreus*, *A. flavus*, *A. fumigatus*, *C. albicans*, *Saccharomyces cerevisiae*, *Fusarium* sp., *Microsporum canis*, *Mucor* sp., *Penicillium expansum*, *Trichoderma viride*, *T. horzianum*, and *Trichophyton mentagrophytes*.

Rautray et al (2018) reported antifungal activity against *T. rubrum*, *Scedosporium apiospermum*, *A. fumigatus*, *A. niger*, and *A. flavus*, followed by the observation of Sallam et al (2019) who noted antifungal effects on *S. cerevisiae* and highlighted flavonoids, triterpenoids, phenylpropanoids, carbohydrates, carotenoids, and alicyclics as potential bioactive compounds of *A. capillus-veneris*.

3.4. Antiviral activity

Antiviral drugs are a specific class of medicines used for the treatment of viral infections. Since the viruses use the host's cell for replication, the design of a safe and effective antiviral drug is challenging (Kausar et al, 2021). There are some data regarding the antiviral properties of *A. capillus-veneris*. One of them refers to the *in vitro* antiviral activity of ethanolic extract made from a rhizome, that acts against vesicular stomatitis virus (Husson et al, 1986). Ansari & Ekhlasi-Kazaj (2012) noted that this particular activity could be related to the traditional usage of Maidenhair fern preparations in the treatment of respiratory and urinary infections.

Moradi et al (2017; 2018) investigated the antiviral potential of *A. capillus veneris* against Herpes simplex virus-1 and Influenza, but despite other observed bioactive properties, there was no antiviral activity. In contrast, there are recorded antiviral properties of this plant against the Tobacco mosaic virus (Biniaz et al, 2023). Since viruses don't act in a taxonomically limited host range, this observation could be promising in future investigations.

4. Conclusions

Our review showed that *A. capillus-veneris* exhibit large antibacterial potential, with the capacity to inhibit the growth of different Gram-positive and Gram-negative bacteria, including multidrug-resistant strains, as well as some species recognized as ESKAPE pathogens. The antifungal and antiviral activity of investigated plant was also recorded. Considering the growing emergence of antimicrobial resistance, the need for the identification and characterization of novel antimicrobial agents couldn't be overemphasized. Due to the fewer side effects, low toxicity, and variable phytochemical profile, plant products are a promising source of new antibacterial, antifungal, and antiviral compounds. Ferns are generally poorly investigated in antimicrobial terms when compared to angiosperms, but data presented in this review suggest that they should be a focus of such investigations. This review summarizes current knowledge on the antimicrobial potential of *A. capillus-veneris* and could be used as the starting point in future studies regarding the antimicrobial, phytochemical, toxicological, and molecular properties of ferns.

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