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FICUS MACROPHYLLA DESF. EX PERS. LEAVES (MORACEAE) POSSESS ANTIMICROBIAL POTENTIAL FOR THE PREVENTION OF BACTERIAL INFECTIONS: PRELIMINARY *IN VITRO* STUDY

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The aim of this study was to test the efficacy of ethanolic extract prepared from *Ficus macrophylla* Desf. Ex Pers. leaves against Gram-positive and Gram-negative bacteria in order to evaluate the possible use of this plant in the prevention of bacterial infections. The testing of the antibacterial activity of the plant extract was carried out *in vitro* by the Kirby-Bauer disc diffusion technique. Gram-negative bacteria *Klebsiella pneumoniae* (ATCC 700603), *Pseudomonas aeruginosa* (ATCC 27853), and *Escherichia coli* (ATCC 25922), as well as Gram-positive bacteria *Staphylococcus aureus* (ATCC 25923), methicillin-resistant *Staphylococcus aureus* (NEQAS 3679) and *Streptococcus pneumoniae* (ATCC 49619), as well as fungus *Candida albicans* locally isolated were used as test organisms. Our results revealed that the ethanolic extract of *F. macrophylla* leaves possessed mild activity against the Gram-positive and Gram-negative bacteria. However, *S. pneumoniae* and *E. coli* appeared to be less sensitive to the *F. macrophylla* extract. Thus, *F. macrophylla* possesses the medicinal potential for the therapy of bacterial infections induced by *S. aureus* and may be used as a natural antiseptic and antimicrobial agent in medicine. Moreover, the antibacterial activity of this plant would help for the development of a new alternative medicine system which has no adverse effects. Further investigation is necessary to identify those bioactive compounds, which will be a platform for clinical applications. Finally, we believe that these findings are important in order to evaluate the significance of collections of tropical plants maintained under glasshouse conditions at Botanical Gardens worldwide and to plan the conservation strategy by the establishment of national collections of plants with valuable characteristics with the prospects of their use as sources of antimicrobial agents.

Keywords: *Ficus macrophylla*, ethanolic extract, antibacterial activity, inhibition zone diameters, Kirby-Bauer disc diffusion method

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Introduction

The family Moraceae traditionally treated as a member of the order *Urticales* comprises 37 genera and 1,050–1,100 species worldwide, most of which are distributed in the tropics and subtropics. The Moraceae are largely woody and highly diverse in the morphology of both vegetative and reproductive structures. They include terrestrial trees, shrubs, climbers, hemi-epiphytes, and rarely subshrubs and herbs. Their leaves are usually alternate and then arranged in spirals or distichous, although some species have a characteristic phyllotaxis, which may differ between the main axis and lateral branches of a plant. The lamina is simple and entire in most of the species, sometimes more or less deeply lobed, and the latter can feature either only juvenile leaves or both juvenile and adult ones. The flowers are small, pedicellate or sessile, unisexual, and are arranged into inflorescences which typically occur in pairs in the leaf axils or (more rarely) are solitary and cauliflorous. The inflorescence of Moraceae is considerably diverse with regard to structure, shape, and degree of condensation and fusion. Two of its main types can be recognized, the one being largely bisexual and circular in outline and the other unisexual and elongate, racemose or spicate, although within these types variations occur. The fruits are drupaceous or achene-like. Among the members of the order, Moraceae are distinguished by the combination of milky latex, anatropous ovules, and apical placentation (Berg, 2001; Datwyler and Weiblen, 2004; Clement and Weiblen, 2009).

The pantropical genus *Ficus* L. is by far the largest in the family and includes approximately 750 species with the hotspot of species richness in SE Asia. Some *Ficus* species are reported to be among the oldest human food sources (Kislev et al., 2006).

The genus is represented by evergreen and (semi)deciduous trees, shrubs, and lianas, often with aerial adventitious roots. More than half of the species are hemi-epiphytes that start life as an epiphyte in the crown of another tree and then send roots down to the ground enveloping the trunk of the host tree. In the most extreme case, the adventitious roots growing down from the branches form additional woody trunks, enabling the tree to spread out laterally and cover a wide area (the banyan-type tree). The leaves are spirally arranged, distichous, (sub)opposite or subverticillate. The most striking feature of *Ficus* is the pollination syndrome based on the species-specific mutualism with insects from the family Agaonidae (Hymenoptera) commonly referred to as "fig wasps".

Flowering phenology is central to the ecology and evolution of most flowering plants. It was assumed that in highly-specific pollination systems, such as that involving fig trees (*Ficus* species) and fig wasps (Agaonidae), any mismatch in timing has serious consequences because the plants must balance seed production with the maintenance of their pollinator populations (Zhao et al., 2014).

The inflorescence represents an urceolate receptacle (called syconium or fig) with a narrow orifice (ostiole) at the top lined with numerous unisexual flowers. The ostiole functions as a passage for the fig wasps entering the syconium to pollinate flowers and lay eggs. Several types of flowers occur inside the figs, namely the long-styled pistillate "seed flowers" producing seeds, short-styled pistillate "gall flowers" targeted by the fig wasps to lay eggs in, and staminate flowers from which the pollen attaches to newly born wasp individuals aiming to leave the syconium. Figs of monoecious species contain all the three flower types, the long style of seed flowers preventing wasps from laying eggs in. In (gyno-)dioecious species, syconia developed on separate plants contain either only the seed flowers or both the gall and staminate ones, and pollination of the "right" seed-producing flowers appears rather accidental due to the wasps being incapable of distinguishing between these syconia types. The figs are also featured in a pronounced protogyny when the pistils precede anthers in maturation; its functional role is to enable pollination by one generation of fig wasps and collecting pollen by the next one that came out from the gall flowers. The fruitlets of *Ficus* function mostly as seeds of a fleshy fruit (mature syconium), which appears the functional entity for dispersal by fruit-eating animals (Cook and Rasplus, 2003; Berg and Corner, 2005).

Along with being an object of extreme interest for researchers during the last two centuries, *Ficus* has a long history of use by humans as a food source, in medicine, planting, and other industries and fields of human activity, partly owing to its great diversity and wide distribution range. Among popular ethnomedicinal uses of *Ficus* are treatments of skin damages, disorders of the digestive system and related organs, and parasitic infections. Besides these, the range of healing targets for particular *Ficus* species compiled from local medicines can be competitive with that of broad-spectrum traditional remedies (Lansky and Paavilainen, 2011).

Over the past several decades, the incidence of nosocomial fungal infections (i.e., invasive fungal infections acquired in a healthcare-associated setting) has dramatically increased. Factors responsible for the rise of these infections include aging populations in countries with advanced medical technologies, the resultant increase in the incidence of many cancers, increasingly intensive myeloablative therapies for these cancers, increasingly intensive care for critically ill patients (Perlroth et al., 2007).

Among the species of genus *Ficus*, *Ficus macrophylla* Desf. ex Pers. (Moreton Bay fig) is a monoecious evergreen tree reaching up to 30 m in height, hemi-epiphytic or terrestrial, with glabrous or puberulous leafy twigs, native to eastern Australia (Figure 1).

This species normally starts life in the forest as an epiphyte growing on the branch of another tree. As it grows larger, it sends down aerial roots which root into the ground below, providing the plant with extra nutriment and allowing it to out-compete the host tree, eventually smothering it. The trees gradually reach large proportions, with immense buttresses, trunks up to 8 meters or more in circumference, and branches both high and spreading. Aerial roots (if produced) grow mainly from large, framework branches near the ground, and these may produce a few extra trunks or props. Its leaves are 7–30 cm long and 4–13 cm wide, alternate, ovate to elliptic, with acute to the obtuse apex and rounded to obtuse base. The upper leaf surface is glabrous, glossy green, sometimes puberulous on the midvein, while the lower surface is mostly silvery to rusty or brownish, tomentose with weak ferruginous hairs, rarely glabrous. The syconia are pedunculate, spheroid to cubical or oblong, 18–25 mm long and 15–24 mm in diameter, puberulous to pilose, glabrescent, red to red-brown with pale spots when mature (Dixon, 2001).

Figure 1 A specimen of *Ficus macrophylla* Desf. Ex Pers. at Botanic Garden of Ivan Franko Lviv National University (Lviv, Ukraine) (A, B), branch with leaves (C), adaxial and abaxial leaf surface (D, E, F)

Moreover, Australian Aborigines found a myriad of uses for the *F. macrophylla* long before European settlement. The most obvious use is the year-round fruit, the figs. Next, the inner bark or roots were used to make a sturdy cloth and cord for bags as well as woven fishing nets. Also, the branches, as well as the bark, were used to make waterproof dug-out canoes. Lastly, the milky sap, which exudes when the tree is cut was prepared as a medicine to treat infections and to dress small wounds (http://hpathy.com/).

The literature survey indicates that the genus of *Ficus* has multiple pharmacological actions that include antidiabetic, antioxidant, antidiarrhoeal, anti-inflammatory, antipyretic, antifungal, antibacterial, hypolipidemic, anti-filarial, and hepatoprotection (Yadav et al., 2015). Moreover, their leaves are used for alleviation of infectious and inflammatory conditions in many countries (Yadav et al., 2015). Widespread medicinal use and significant biological activities of the extracts from the plants of genus *Ficus* justified a continued investigation of *F. macrophylla*. Based on the above considerations, the aim of this study was to test the efficacy of ethanolic extract prepared from *F. macrophylla* leaves against Gram-positive and Gram-negative bacteria to evaluate the possible use of this plant in the prevention of bacterial infections.

Material and methods

Plant materials

The leaves of *F. macrophylla* were sampled in M.M. Gryshko National Botanic Garden (Kyiv, Ukraine) and Botanic Garden of Ivan Franko National University in Lviv (Lviv, Ukraine). The whole collections of tropical and subtropical plants both at M.M. Gryshko National Botanic Garden and Botanic Garden of Ivan Franko National University in Lviv (including *Ficus* spp. plants) have the status of a National Heritage Collection of Ukraine and are supported through State funding (Buyun et al., 2018). At the M.M. Gryshko National Botanic Garden, the plant of *F. macrophylla* has been in cultivation since 1950. The species author abbreviations were followed by Brummitt and Powell (1992).

Preparing Plant Extracts

The sampled leaves of *F. macrophylla* were brought into the laboratory for antimicrobial studies. Freshly collected leaves were washed, weighed, and homogenized in 96% ethanol (in proportion 1 : 10) at room temperature. The extract was then filtered and investigated for their antimicrobial activity. The extract was stored at 4 °C until use.

Bacterial strains

The testing of the antibacterial activity of the plant extract was carried out *in vitro* by the Kirby-Bauer disc diffusion technique (Bauer et al., 1966). Gram-negative bacteria *Klebsiella pneumoniae* (ATCC 700603), *Pseudomonas aeruginosa* (ATCC 27853), and *Escherichia coli* (ATCC 25922), as well as Gram-positive bacteria *Staphylococcus aureus* (ATCC 25923), methicillin-resistant *Staphylococcus aureus* (NEQAS 3679) and *Streptococcus pneumoniae* (ATCC 49619), as well as fungus *Candida albicans* locally isolated were used as test organisms. The clinical strain of *C. albicans* was also used in this study. *C. albicans* were differentiated from other *Candida* and *Cryptococcus* species by its ability to grow on the Levine formula of EMB agar and to produce germ tubes within 3 h, and pseudohyphae and budding cells at 18–24 h when incubated at 35 °C in 5–10% CO_2. The addition of tetracycline to the Levine formulation aids in the selection of *C. albicans* from clinical sources that are contaminated with bacteria. Susceptibility testing of the isolate was performed by disk diffusion according to the Guidelines of Clinical and Laboratory Standard Institute (CLSI).

Evaluation of Antibacterial Activity of Plant Extracts by the Disk Diffusion Method

Strains tested were plated on TSA medium (Tryptone Soy Agar) and incubated for 24 hr at 37 °C. Then the suspension of microorganisms was suspended in sterile PBS and the turbidity adjusted equivalent to that of a 0.5 McFarland standard. The antimicrobial susceptibility testing was done on Muller-Hinton agar by the disc diffusion method (Kirby-Bauer disk diffusion susceptibility test protocol). Muller-Hinton agar plates were inoculated with 200 µl of standardized inoculum (10^8 CFU/mL) of the bacterium and spread with sterile swabs.

Growth from freshly subcultured *C. albicans* isolates was suspended in 10 mL of sterile saline to obtain turbidity of 0.5 McFarland standard. Using a sterile swab, the Sabouraud dextrose agar plates were evenly inoculated with the *C. albicans* suspension. The plates were then incubated at 27 °C for 48 h. The antifungal activity was evaluated by measuring the diameter of inhibition zones (mm). Each test was repeated eight times.

Sterile filter paper discs impregnated by extract were applied over each of the culture plates, 15 min after bacteria suspension was placed. A negative control disc impregnated by sterile ethanol was used in each experiment. After culturing bacteria on Mueller-Hinton agar, the disks were placed on the same plates and incubated for 24 hr at 37 °C. The assessment of antimicrobial activity was based on the measurement of the diameter of the inhibition zone formed around the disks. The diameters of the inhibition zones were measured in millimeters and compared with those of the control and standard susceptibility disks. The activity was evidenced by the presence of a zone of inhibition surrounding the well.

Statistical analysis

Zone diameters were determined and averaged. Statistical analysis of the data obtained was performed by employing the mean ± standard error of the mean (S.E.M.). All variables were randomized according to the phytochemical activity of extract tested. All statistical calculation was performed on separate data from each bacterial and fungal strains. The following zone diameter criteria were used to assign susceptibility or resistance of bacteria to the phytochemicals tested: Susceptible (*S*) ≥15 mm, Intermediate (*I*) = 10–15 mm, and Resistant (*R*) ≤10 mm (Okoth et al., 2013).

Results and discussion

The results of the antimicrobial activity of ethanolic extract obtained from *F. macrophylla* leaves are presented in Figure 2 and 3. The antibacterial activity against each bacterium was observed to be varied.

In particular, our results revealed that the ethanolic extract of *F. macrophylla* leaves possessed mild activity against the Gram-positive bacteria (14.06 ±0.67 mm inhibition zone diameter for *S. aureus* and 12.5 ±1.61 mm methicillin-resistant *S. aureus*), the Gram-negative bacteria (10.88 ±0.54 mm for *K. pneumoniae*, 10.19 ±0.25 mm for *P. aeruginosa*) and fungus strain (10.13 ±0.74 mm for *C. albicans*) (Figure 2). However, *S. pneumoniae* and *E. coli* appeared to be less sensitive to the *F. macrophylla* extract; the inhibition zones were 9.75 ±0.58 mm for *E. coli* 9.0 mm and 9.5 ±0.49 mm for *S. pneumoniae*, respectively (Figure 2).

In agreement with the results obtained from the present study, previous studies undertaken by numerous researchers have found that various *Ficus* species possess noticeable antibacterial activity against bacterial and fungus strains. According to Atindehou et al. (2002) tested crude ethanol extracts from 115 plant species against Gram-negative bacteria (*E. coli* and *P. aeruginosa*), Gram-positive bacteria (*Enterococcus faecalis* and *S. aureus*), and fungi (*Candida albicans* and *Cladosporium cucumerinum*). Among the examined plants, there were three *Ficus* species, namely *F. exasperata*, *F. mucuso*, and *F. sur*. The Gram-negative bacteria appeared unaffected by any plant extract tested, whereas the Gram-positive bacteria and fungi were inhibited by at least several plant species. Among *Ficus* species tested, *F. exasperata* and *F. mucuso* had no significant effect on any microorganism, while *F. sur* appeared among the most active plant species against Gram-positive bacteria. No effect was shown for *F. sur* against *C. albicans*.

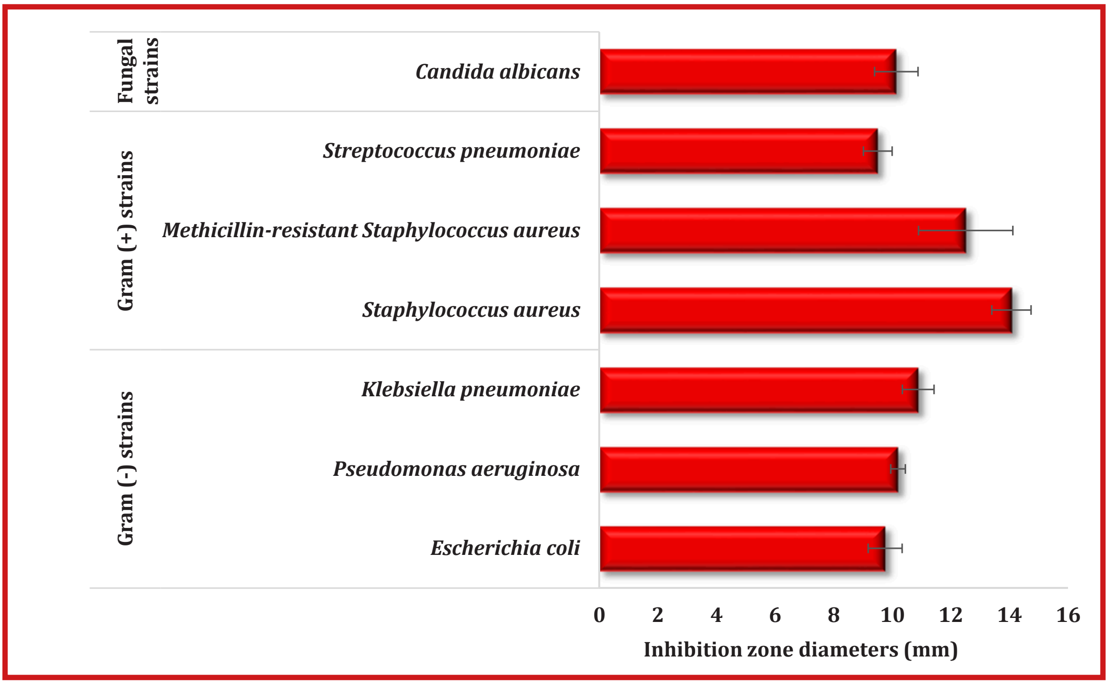

Figure 2 Antimicrobial activity of the ethanolic extract obtained from *Ficus macrophylla* Desf. Ex Pers. leaves against bacterial and fungal strains measured as inhibition zone diameter (M ±m, *n* = 8). The data were presented as the mean ± the standard error of the mean (S.E.M.)

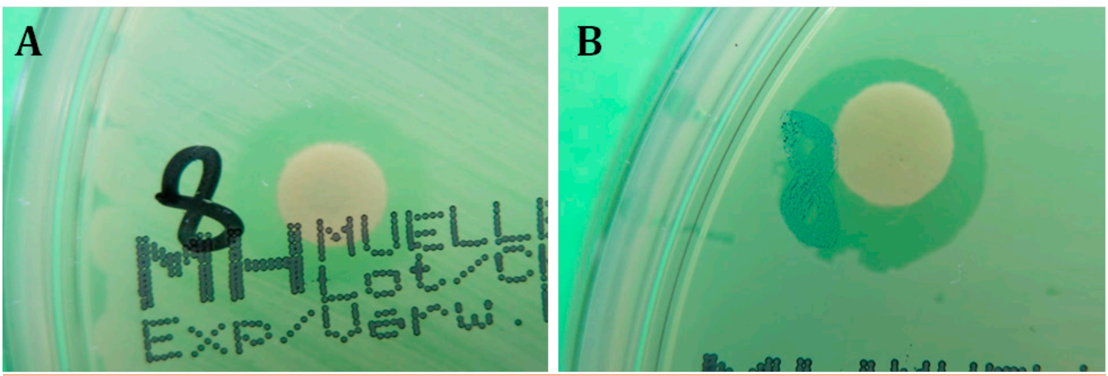

Figure 3 A disc diffusion assay plate showing the halos in the bacterial lawn resulting from the antibacterial activity of the ethanolic extract of *Ficus macrophylla* leaves against *Escherichia coli* (A) and *Pseudomonas aeruginosa* (B)

Antifungal activity of African plant methanol extracts against *Cryptococcus* neoformans and five *Candida* species (*C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*) analyzed by Hamza et al. (2006) showed *C. albicans* among the least susceptible pathogens. The stem bark extract from *F. sur* was ineffective against all tested organisms.

Many studies have demonstrated that plants belonging to the *Ficus* genus possess antibacterial activity. For example, Steenkamp et al. (2007) tested a wide spectrum of South African medicinal plant species for *in vitro* activity of their crude methanol and water extracts (of bark, roots, and fruits) against *Candida albicans* standard strain (ATCC 10231) and five clinical isolates (U1, U7, M42, M43, and M44). Among *Ficus* species examined, whose fruits were analyzed, *F. capensis* Thunb. (currently *F. sur* Forssk.) extracts showed no effect and *F. sycomorus* L. water extract was only active against two *Candida* isolates (M42 and M43; MIC 3,72 mg/ml). Samie and co-workers (2010) reported no effect of *F. sycomorus* bark acetone and hexane extracts against *C. albicans* as well as other fungi studied (i.e., *C. krusei* and *Cryptococcus* neoformans). The authors suggested such a discrepancy with the study of Steenkamp et al. (2007) to have resulted from the use of solvents of opposite polarity (hence this feature may potentially influence the effectiveness of antimicrobial agents), phytochemical differences in plant parts used, and geographical location of specimens sampled.

On the other hand, Kubmarawa and co-workers (2007) carried out an antimicrobial and phytochemical screening of 50 Nigerian plant species ethanolic extracts, among which were five species of *Ficus* (i.e., *F. abutifolia* (Miq.) Miq., *F. platyphylla* Del., *F. polita* Vahl, *F. sycomorus* L., and *F. thonningii* Blume). Microbial strains used in the study were *Bacillus subtilis* NCTC 8236, *E. coli* ATCC 9637, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 13709, and *Candida albicans* ATCC 10231. *Ficus* stem bark extracts demonstrated comparatively low antimicrobial activity, with the broadest activity spectrum being of *F. thonningii* extract (active against all microorganisms except *P. aeruginosa* and *S. aureus*). Extracts from *F. polita* and *F. sycomorus* showed no activity at all. *C. albicans* showed generally low susceptibility compared to other organisms tested. Among *Ficus* species, only *F. thonningii* extract affected *C. albicans* (with MIC value of 1.0 mg/ml). Phytochemical analysis revealed the presence of only saponins and volatile oil in *F. thonningii* extract and saponins and flavonoids in *F. polita* extract, while richer chemical content was found in *F. abutifolia* (tannins, alkaloids, and volatile oil), *F. platyphylla* (saponins, flavonoids, alkaloids, and volatile oil), and *F. sycomorus* (glycosides, tannins, flavonoids, and volatile oil) extracts. However, the authors do not make any speculations regarding the contribution of particular chemical classes to the antimicrobial activity of plant extracts tested. Authors also suggest the presence of some compound classes (such as alkaloids) in plants to be affected by climatic and environmental factors.

A number of experimental insights have elucidated the antimicrobial and antifungal efficacy of extracts derived from various organs of *Ficus* plants. Assessment of antimicrobial activity of the methanolic extract, its fractions and isolated compounds from *F. polita* Vahl. roots against a number of microbe strains (*Candida albicans* ATCC9002, *Escherichia coli* ATCC8739 and AG100, *Klebsiella pneumoniae* ATCC11296, *Providencia smartii* ATCC29916, *Pseudomonas aeruginosa* PA01, *Salmonella typhi* ATCC6539, and *Staphylococcus aureus* ATCC25922) revealed that *C. albicans* susceptible to the crude extract and two its fractions, namely hexane 100% and Hex-EtOAc 75%, with MICs 64, 32, and 64 μg/ml respectively (Kuete et al., 2011). Ethyl acetate and hexane-ethyl acetate fractions, as well as isolated compounds (the latter showing relatively high inhibition of tested bacteria), appeared the least effective against *C. albicans* with MICs 128 μg/ml and higher.

The microbial activity of ethyl acetate, methanol and aqueous extracts of leaves of *Ficus arnottiana* Miq. was evaluated for potential antimicrobial activity against medically important bacterial and fungal strains: Gram-positive – *Staphylococcus aureus*, *Bacillus subtilis*; two Gram-negative *Escherichia coli*, *Pseudomonas aeruginosa* human pathogenic bacteria; and two fungal strains *Fusarium solanii*, *Candida albicans* (Kaur and Singh, 2016).

The development of antifungal agents to clinical use is particularly challenging due to significant commonality in the molecular targets expressed by eukaryotic fungal and mammalian cells. Many compounds with potent antifungal activity are therefore unacceptably toxic to humans. The lack of emerging therapeutic options is particularly concerning in an era of increasing antifungal resistance. Thus, there is a pressing need for innovative strategies to prevent and treat fungal OIs, particularly among the most vulnerable, immunosuppressed patients (Eades and Armstrong-James, 2019).

Supposedly, the broad antibacterial activities of this extract could be a result of the plant secondary metabolites. The phytochemical screening on genus *Ficus*, reveals the presence of sterols and/or terpenes (Kuo and Li, 1997; Kuo and Chaiang, 1999), coumarins (Chunyan et al., 2009), furanocoumarin glycosides (Chang et al., 2005), isoflavones (Li and Kuo, 1997), lignans (Li and Kuo, 2000), phenolic acids (Oliveira et al., 2009), and chromone (Basudan et al., 2005).

In general, *Ficus* species are rich sources of polyphenolic compounds. In particular, flavonoids and isoflavonoids are responsible for the extract‘s strong antioxidant activity that may be useful in preventing diseases involving oxidative stress (Sirisha et al., 2010). All the detected phenolic acids are known to have antimicrobial and antioxidant properties (Jaafar et al., 2012). The antimicrobial property of *F. macrophylla* extract may be due to its constituents. As it was suggested by Kumar and Pandey (2013), antibacterial flavonoids might be having multiple cellular targets, rather than one specific site of action. One of their molecular actions is to form a complex with proteins through nonspecific forces such as hydrogen bonding and hydrophobic effects, as well as by covalent bond formation. Thus, their mode of antimicrobial action may be related to their ability to inactivate microbial adhesins, enzymes, cell envelope transport proteins, and so forth. In addition, lipophilic flavonoids may also disrupt microbial membranes (Kumar and Pandey, 2013).

It was evidenced that phytochemicals are able to inhibit peptidoglycan synthesis, damage microbial membrane structures, modify bacterial membrane surface hydrophobicity and also modulate quorum-sensing (QS) (Rasooli et al., 2008).

Conclusions

To conclude, the ethanolic extract obtained from *F. macrophylla* leaves showed varying inhibitory activities against all the test organisms. *F. macrophylla* possesses the medicinal potential for the therapy of bacterial infections induced by *S. aureus* and may be used as a natural antiseptic and antimicrobial agent in medicine. Moreover, the antibacterial activity of this plant would help for the development of a new alternative medicine system which has no adverse effects. Further investigation is necessary to identify those bioactive compounds, which will be a platform for clinical applications. Additionally, we have to keep in mind that, even though we have revealed potent *in vitro* antimicrobial activity of *F. macrophylla* extract for certain bacteria, it may not be expressed *in vivo*.

Finally, these findings are important in order to evaluate the significance of collections of tropical plants maintained under glasshouse conditions at Botanic Gardens worldwide and to plan the conservation strategy by the establishment national collections of plants with valuable characteristics with the prospects of their use as sources of antimicrobial agents.

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