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Antimicrobial Activity of Selected Alien Plants

Overview of The Dissertation Thesis

Prague, 2017

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FAKULTA ŽIVOTNÍHO PROSTŘEDÍ

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Czech University of Life Sciences Prague

Faculty of Environmental Sciences

Department of Applied Ecology

Ph.D. Thesis

Antimicrobial Activity of Selected Alien Plants

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ABSTRACT

For decades, plants and their bioactive compounds have been shown to possess various biological activities including but not limited to antimicrobial activities. In this dissertation thesis, several alien plants were investigated for their antimicrobial inhibitory properties against various plant and human pathogens. The results showed that the ethanolic extracts of *Ecballium elaterium*, *Plumbago indica*, *Crisium arvense*, *Stellaria pallida* and *Atriplex sagittata* were the most effective plants against *Fusarium oxysporum* and *Blumeria graminis* at MIC value of 156 µg/mL, while against *Erwinia amylovora* and *Pseudomonas syringae* showed antimicrobial inhibitory properties at MIC value of 220 µg/mL. Plumbagin, the major active compound of *Plumbago indica* L. exerted inhibitory effect against all *Candida albicans* strains with MICs values ranging from 7.41 to 11.24 µg/mL. The additive effect of plumbagin when combined with amphotericin B at concentrations of (0.12, 0.13 and 0.19, 1.81 µg/mL, respectively) was obtained against five of seven strains tested with ΣFIC ranging from 0.62 to 0.91. In addition, plumbagin was found to be used safely for topical application when combined with amphotericin B at concentrations corresponding to the additive effect. Plumbagin exerted anti-HCV activity compared with that of telaprevir with IC_{50} values of 0.57 and 0.01 µM/L, respectively and selectivity indices SI= 53.7 and SI= 2127, respectively. Cucurbitacin B (Cuc B), an active compound of *Ecballium elaterium* exerted direct growth-inhibitory activity against all *Staphylococcus aureus* (*S. aureus*)

strains tested with MICs values ranging from 0.15 to 0.44 µg/mL, as well as synergy effect with tetracycline or oxacillin against four of six *S. aureus* strains tested (ΣFIC ranging from 0.29 to 0.43). Cuc B showed remarkable anti-HSV-1 activity compared with that of acyclovir with IC_{50} values of 0.94 and 1.74 µM, respectively and selectivity indices SI= 127.7 and SI>132.2, respectively. The aqueous extract of *Hibiscus sabdariffa* (AEHS) exerted remarkable bacteriostatic effect against all *Helicobacter pylori* (HP) strains tested with MICs values ranging from 9.18 to 16.68 µg/mL. Synergy effect of AEHS with clarithromycin or metronidazole was obtained against four out of seven HP strains tested with ΣFIC ranging from 0.21 to 0.39. The additive effect of AEHS with amoxicillin was obtained against five out of seven HP strains tested with ΣFIC ranging from 0.61 to 0.91. Protocatechuic acid, an active substance of *Hibiscus sabdariffa* showed potent anti-HSV-2 activity compared with that of acyclovir, with EC_{50} values of 0.92 and 1.43 µg/mL, respectively, and selectivity indices > 217 and > 140, respectively. Based on these results, we can conclude that alien plants and their bioactive substances have potential application in the development of antimicrobial agents for combating diseases caused by plant and human pathogens, and could serve as safe and eco-friendly agents to environment and human health as well.

Keywords: antimicrobial activity; alien plant species; plant and human diseases; allelopathic effect; fungicides; bactericides; phytochemicals

SOUHRN

Po desetiletí bylo prokázáno, že rostliny a jejich bioaktivní sloučeniny vykazují různé biologické aktivity včetně antimikrobiálních aktivit. V této dizertační práci bylo zkoumáno několik zavlečených druhů rostlin, za účelem jejich antimikrobiálních inhibičních vlastností proti různým rostlinným a lidským patogenům. Výsledky ukázaly, že etanolové extrakty *Ecballium elaterium*, *Plumbago indica*, *Crisium arvense*, *Stellaria pallida* a *Atriplex sagittata* byly nejúčinnější proti *Fusarium oxysporum* a *Blumeria graminis* při MIC hodnotě 156 µg/mL, zatímco proti *Erwinia amylovora* a *Pseudomonas syringae* ukázaly inhibiční antimikrobiální vlastnosti při hodnotě MIC 220 µg/mL. Plumbagin, hlavní aktivní složka *Plumbago indica* L. vykazovala inhibiční účinek proti všem kmenům *Candida albicans* (*C. albicans*) s hodnotami MIC v rozmezí od 7,41 do 11,24 µg/mL. Aditivní účinek plumbagin v kombinaci s amfotericinem B v koncentracích (v tomto pořadí 0,12, 0,13 a 0,19, 1,81 µg/mL) byl získán na pěti ze sedmi kmenů testovaných *C. albicans* s ΣFIC v rozmezí od 0,62 do 0,91. Kromě toho bylo zjištěno, že plumbagin je bezpečně používán pro topickou aplikaci, jestliže je kombinován s amfotericinem B v koncentracích odpovídajících aditivnímu účinku. Plumbagin vykazoval anti-HCV aktivitu ve srovnání s aktivitou telapreviru s hodnotami IC_{50} 0,57 a 0,01 µM/L a indexy selektivity SI = 53,7 a SI = 2127. Cucurbitacin B (Cuc B), aktivní sloučenina *Ecballium elaterium* vyvíjela růstově inhibiční účinek proti všem kmenům *Staphylococcus aureus* (*S. aureus*) testovaných s průměrnými hodnotami v rozmezí od 0,15 do 0,44 µg/mL a ukázala synergický účinek s tetracyklinem nebo oxacilinem proti čtyřem ze šesti testovaných kmenů *S. aureus* (ΣFIC v rozmezí od 0,29 do

0,43). Cuc B vykazoval pozoruhodnou anti-HSV-1 aktivitu ve srovnání s aktivitou acykloviru s hodnotami IC_{50} 0,94 a 1,74 µM a indexy selektivity SI = 127,7 a SI> 132,2. Vodní extrakt *Hibiscus sabdariffa* (AEHS) působí významným bakteriostatickým účinkem proti všem testovaným kmenům *Helicobacter pylori* (HP) s průměrnými hodnotami v rozmezí od 9,18 do 16,68 µg/mL. Synergický efekt AEHS s klarithromycinem nebo metronidazolem byl získán proti čtyřem ze sedmi kmenů HP testovaných s ΣFIC v rozmezí od 0,21 do 0,39. Doplňkový účinek AEHS s amoxicillinem byl získán proti pěti ze sedmi kmenů HP testovaných s ΣFIC v rozmezí od 0,61 do 0,91. Kyselina protokatechová, účinná látka *Hibiscus sabdariffa*, ukázala silnou anti-HSV-2 aktivitu, ve srovnání s acyklovirem, s EC_{50} hodnotami 0,92 a 1,43 µg/mL, a selektivita indexy> 217 a > 140. Na základě těchto výsledků lze konstatovat, že nepůvodní rostliny (zavlečené druhy rostlin) a jejich bioaktivní látky mají potenciál uplatnění ve vývoji antimikrobiálních látek pro boj s nemocí, způsobených rostlinnými a lidskými patogeny. A může být užívaný bezpečně a šetrně k životnímu prostředí prostředky a pro lidské zdraví.

Klíčová slova: antimikrobiální aktivita; zavlečené druhy rostlin; choroby rostlin a lidské nemoci; alelopatický účinek; fungicidy; baktericidy; fytochemikálie

Table of content

1. Introduction

Plant diseases caused by pathogenic microorganisms significantly attribute to the overall loss in crop yield worldwide and many of them cause reduction of the shelf life and market values of food commodities and render them unfit for human consumption (Choi and Kim, 2008). Application of synthetic chemicals has long been the major choice to control variety of plant diseases. However, extensive use of agrochemicals has raised serious problems including appearance of resistant pathogens, chemical residues, and threats to human health and the environment (Mdee, et al 2009). There has been a growing interest in the research of the possible use of the plant-derived natural fungicides and bactericides such as plant extracts or pure isolated compounds, which can be relatively eco-friendly for disease control in agriculture or humans (Choi et al., 2008). Some of alien plants adversely affect on native ecosystem by unbalancing nutritional flows among the members, eventually threaten biodiversity. Extensive efforts for integrated management of harmful alien species have been being conducted including cataloging alien species and ecological risk assessment (Psysek et al., 2012). One of the main activities for management of alien plant species has been the physical eradication with little success due to their prolific nature. On the other hand, the successful habitation of the alien species has prompted intense interest in the mechanisms for the success (Pimentel et al., 2005). The prolific nature and successful invasion in new habitats suggest that the non-native species are hypothesized to be equipped with novel biochemistry that repels native species or unique compounds in the native flora. In this aspect, alien plant species can be useful sources for discovering new active compounds

serving as antimicrobial agents (Cappuccino & Arnason, 2006). It has been reported that the leaf extracts of *Oxalis corniculata, Chromolaena odorata, Antigonon leptopus* have promising potential antifungal and antibacterial activities with a low MIC values renging from 0.3 to 1.9 µg/mL (Bajpai et al., 2011). The aim of this theis is to investigate selected alien plant species for their antimicrobial activity against plant and human pathogens in order to produce an eco-friendly product, which could be useful for the treatment of plant diseases and human diseases as well.

2. The histroy of plant-derived chemicals in medicinal and agricultural practices

The history of plants and their ethnopharmacologic properties is rather old and dates back to the time when the early man became conscious of his environment. Plants have been used in virtually all cultures as a source of medicine (Lanfranco, 1999). The earliest record of human civilization and culture of China, Egypt, Assyria, and Indies valley reveals that the elders and wise men of those times used herbal medicines to treat various diseases. Information regarding these medicinal herbs is available in the old literature, epic poems and copper plates which are preserved even today. The excavation of Shanidar cave in Iraq in 1963 revealed the grave of Neanderthal man buried sixty thousand years ago along with many flowers of his time.
The plants found in the grave were later identified having various medicinal properties (WHO, 2002).

One of the earliest records of the use of plants is that of Chaulmoogra oil from *Hydnocarpus gaertn*, which was known to be effective in the treatment of leprosy. Such a use was recorded in the pharmacopoeia of the Emperor of China between 2730 and 3000 B.C. Similarly, the seeds of the opium poppy (*Papaver somniferum*) and castor seeds (*Ricinus communis*) were excavated from some ancient Egyptian tombs, which indicated their use in that part of Africa as far back as 1500 B.C. The records available in "Ebers papyrus" also confirm that alien plants were used at that time in Egypt (Baquar, 1995). The ancient use of plants for healing purposes forms the origin of much of modern medicine. Many conventional drugs originate from plant sources, a century ago. Examples include aspirin (from willow bark), digoxin (from foxglove), quinine (from cinchona bark), and morphine The development of drugs from plants including alien plants continues, with drug companies engaged in large scale pharmaceutical screening of herbs (Tyler et al., 1976).

More than 800 million people in developing countries do not have adequate food supplies and at least 10% of food is lost due to plant diseases (Strange and Scott, 2005). Plant diseases are caused by pathogens such as fungi, bacteria, and viruses. Compared to other plant parasites, fungi cause the greatest impact with regard to diseases and crop production losses. This includes considerable foliage and post-harvest losses of fruits and vegetables which are brought about by decay due to fungal plant pathogens.

Common fungal diseases include powdery mildew, rust, leaf spot, blight, root and crown rots, damping-off, smut, anthracnose, and vascular wilts. Some notorious plant pathogenic fungi include *Pythium*, *Phytophthora*, *Fusarium* and *Rhizoctonia* spp, which cause root and crown rot, and seedling

damping-off in many vegetables and ornamental plants. Apart from causing diseases in plants, many species of Fusarium, Aspergillus, Penicillium and Alternaria are also sources of important mycotoxins of concern in animal and human health (Robert and Richard, 1992; Eaton and Gallagher, 1994; Smith, 1997; Placinta et al., 1999). For example, aflatoxins produced by *Aspergillus flavus* and *Aspergillus parasiticus* may cause liver cancer. The most important method of protecting plants against fungal attack is, the use of fungicides. However, many fungicidal agents in the market are toxic and have undesirable effects on other organisms in the environment. Furthermore, halogenated hydrocarbons such as methyl bromide, widely used to control soil-borne pathogens, have ozone-depleting potential (Abritton and Watson, 1992). Some synthetic fungicides are non-biodegradable, and hence can accumulate in soil, plants and water, and consequently effect humans through the food chain. The development of resistance of pathogenic fungi towards synthetic fungicides is of great concern. There is, therefore, a motivation to find safe, efficacious and environmentally friendly fungicides. Plants have, and continue to be, sources of antifungal agents (Hostettmann et al., 2000).

3. The role of alien plants as a source of new antimicrobial agents

Many plant species contain vast quantity of antimicrobial compounds. To develop commercial products, a large quantity of the species has to be cultivated, raising an additional level of complication. If alien species contain

good antifungal activity they may be a useful source of antifungl compounds or extracts because large quantities of material are available. (Vila and Weiner, 2004) considered whether alien plant species are better competitors than native plant species and concluded that this may be the case. There is another possibility that have not been addressed as far as we could ascertain. If fungal pathogens play an important role in the growth or establishment of plant species, alien species may have better resistance against plant pathogens. It has been found that the alien plant *Melianthus comosus* has excellent antifungal and antibacterial activities (Eloff et al., 2006). *Robinia pseudoacacia* has shown to possess antibacterial activity against *Escherichia coli* and *Proteus myxofaciens*. Its antibacterial activity was found to be related to its rich content of polyphenols (Lukasiewicz et al., 2015; Marutescu et al., 2017). Resveratrol, a stilbene-type phenolic compound found in *Fallopia* spp., reported to exert antimicrobial activity agaisnt wide range of microorganisms (Ferreira and Domingues, 2016). Ethanolic extract of *Fallopia japonica* showed antibacterial activity against *Acinetobacter baumanii* and antifungal activity against *Candida albicans* (Bardon et al., 2014). It is believed that the antimicrobial activities of alien plants are related to their allelopathy effect in a form of production of chemicals that inhibit the growth of other plants or/and microorganisms (Chengxu et al., 2011). Considering the importance of alien plants as a source of antimicrobial agents, it should be taken into consideration the risk of their invasion and hence their impact on environment. Also, it should be taken into consideration the safe means of planting and harvesting these plants from wild populations in order to use them in medicinal or agricultural practices.

4. Aim of the dissertation thesis

- Investigation and screening of selected alien plant species for antimicrobial activity against plant and human pathogens.
- Produce a useful product that can be used for the treatment of plant and human diseases, and to be relatively eco-friendly for disease control and to environment as well.

4.1. Objectives

- Evaluation and initial screening of the selected alien plants for antimicrobial activity *in vitro*.
- Selection of one or more plant species with promising activities for further study.
- Identification of the active compound(s) from the selected plant(s) species.
- Determination of antimicrobial activity of isolated compound(s) *in vitro*.

5. Overall of the importance of the results

The results confirmed the beneficial effects of the crude extracts of alien plant species and their active phytochemicals against plant and human pathogens. The crude extracts may be purified for the isolation of compounds

with antimicrobial activity. These results also validate the possibility of using these plants for the treatment of infections caused by plant and human pathogens.

6. Concluding remarks

The European Union defines alien plant species as those that are introduced accidentally or deliberately into a natural environment where they are not normally found, with serious negative consequences for their new environment. They represent a major threat to native plants in Europe, causing damage worth billions of euros to the European economy every year. Different plant pathogens threaten food security worldwide, therefore the most important method of protecting plant against pathogens attack is, the use of synthetic fungicides and bactericides (as well as useful for the treatment of human bacterial, fungal pathogens) but the development of resistance towards synthetic fungicides and bacreicides is a great concern. Moreover, the health risk and hazardous effects on environments associated with the use of chemical fungicides and bactericides increase the need to search for safe, efficacious and environmentally friendly fungicides and bactericides. Many alien plant species release chemical compounds into the environment, which are not generally harmful to them, but those chemicals suppress the growth of other plant species growing in close proximity of such alien species. Prime importance can be given for the bioprospecting of novel active compound which can be utilized for the management of several plant diseases. This

negative effect (often referred to as allelopathic effect) of invaders on the native species confers a tremendous competitive advantage on the former.

In summary, alien plant species can be considered as a rich source of bioactive compounds with promising activity against various plant and human pathogens. Despite relatively few of isolated antimicrobial compounds from alien plant species advance to become practically effective drugs in their own right, these substances can be used as models for the preparation of analogues using chemical methodology such as total or combinatorial synthesis, or manipulation of biosynthetic pathways. Thus, plant-derived natural substances may open new options for the development of new antimicrobial agents and may play an essential role in agriculture, environmental protection and pharmaceutical industy as well.

7. List of publications related to dissertation thesis

All articles related to dissertation thesis that were published in international peer-reviewed journals with impact factors are listed as follows:

Hassan STS, Švajdlenka, E.; Berchová-Bímová, K. Hibiscus sabdariffa L. and its bioactive constituents exhibit antiviral activity against HSV-2 and anti-enzymatic properties against urease by ESI-MS based assay. Molecules. **2017;** 22(5). pii: E722.

Hassan STS, Berchová-Bímová, K, Petráš J, Hassan KTS. Cucurbitacin B interacts synergistically with antibiotics against Staphylococcus aureus clinical isolates and exhibits antiviral activity against HSV-1. S. Afr. J. Bot. **2017**; 108:90-94.

Hassan STS, Berchová-Bímová K, Petráš J. Plumbagin, a Plant-Derived Compound, Exhibits Antifungal Combinatory Effect with Amphotericin B against Candida albicans Clinical Isolates and Anti-hepatitis C Virus Activity. Phytother Res. **2016**;30(9):1487-92.

Hassan STS, Berchová K, Majerová M, Pokorná M, Švajdlenka E. In vitro synergistic effect of Hibiscus sabdariffa aqueous extract in combination with standard antibiotics against Helicobacter pylori clinical isolates. Pharm Biol. **2016**;54(9):1736-40.

Hassan STS, Berchová K, Šudomová M. Antimicrobial, antiparasitic and anticancer properties of Hibiscus sabdariffa (L.) and its phytochemicals: in vitro and in vivo studies. Ceska Slov Farm. **2016**;65(1):10-4.

Hassan STS, Masarčíková R.; Berchová, K. Bioactive natural products with anti-herpes simplex virus properties. J Pharm Pharmacol. **2015**; 67(10):1325-1336.

Hassan STS, Majerová M, Šudomová M, Berchová, K. Antibacterial activity of natural compounds – essential oils. Ceska Slov Farm. **2015**; 64(6):243-53.

8. Published papers in international conferences related to dissertation thesis

The results of the dissertation thesis were presented as posters and published in the book of abstracts of the following international conferences.

Hassan STS, Berchová K. Antimicrobial activity of isolated phenolic compounds from selected invasive plants. **2014**. Drug Analysis. June 22-25, 2014. Liege, Belgium. As a form of abstract in Book of Abstracts and poster presentation.

Hassan STS, Berchová K. Plant-derived chemicals exhibit antimicrobial activity: a new therapeutic agents in the treatment of bacterial and viral infections. Frontiers in Medicinal Chemistry. **2015**. September 14-16, 2015, Antwerp, Belgium. As a form of abstract in Book of Abstracts and poster presentation.

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CURRICULUM VITAE

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Professional history and education

2012 – present: Doctoral study program (Ph.D.) in Applied Ecology, Department of Applied Ecology, Faculty of Environmental Sciences, Czech University of Life Science Prague, Czech Republic.

2012-Doctor of Pharmacy. University of Veterinary and Pharmaceutical Sciences Brno, Czech Republic.

2011: MSc. (Ing.) – Czech University of Life Science Prague, Czech Republic.

2001–2006: BSc in Pharmaceutical Sciences, Alexandria University, Egypt

Teaching activities

2013- present: Supervisor and lecturer of Subject (Phytopathology) for master study program Pharmacy (Czech and English Study Programs). Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic.

Supervisor of 14 master theses for master study program Pharmacy M5206. Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic.

Membership in international societies

1. Member of the American Society of Pharmacognosy.

http://www.pharmacognosy.us/

2. Member of Czech Pharmaceutical Society.

http://www.cfs-cls.cz/

Internship abroad

2013 - Research stay (1 months) - Faculty of Pharmacy, Alexandria University, Alexandria, Egypt.

2010 - Research stay (2 months) - School of Pharmacy – University of

California, San Francisco, USA.

Employment history

2016- present: Research assistant and at Department of Natural Drugs, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences Brno, Czech Republic.

2013-2015: Research assistant (external employee) at Department of Natural Drugs, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences Brno, Czech Republic.

Lectures and seminars

Presentation of more than 10 research seminars and lectures at international and national scientific meetings in Czech Republic, Belgium, Austria, USA, Egypt and Brazil.

List of publications till August 2017

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