

It is estimated that nearly a billion people have skin, nail and hair fungal infections, many 10s of millions mucosal candidiasis and more than 150 million people have serious fungal diseases, which have a major impact on their lives or are fatal. In most cases fungal infections are caused by the yeasts from the genus *Candida* spp. and are called candidiasis. *Candia albicans* and other species of genus *Candida* belong to the natural microflora of human and animals' organisms. Candidiasis usually are derived from the individual's own endogenous reservoir when the host presents certain risk factors such as immunosuppressive and anti-cancer therapies, treatment with broad-spectrum antibacterial antibiotics, AIDS, diabetes and drug abuse. Despite the high incidence and the severity of *Candida* spp. infections, treatments are still limited and insufficient. In the treatment of fungal infections, there are only a few drug classes available: polyenes, triazole derivatives, echinocandins, allylamines, and flucytosine. In fact, none of the currently used antifungal agents meets all expectations: polyenes such as amphotericin B are toxic and characterized by low solubility in water, echinocandins such as caspofungin can only be administered intravenously, allylamines such as terbinafine lack anticandidal activity. Moreover, yeasts quickly develop different mechanisms of resistance against antifungal agents. Thus, there is an urgent need to look for other active and safe agents which could be used in the treatment of candidiasis. The results of our preliminary investigations revealed high antifungal potential of ethanolic extracts of propolis (EEPs) harvested in Polish apiaries. Propolis is a highly agglutinative, resinous substance of complex chemical composition that is collected by bees from flower and leaf buds. Some of its ingredients, mainly polyphenols and flavonoids, exhibit high antimicrobial activity. As a consequence, bees use this product for the protection against dangerous pathogens from the hive. We also observed synergistic effect of Polish propolis in combination with fluconazole and voriconazole and higher antifungal potential of the products rich in flavonoids. Besides of many advantages application of ethanolic extracts of propolis (EEPs) for treatment infectious disease, including candidiasis is very limited. The most important limitations, which in fact eliminates propolis from clinical practice are: important differences in concentration of active components – which in fact are not well recognized to date, not known mechanisms of biological activity, irritating properties of EEPs (a consequence of high concentration of ethanol, usually 70% v/v) and inability of the active components of EEPs to cross the biological membranes. This project aims to solve these limitations. The identification of the crucial ingredients will be based on correlation analysis between chemical composition and antifungal potential of the samples of EEPs that exhibit the highest activity. Based on our previous observations the investigation of the modes of antifungal activity of EEPs/CIEEPs (crucial ingredients of ethanolic extracts of propolis) against *Candida* spp. will be performed particularly in relation to the cell wall, cell membrane, drug transporters, biofilm formation and the process of phenotypic switching. The researches will be carried out with modern microscopic techniques (confocal and fluorescence microscopy) and flow cytometry. The influence of propolis and its components on the level of expression of genes coding for most important virulence factors will be studied with Real-time PCR and RNA sequencing. From the point of view of the abilities of application of propolis (and its ingredients) in clinical practice particularly important would be identification of the components of this product that exhibit synergism with conventional antifungal agents. Using combinations of these agents could inhibit the process of acquiring resistance of *Candida* spp. to the activity of azoles – currently the drugs of choice in the treatment of most of candidiasis. New formulations e.g. suspensions of propolis nanoparticles in water, water/glycerol and water/polyethylene glycol extracts will be proposed for the elimination of the problems associated with strong irritant properties of EEPs. For better cell uptake the conjugates of CIEEPs with nanocarriers - cell penetrating peptides (Trojan Horse strategy) and triphenylphosphonium cation (TPP) will be prepared. In cooperation with our abroad partners: Prof Patrick Van Dijck from the Catholic University of Leuven and David Williams from Cardiff University antifungal potential of most effective EEPs/CIEEPs and compositions of CIEEPs will be also investigated using *in vitro* model of oral candidiasis (Prof. Williams laboratory) and *in vivo* models of mouse vaginal infection and the subcutaneous catheter biofilm model system (Prof. Van Dijck laboratory).