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METHOXYLATED FLAVONES FOR THE TREATMENT OF FUNGAL INFECTIONS

Fungal infections (FIs) are increasingly becoming a global health burden with devastating socioeconomic consequences. Although a number of pharmacological options for antifungal treatment do exist, they are currently limited to four distinct chemical classes, with the azoles representing the clinically most relevant subgroup. The incidence of invasive FIs accentuated by antifungal resistance strongly highlights the urgent need for the development and investigation of new antimycotics. The University of Graz offers unique lead compounds of a novel class (flavonoids) that are feasible as both stand-alone antifungal agents and potentiators of currently employed antimycotics.

BACKGROUND

Invasive candidiasis (FIs due to *Candida spp.*) is estimated to be lethal in 30-40% and invasive aspergillosis (FIs due to *Aspergillus spp.*) in 20–30% of the cases. Altogether, this results in at least 1.5 million deaths worldwide every year. Furthermore, *Candida spp.* are the fourth and seventh common cause for hospital-acquired infections in the U.S. and Europe, respectively.

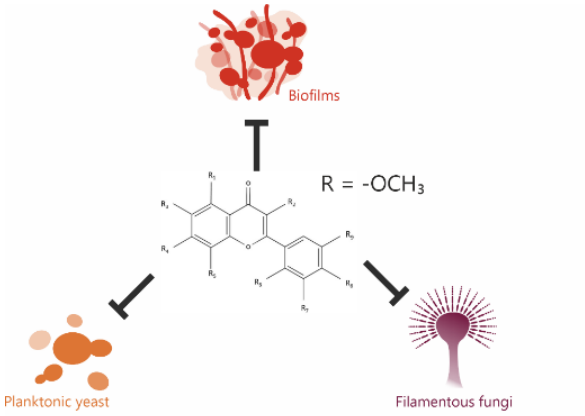

Fig.1 Activity spectrum of identified flavonoids

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The technology describes the identification of a number of methoxylated flavonoids that demonstrate *in vitro* and *in vivo* activity against planktonic cells (the single-celled form of a fungal pathogen), thus inhibiting proliferation of the pathogen, as well as against biofilms (Fig. 1). Intriguingly, the latter effect comprises both the inhibition of biofilm formation and the eradication of existing biofilms. In addition, these compounds are effective either as stand-alone agents or as potentiators of known azole-based antimycotics that boost their effect. Of note, some of these compounds were effective against both filamentous and non-filamentous fungal species (Fig. 1). Altogether, these polypharmacological effects underline the potential of these compounds for treatment of severe (and lethal) fungal infections.

ADVANTAGES

- Polypharmacological effect: the same molecules act as stand-alone agents and as potentiators of azole-based antifungals
- Broad spectrum of applicability: the substances act against non-filamentous (*Candida spp.*) and filamentous (*Aspergillus spp.*) species
- The chemical structure allows the implementation of medicinal chemistry to improve the lead compounds (e.g. increase half-life, pharmacological effects)
- Natural compounds: flavonoids belong to the familiy of polyphenols, secondary metabolites naturally occurring in plants, and are often human-tolerable and show no or minor side effects.

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