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Review

Review of flavonoids: A diverse group of natural compounds with anti-*Candida albicans* activity *in vitro*

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ABSTRACT

Flavonoids are a subdivision of polyphenols, a versatile class of natural compounds that represent secondary metabolites from higher plants and are abundant in human diet. Various protective effects of flavonoids have been reported, including antimicrobial and antifungal activities. Due to the nature of oral candidiasis and the increased use of antifungal agents, several drug-resistant strains have emerged making it impractical to rely on one standard therapeutic regime. The aim of this review is to summarize the antifungal activity of some examples of the major subclasses of flavonoids in pure extract forms against *C. albicans in vitro*, as reported in literature over the past 10 years (2004–2015). In addition, this review outlines the potential mechanism of actions of flavonoids studied *in vitro*, which may contribute to a better understanding of flavonoids as multi-targets agents in the treatment and/or prevention of oral candidiasis in clinical settings.

Contents

1. Introduction

Oral candidiasis (OC) is one of the most common fungal infections affecting the oral cavity (Das, Nightingale, Patel, & Jumaa, 2011). *Candida albicans* is a prevalent opportunistic human fungal pathogen that is often implicated in OC and is the most common isolated *Candida* specie in clinical cases of invasive fungal infections (Liu et al., 2014). *C. albicans* lives commensally in the gut, oral pharyngeal, genito-urinary tract and skin (Prieto, Correia, Pla,

Abbreviations: IC50, 50% inhibitory concentration; MIC, minimum inhibitory concentration; MIC50, 50% minimum inhibitory concentration; SAR, structure activity relationship; MABA, microplate alamar blue assay.

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& Roman, 2016). However, pathogenicity of *C. albicans* and subsequent candidiasis can occur under immunocompromised conditions (Lalla, Patton, & Dongari-Bagtzoglou, 2013). For instance, the incidence of at least one episode of oral candidiasis in HIV patients is estimated to be 80–95% (Borg-von Zepelin et al., 1999). Furthermore, chemotherapy, certain medications, such as steroids and multiple antibiotic treatments, along with the use of removable dentures may predispose to OC infections (Darwazeh, Hammad, & Al-Jamaei, 2010). As a consequence of oral fungal infections, patients may have dysphagia, weight loss, or disseminated candidiasis. The disseminated forms of the disease can be life-threatening with mortality rates of 35–60% among immunocompromised, cancer patients, and those exposed to multiple treatments, such as broad spectrum antibiotics, chemotherapy, immunosuppressive therapy, and anti-retroviral therapy (Eggimann, Que, Revelly, & Pagani, 2015; Gillies et al., 2015; Tang, Liu, Lin, & Lai, 2014).

Despite the availability of broad spectrum triazoles as conventional medical therapies, the incidence of invasive candidiasis continue to increase due to antifungal resistance and the emergence of non-*albicans* strains of *Candida*, such as *Candida glabrata*. The azole fluconazole is currently considered the first-line of drugs that is effective against most *Candida* species (Lalla et al., 2013; Serpa et al., 2012). However, certain *Candida* species, such as C. *glabrata*, *C. albicans*, *C. tropicalis*, and *C. parapsilosis* were found to have different degrees of susceptibility and were reported to have fluconazole resistance (Sanguinetti, Posteraro, & Lass-Florl, 2015). These factors present an urgent need to evaluate novel compounds with antifungal activity. Natural compounds as sources for anti-*Candida* therapeutics from botanical sources have gained attention in the past decade (2004–2015) mainly because they display structural diversity and uniqueness in functional modes of action, which renders them as attractive candidates to counteract the emergence of *Candida* drug resistances (Kamba & Hassan, 2010; Toure, Bahi, Ouattara, Djama, & Coulibaly, 2011).

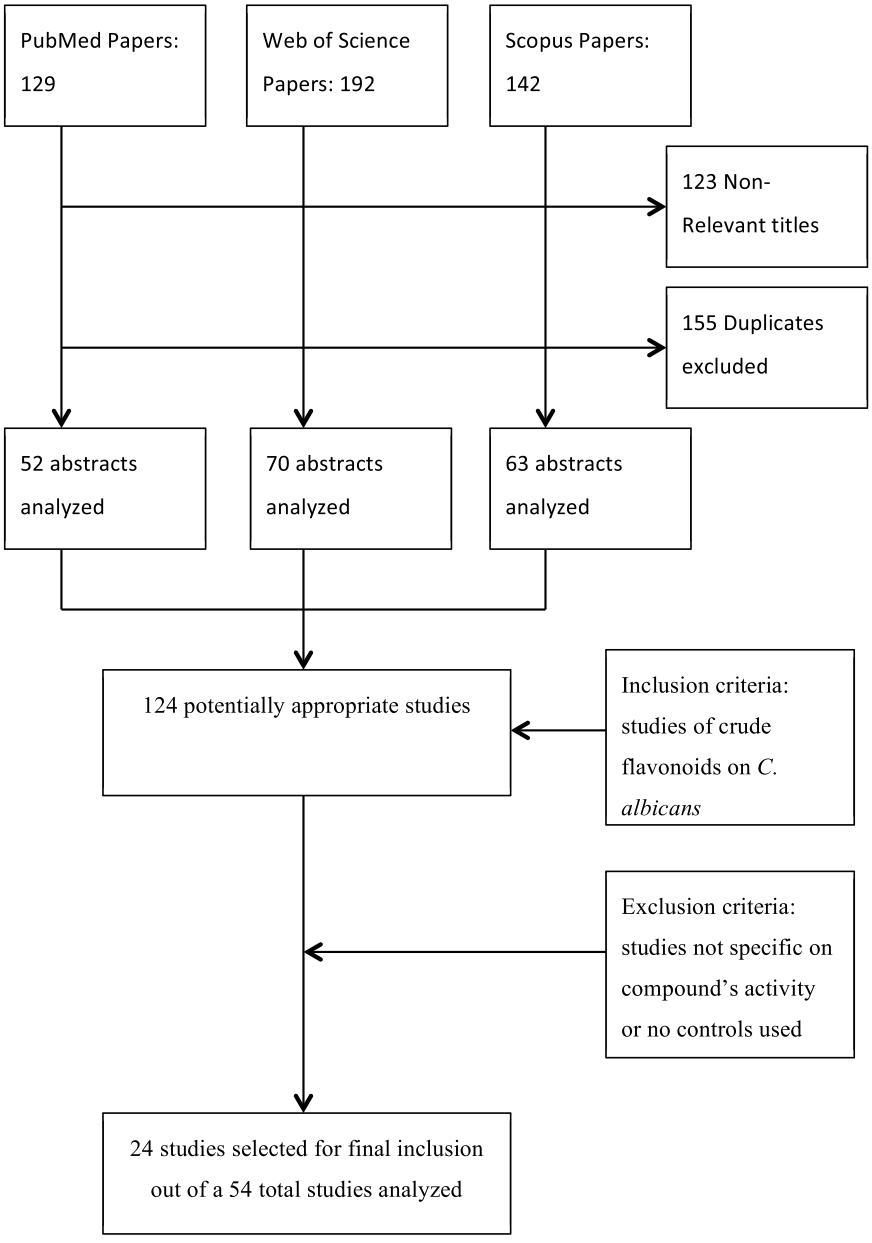

Fig. 1. Search strategy and papers selection flowchart.