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CURRENT PERSPECTIVES IN DRUG DISCOVERY AGAINST MADURELLA MYCETOMATIS, THE CAUSATIVE AGENT OF BLACK-GRAM MYCETOMA

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ABSTRACT – PL 03

Mycetoma is a progressively destructive chronic infectious disease with a high morbidity. The disease begins with a small trauma leading to a localized suppurative and deforming granulomatous chronic infection of subcutaneous tissue, skin and bones, which eventually results in the formation of tumour like swellings and sinuses containing grains. The causative agents could be of a fungal (eumycetoma) or a bacterial (actinomyctoma) origin (van de Sande, 2013). Due to the concerted efforts of the mycetoma consortium the World Health Organization (WHO) has eventually added mycetoma to the WHO list of neglected tropical diseases (Samy et al., 2014). The fungus Madurella mycetomatis is one of the most prevalent causative agents of black-grain eumycetoma. Most cases were reported from Mexico, Sudan and India (van de Sande, 2013). M. mycetomatis is notoriously difficult to treat and lack of adequate therapy leads eventually to amputation of the infected limb. Prolonged follow-up after surgery with currently available antifungals, however, might improve the clinical outcome. Nevertheless, the increasing resistance of these pathogenic microorganisms to existing antibiotics (e.g. amphotericin B, various azoles, 5-flucytosine, and the echinocandins) and its growing threat to public health warrant an immediate search for novel classes of bioactive agents against M. mycetomatis (Belkum et al., 2011).

The unique biology of Mycetoma coupled with the absence of appropriate treatment present real challenge to develop a facile, cheap, accurate and reproducible in vitro 96-microtiter assay for screening potential novel antymycetomal compounds.

The present presentation is dealing with development of 96-well microplates assay based on resazurin dye (7-hydroxy-3H-phenoxazin-3-one 10-oxide) as an indicator of cell viability of M. mycetomatis. Mitochondrial enzymes, as carriers of diaphorase activities, like NADPH dehydrogenase, are probably responsible for the transference of electrons from NADPH + H+ to resazurin, which is reduced to resorufin (Zhang et al., 2004).

Although an in vitro method to assess the antifungal activity of variousazole derivatives has been previously attempted employing 2,3-bis(2-methoxy-4-nitro-5-sulphophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolum hydroxide (XTT) as indicator to determine the MIC (Belkum et al., 2011), the present assay allows rapid bioactivity-guided fractionation of large numbers of samples, with simple equipment and at reduced cost.

The validity of our newly developed assay has been verified by screening of a series of natural products including various plants extracts, propolis of Sudanese origin and a number of volatile oils. The validity of this method has been further consolidated by the isolation of promising hits applying bioactivity guided fractionation.

References: