Mycetoma – perspectives of natural products from plants as leads to new therapeutics for the 18th neglected tropical disease

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Mycetoma is a chronic, granulomatous, progressive and disfiguring inflammatory disease caused by certain bacteria (e.g. *Streptomyces somaliensis* and *Nocardia brasiliensis;* "actinomycetoma") or fungi (e.g. *Madurella mycetomatis;* "eumycetoma").
The disease is usually manifested as a painless subcutaneous mass with sinus formation and purulent discharge containing grains is pathognomonic of mycetoma. The mass may spread from the skin to involve deep structures, resulting in destruction, deformity, and occasionally it can be fatal. The foot and hand are the most frequently affected sites seen in 82% of cases (Madurella foot) but other parts of the body may be involved. Mycetoma is endemic in many tropical and subtropical regions and prevails in the "mycetoma belt" between 15°S to 30°N including Sudan, Somalia, Senegal, India, Yemen, Mexico, Venezuela, Columbia, Argentina, and a few others. The African continent seems to have the highest burden and prevalence of the disease. However, mycetoma has also been reported from temperate regions with few reports even from the USA, Germany and Japan.
The fungus *Madurella mycetomatis* is one of the most prevalent causative agents of black-grain eumycetoma. *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 this pathogenic microorganism to existing antifungals and its growing threat to public health call for an immediate search for novel classes of bioactive agents against *M. mycetomatis* (Belkum *et al*., 2011). Currently, the mean antifungal treatment duration for eumycetoma is one and half year and treatment is associated with serious side effects. This treatment, furthermore, is not affordable to a wide segment of patients in endemic areas. This is further aggravated by the disappointingly poor treatment outcome which is characterized by low cure rate and high recurrence rates which eventually lead to amputation. Therefore, there is an urgent need for novel effective and potent antifungals for eumycetoma. Due to these and further reasons, Mycetoma has very recently been recognized by WHO as a neglected tropical disease. (http://www.who.int/neglected_diseases/diseases/en/). Refer to the WHO/NTD site for more information about the disease (http://www.who.int/buruli/mycetoma/en/).

Research in the two collaborating groups has been directed towards natural products as leads against neglected tropical diseases with a major focus on unicellular eukaryotic ("proptozoan") parasites for several years and is documented in a variety of joint publications. Currently, only few reports exist on tests of natural products against Mycetoma, but some of them are promising (e.g. Elfadil H *et al.*, 2015), so that a broader investigation appears very desirable. The research proposed here is hence directed at extending the joint efforts of the two involved groups to the search for new active principles of natural origin against eumycetoma, which is a grave problem in Sudan and has already been a focus of research in the group of S.A.K. for several years. An *in vitro* assay system at the 96-well microtiter scale for *M. mycetomatis* is established at the Univ. of Khartoum which is supposed to be applied to a variety of natural products from the Münster group, including approved herbal medicines from the German market. These efforts require some financial support to be started and in order to obtain sufficient results to apply for a bigger grant. The prize money will hence mainly be used for the necessary laboratory consumables in the S.A.K. lab; the research award of the foundation "Plants for Health" would hence constitute a small but very significant "kick off" support for this work.

It is to be noted that this research will be part of the activities of the Research Network Natural Products against Neglected Diseases (ResNet NPND; see http://www.resnetnpnd.org/) so that, ultimately, an international initiative of natural product scientists uniting their efforts against neglected tropical diseases will benefit from this award.

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