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Review

Ethnopharmacological reports on anti-Buruli ulcer medicinal plants in three West African countries



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ABSTRACT

Ethnopharmacological relevance: Buruli ulcer (BU) is the third most common mycobacterial infection in the world, after tuberculosis and leprosy and has recently been recognized as an important emerging disease. This disease is common in West Africa where more than 99% of the burden is felt and where most affected people live in remote areas with traditional medicine as primary or only option. Reports indicate that the ethnopharmacological control approach of the disease in such settings has shown promise. However, no or very few compilations of traditional knowledge in using medicinal plants to treat BU have been attempted so far. This review aimed to record medicinal plants used traditionally against BU in three countries in West Africa: Ivory Coast, Ghana and Benin and for which ethnopharmacological knowledge supported by pharmacological investigations has been reported. The information recorded in this review will support further pharmacological research to develop appropriate drugs for a better BU control.

Material and methods: A systematic review of the literature on ethnobotanical use and anti-BU activity of plants reported for BU treatment was performed. The approach consisted to search several resources, including Technical Reports, Books, Theses, Conference proceedings, web-based scientific databases such as publications on PubMed, Science direct, Springer, ACS, Scielo, PROTA, Google and Google scholar reporting ethnobotanical surveys and screening of natural products against *Mycobacterium ulcerans*. This study was limited to papers and documents published either in English or French reporting ethnopharmacological knowledge in BU treatment or pharmacological potency *in vitro*. This review covered the available literature up to December 2014.

Results: The majority of reports originated from the three most affected West African countries (Cote d'Ivoire, Ghana and Benin). Though, 98 plant species belonging to 48 families have been identified as having anti-BU use, many have received no or little attention. Most of the pharmacological studies were performed only on 54 species. To a lesser extent, ethnopharmacological knowledge was validated *in vitro* for only 13 species. Of those, seven species including *Ricinus communis*, *Cyperus cyperoides* (cited as *Mariscus alternifolius*), *Nicotiana tabacum*, *Mangifera indica*, *Solanum rugosum*, *Carica papaya*, and *Moringa oleifera* demonstrated efficacy in hospitalised BU patients. Four isolated and characterized compounds were reported to have moderate bioactivity *in vitro* against *M. ulcerans*.

Conclusions: This review compiles for the first time ethnopharmacologically useful plants against BU. The pharmacological potential of 13 of them has been demonstrated *in vitro* and support BU evidence-based traditional medicines. In addition, 7 species showed activity in BU patients and have emerged as a promising source of the traditional medicine for treatment of BU. Yet, further safety and efficacy study should be initiated prior any approval as alternative therapy. Overall, a huge gap in knowledge appeared,

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suggesting further well-planned and detailed investigations of the *in vitro*, *in vivo*, and safety properties of the claimed anti-BU plants. Therefore, plants with medicinal potential should be scrutinized for biologically active compounds, using bioassay-guided fractionation approach to provide new insights to find novel therapeutics for BU control.

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1. Introduction

Buruli ulcer (BU) is a necrotizing disease of the skin, subcutaneous tissue and bone and it is caused by the environmental pathogen *Mycobacterium ulcerans*. This disease is the third most common mycobacterial infection in the world, after tuberculosis and leprosy (WHO, 2011). The pathogenesis of BU is associated with mycolactone, a lipidic exotoxin produced by *M. ulcerans* that has cytotoxic and immunosuppressive properties (Martins et al., 2012). It is largely a problem of people living in remote rural areas. How exactly *M. ulcerans* is transmitted to humans remains unknown, but in contrast to tuberculosis or leprosy, the infection is acquired directly or indirectly from the environment and not through contact with other patients (Stinear and Johnson, 2008). At least 33 subtropical and temperate countries have reported cases of BU. Fifteen of these countries have reported 5000–6000 annual cases. In Asia and the Western Pacific, most cases occur in tropical and subtropical regions except in Australia, China and Japan. In West Africa, Benin, Ivory Coast and Ghana reported most of the cases of which almost half occurred in Ivory Coast (WHO, 2013). According to WHO, Africa bears 99% of the global burden of this disease.

Early reports have suggested that wide surgical excision was the only effective treatment (MacCallum et al., 1948) for BU and also, early trials with clofazimine (Revill et al., 1973) in the

antibiotic era demonstrated only marginal benefits. In 2005, the WHO introduced new provisional antibiotic treatment guidelines for BU following a successful pilot study from Ghana which confirmed that human lesions can be sterilised with antibiotics (Etuaful et al., 2005). This was supported by encouraging reports of success with the protocol in a series of cases from Benin (Chauty et al., 2007). The WHO protocol has led to a new approach to treatment with the potential to reduce cost, to allow delivery of care closer to the homes of patients, and to encourage patients to present earlier as the fear of requiring major surgery is lessened. The combination treatment protocol involves oral intake of Rifampicin, 10 mg/kg body weight daily for 8 weeks plus Streptomycin, 15 mg/kg body weight by intramuscular injection daily for 8 weeks. Although recent experience indicates that combination chemotherapy with Streptomycin and Rifampicin improves cure rates, the utility of this regimen is limited by the 56 days duration of treatment, potential toxicity and required parenteral administration of streptomycin (Johnson, 2010; Zhang et al., 2013). In addition drug–drug interactions caused by Rifampicin (Chauty et al., 2007; Johnson, 2010; Zhang et al., 2013) and the indirect cost to family due to the long stay associated with the economic burden limit this protocol. On the other hand, surgery, which is however necessary for some severe forms of the disease (large ulcerated forms, disseminated forms, and osteomyelitis) to correct deformities and improve wound healing (Kibadi et al., 2010) is

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