Review

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

Patrick Valere Tsouh Fokou a,b,a, Alexander Kwadwo Nyarko a,c, Regina Appiah-Opong a, Lauve Rachel Tchkouaha Yamthe b,e, Phyllis Addo a, Isaac K Asante d, Fabrice Fekam Boyom b

a Noguchi Memorial Institute for Medical Research, College of Health Sciences, University of Ghana, PO Box LG 581, Accra, Ghana
b Antimicrobial Agents Unit, Laboratory for Phytochemistry and Medicinal Plants Study, Faculty of Science, University of Yaoundé 1, PO 812, Yaoundé, Cameroon
c Department of Pharmacology and Toxicology, School of Pharmacy, College of Health Sciences, University of Ghana, PO Box LG 43, Legon, Ghana
d Department of Botany, Faculty of Science, University of Ghana, PO Box LG 55, Legon, Ghana
e Institute of Medical Research and Medicinal Plants Studies (IMPM), PO Box 6163, Yaoundé, Cameroon

A R T I C L E   I N F O

Article history:
Received 18 February 2015
Received in revised form 12 June 2015
Accepted 14 June 2015
Available online 20 June 2015

Keywords:
Ethnobotanical
Antimycobacterial potency
Buruli ulcer
Mycobacterium ulcerans
Phytochemistry
Toxicity
Traditional uses

Chemical compounds studied in this article:
1. Holadysamine
2. Holaphyllin

A B S T R A C T

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 these, seven species including Ricinus comminissus, Cyperus cypertoides (cited as Marcosia alternifolius), Nicotiana tabacum, Mangifera indica, Solanum rugasum, 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,

* Corresponding author at: Noguchi Memorial Institute for Medical Research, College of Health Sciences, University of Ghana, PO Box LG 581, Legon, Accra, Ghana.
Tel.: +233 245845344; fax: +233 21 502182.
E-mail addresses: ptsouh@noguchi.ug.edu.gh, tsouh80@yahoo.fr (P.V. Tsouh Fokou).

http://dx.doi.org/10.1016/j.jep.2015.06.024
0378-8741/© 2015 Published by Elsevier Ireland Ltd.
suggested 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.

© 2015 Published by Elsevier Ireland Ltd.

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 lipodic 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, the West Coast of 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
neither affordable nor accessible to a large proportion of the population (Johnson et al., 2004). Furthermore, although BU is a treatable disease, its burden is increasingly felt due to inappropriate control measures and poor emphasis in developing new anti-BU drugs.

Because of cultural believes and/or budgetary constraints, traditional plant-based treatments remain the first option for many populations in poor remote areas (Johnson et al., 2004). For poor and sick persons, modern treatment is not only expensive, but is also subject to side effects, mutilation and amputation (Stienstra et al., 2002). Reports have indicated that plant products selected based on traditional knowledge might be of great importance in the early treatment and prevention of Buruli ulcer at an affordable cost. However, there remain huge gaps in knowledge about the real efficacy of potions, their standardization, and active principles.

The scope of this review is a survey of current knowledge on medicinal plants used traditionally to treat BU and for which ethnopharmacological reports supported by pharmacological data have been documented. It is anticipated that information recorded herein will support further detailed investigations opening on improved tools for better control of BU and eventually other mycobacterial infections.

The data presented here were obtained from web-based search of publications on PubMed, Science direct, Springer, ACS, Scielo, Google and Google scholar databases reporting ethnobotanical uses and screening of natural products against BU using the keywords “medicinal plants+Buruli ulcer”, “ethnobotanical+Buruli ulcer”, “natural products”, “antimycobacterial screening”, “Buruli ulcer”, “M. ulcerans”, “mycobacteria”, and “Traditional medicine+Buruli ulcer”. In addition, Technical Reports, Books, Theses, and Conference proceedings were study. This literature survey was limited to papers and documents published either in English or French. All retrieved information from documents reporting either ethnopharmacological knowledge in BU treatment or pharmacological potency in vitro against M. ulcerans is discussed here. This review covers the available literature up to December 2014. All plant species have been validated taxonomically with www.theplantlist.org (accessed December 2014).

2. Ethnopharmacological use of plants to control BU

Globally, the proportion of the populations using traditional remedies based on plants to treat BU varies widely. Mostly in the rural African areas, the use of plant medicines plays an important role in daily health care. These medicines are sometimes preferred to modern medicines. Generally, specialized pharmacopoeia is practiced by traditional healers, and the popular or general pharmacopoeia is common knowledge in specific communities. From data collected in the framework of this review, parts or whole plants are prepared and administered per os and/or locally as pomade and bandage. Most remedies are mixtures of parts of two or more plant species and water is the main solvent.

Generally, traditional treatment for BU is done in four steps, diagnosis, necrosis ablation, wound curing, and excorision. Plants are used in the second and third steps of treatment (Johnson et al., 2004).

2.1. Overview of studies on plants used as treatment for Buruli ulcer in traditional medicine

2.1.1. Ethnopharmacological studies

Ethnopharmacological investigations mainly involve in-depth interviews guided by appropriately designed questionnaires consisting of both closed and open-ended questions (Owusu-Sekyere, 2012; Trébissou et al., 2014; Seefeld et al., 2013), check list interview (Sam et al., 2013; Yemoa et al., 2008; Addo et al., 2007; Vangah et al., 2000), observation and focus group discussions (Trébissou et al., 2014; Adjet et al., 2013), and subsequent experimental investigation of indigenous medicines based on determination of invitro activity as an approach to drug discovery. Indeed, the majority of studies reported in this paper were carried out in Health centres specifically dedicated to the treatment of Buruli ulcer; providing almost certainly a guarantee that they were all affected by this pathology. The identity of plants is usually authenticated by competent authorities such Botany department or herbarium. Limitations to the interview approach might be the reluctance of some herbal practitioners to disclose plants names and combinations. Moreover, potions trials on BU patients was of good quality as it provided direct evidence of efficacy with a complete pattern of the disease (Trébissou et al., 2014).

2.1.2. Extraction and isolation

Extraction methods generally mimic herbal practitioners’ approach to prepare decoctions or infusions using mainly water and palm wine (Yemoa et al., 2015, 2011; Addo et al., 2007; Kone et al., 2007, 2009). Other extraction procedures include the use of ethanol or organic solvents of increasing polarity (hexane, dichloromethane, ethyl acetate and water) to partition plant materials. Isolation of active principles generally follows a bio-guided chromatographic fractionation approach (Yemoa et al., 2015). The characterization of isolated compounds is performed using physical and spectroscopic techniques.

2.1.3. Antimicrobial assays

Antimicrobial activity testing assays are generally performed using cultured M. ulcerans strains and isolates. Rifampicin is usually incorporated as positive control (Yemoa et al., 2015). Susceptibility assays are conducted using the proportion method where inhibitors are incorporated into Löwenstein–Jensen media at defined concentrations (Addo et al., 2007; Coulibaly et al., 2011; Kone et al., 2007), or the resazurin method on microtitre plate format where mycobacteria are incubated with inhibitors in supplemented Middlebrook 7H9-S broth (Yemoa et al., 2011, 2015). In all cases, activity is usually defined as minimal inhibitory concentration (MIC) considered as the lowest drug concentration that inhibits the growth of at least 99% of mycobacteria in culture relative to negative control.

2.1.4. Toxicity studies

Toxicity studies were not considered in all retrieve information, but for the sake of providing holistic information on medicinal plants used, data on toxicity of plants that showed activity either invitro or on BU patients are provided and they are often conducted in rodent models.

The present review has identified plants that are reported to be used to treat BU (Table 1). Some of these plants have undergone various degrees of scientific investigation, including testing on patients. In the following subsections, plants which have been investigated so far as potential sources of therapy against BU are presented.

2.1.5. Traditional medicine reports

2.1.5.1. Places and frequency of citation of plant species. The review has identified 98 plant species belonging to 88 genera and 48 plant families that are used for the treatment of BU or related symptoms. Places and frequency of citation of species used to treat BU are summarized in Table 1.

Most of the cited plants were from Benin, Ivory Coast, and Ghana (Table 1, Fig. 1) where 79 species were individually reported in only one country, including 35 in Ghana, 32 in Benin and 12 in
Table 1
Plants used ethnobotanically against Buruli ulcer in three West African countries: Benin, Ghana, and Ivory Coast.

<table>
<thead>
<tr>
<th>Family</th>
<th>Species</th>
<th>Part</th>
<th>Formulation and mode of usage</th>
<th>Country</th>
<th>Common /local name</th>
<th>Frequency of citation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amaranthaceae</td>
<td>Dysphania ambrosioides (L.) Muyakin &amp; Clemants (cited as Chenopodium ambrosioides L.)</td>
<td>Leaves</td>
<td>Decoction used for BU treatment</td>
<td>Benin, Ghana</td>
<td>Dangmbe be (twi)</td>
<td>2</td>
<td>Yemoa et al. (2008, 2011), Seefeld et al. (2013)</td>
</tr>
<tr>
<td>Amaryllidaceae</td>
<td>Allium cepa L.</td>
<td>Bulb</td>
<td>Infusion used in BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td>Anacardiaceae</td>
<td>Lannea kerstingii (Engl.) K. Krause</td>
<td>Leaves</td>
<td>Decoction used in BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td>Mangifera indica L.</td>
<td>Leaves,</td>
<td>Used as pomade or disinfectant: Infusion; the leaves and roots are heated and applied to the wound twice a day</td>
<td>Ivory Coast</td>
<td>Mango bark</td>
<td>2</td>
<td>Adjet et al. (2013), Trebissou et al. (2014)</td>
</tr>
<tr>
<td></td>
<td>Spondias mombin L.</td>
<td>Leaves</td>
<td>Decoction and trituration used in BU treatment</td>
<td>Benin; Ivory</td>
<td>Troman (baoulé)</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td>Annonaceae</td>
<td>Cleistopholis patens (Benth.) Engl. &amp; Diels</td>
<td>Leaves</td>
<td>Exudate from leaves is used for BU treatment</td>
<td>Ghana</td>
<td>Unspecified</td>
<td>1</td>
<td>Owusu-Sekyere (2012)</td>
</tr>
<tr>
<td></td>
<td>Monodora mystica (Gaertn.) Dunal</td>
<td>Seed</td>
<td>Seed decoction is used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td>Xylopia aethiopica (Dunal) A Rich</td>
<td>Fruit,</td>
<td>Pomade with seed for ulcer dressing, Decoction of fruit used for BU treatment.</td>
<td>Benin; Ivory</td>
<td>Sidian (baoulé)</td>
<td>1</td>
<td>Adjet et al. (2013), Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td>Apocynaceae</td>
<td>Alstonia boonii De Wild.</td>
<td>Leaves</td>
<td>Stem bark paste is used to bandage the washed ulcer and changed every other day</td>
<td>Ghana</td>
<td>Sonoro; nyamedua</td>
<td>2</td>
<td>Sam et al. (2013), Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Holarrhena floribunda (G. Don) T. Durand et Schinz</td>
<td>Root</td>
<td>Decoction used for BU treatment</td>
<td>Benin</td>
<td>kpakpatoun</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011, 2015)</td>
</tr>
<tr>
<td></td>
<td>Mondia whitei (Hook.F.) Skeels</td>
<td>Root</td>
<td>Mixed with local alcohol to produce a bitter and spread over the ulcer</td>
<td>Ghana</td>
<td>Asasehuanu</td>
<td>1</td>
<td>Seefeld et al. (2013)</td>
</tr>
<tr>
<td></td>
<td>Perugalaria daemina (Forssk.) Chiov.</td>
<td>Leaves</td>
<td>Leaves are boiled and spread over the ulcer</td>
<td>Ghana</td>
<td>Bankke</td>
<td>1</td>
<td>Seefeld et al. (2013)</td>
</tr>
<tr>
<td>Apocynaceae</td>
<td>Periploca nigrescens Aflz. (cited as Parquetina nigrescens (Aflz.) Bullock)</td>
<td>Leaves</td>
<td>Used as in BU treatment</td>
<td>Ivory Coast</td>
<td>Sroboué (baoulé)</td>
<td>2</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td>Secamone azelii (Roem. &amp; Schult.) K.Schum.</td>
<td>Areal part</td>
<td>Herbs are cooked as an infusion to wash and heal the ulcer</td>
<td>Ghana</td>
<td>Korantemaa</td>
<td>1</td>
<td>Seefeld et al. (2013)</td>
</tr>
<tr>
<td></td>
<td>Strophanthus hispidus DC.</td>
<td>Root</td>
<td>Decoction or maceration of root is used to wash the ulcer 3 times per day</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td>Araceae</td>
<td>Aglaonema commutatum Schott</td>
<td>Leaves</td>
<td>Infusion of leaves is used for BU treatment</td>
<td>Ghana</td>
<td>Ntome (twi), Anyatis (Ewe)</td>
<td>1</td>
<td>Seefeld et al. (2013)</td>
</tr>
<tr>
<td>Arecaceae</td>
<td>Borassus aethiopum Mart.</td>
<td>Flower</td>
<td>The flower is pressed to the wound for BU treatment</td>
<td>Ghana</td>
<td>Fan palm</td>
<td>1</td>
<td>Owusu-Sekyere (2012)</td>
</tr>
<tr>
<td></td>
<td>Elesis guineensis Jacq.</td>
<td>Leaves</td>
<td>The leaf is squeezed and the juice obtained is used as pomade or disinfectant in BU treatment</td>
<td>Ivory Coast</td>
<td>N’mé (baoulé)</td>
<td>1</td>
<td>Adjet et al. (2013)</td>
</tr>
<tr>
<td>Asparagaceae. Bignoniaceae</td>
<td>Dracaena arborea (Willd.) Link Newbouldia laevis (P. Beauv.) Seem</td>
<td>Leaves</td>
<td>Leaves are cooked as an infusion to wash and heal the ulcer</td>
<td>Ghana</td>
<td>Troman (twi)</td>
<td>4</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td>Spathodea campanulata P. Beauv.</td>
<td>Leaves, Root, Stem bark</td>
<td>Treatment of BU relief for skin conditions, swollen cheeks, body rashes. Disinfectants: Leaves and stem bark are used for sorer and ulcer dressing. Paste of bark used to bandage ulcer. Root/bark infusion is used for BU treatment. Cotton wool is soaked in decoction of leaf or fresh stem bark to clean sore, paste of bark used to bandage ulcer</td>
<td>Ghana; Ivory Coast; Benin</td>
<td>Biebiersi (baoulé), Kwaloowo mnu zo (twi)</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
<td></td>
</tr>
<tr>
<td>Capparaceae</td>
<td>Euademia eminens Hook.f.</td>
<td>root</td>
<td>Grinded roots are directly applied on the ulcer</td>
<td>Ghana</td>
<td>Dinsinkro</td>
<td>1</td>
<td>Seefeld et al. (2013)</td>
</tr>
<tr>
<td>Arecaceae</td>
<td>Ritchiea capparoides (Andrews) Britten</td>
<td>Root</td>
<td>Root maceration is used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td>Caricaceae</td>
<td>Carica papaya L.</td>
<td>Root,</td>
<td>Infusion: leaves and roots of papaya (Carica papaya) are heated and applied to the wound twice a day. Pomade: fresh root is mixed with Xylopia aethiopica seed to form a past used for ulcer bandage</td>
<td>Ivory Coast</td>
<td>Papayas Oflé or loflé (baoulé)</td>
<td>2</td>
<td>Adjet et al. (2013), Trebissou et al. (2014)</td>
</tr>
<tr>
<td>Cleomaceae</td>
<td>Cleome gymnandra L.</td>
<td>Whole plant</td>
<td>Grinded herbs are directly applied on the ulcer</td>
<td>Ghana</td>
<td>Sogbi</td>
<td>1</td>
<td>Seefeld et al. (2013)</td>
</tr>
<tr>
<td>Family</td>
<td>Species</td>
<td>Part used</td>
<td>Formulation and mode of usage</td>
<td>Country</td>
<td>Common /local name</td>
<td>Frequency of citation</td>
<td>References</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>------------------</td>
<td>--------------------</td>
<td>-----------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Clusiaceae</td>
<td><em>Garcinia kola</em> Heckel</td>
<td>Root</td>
<td>Root pulverisation or infusion used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td>Compositae</td>
<td><em>Laurnea taraxacifolia</em> (Willd.). Amin ex C.Jeffrey</td>
<td>Leaves</td>
<td>Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td><em>Vernonia amygdalina</em> Delile</td>
<td>Leaves</td>
<td>Used as for BU treatment</td>
<td>Benin, Ghana</td>
<td>Gbotti</td>
<td>2</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td><em>Cyperus cyperoides</em></td>
<td>Leaves</td>
<td>Leaf is washed in hot water and made into paste and used to bandage ulcer. Used as pomade or disinfectant in BU treatment</td>
<td>Ghana, Ivory Coast</td>
<td>Acheampong, Indépendance (baoulé)</td>
<td>2</td>
<td>Trébissou et al. (2014)</td>
</tr>
<tr>
<td></td>
<td><em>Castrca longaifolia</em> (Schumach. &amp; Thonn.) Müll. Arg.</td>
<td>Stem bark</td>
<td>Decoction is used as BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td><em>Euphorbia kamerunica</em> Pax.</td>
<td>Trunk</td>
<td>Decoction is used as BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td><em>Euphorbia unispina</em> N.E.Br.</td>
<td>Trunk</td>
<td>Decoction is used as BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td><em>Jatropha curcas</em> L.</td>
<td>Leaves</td>
<td>Leaves are used as pomade or disinfectant. Decoction of leaves is used as BU treatment.</td>
<td>Ghana, Benin, Ivory Coast</td>
<td>Aplôplô (baoulé)</td>
<td>3</td>
<td>Addo et al. (2007), Adjet et al. (2013), Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td><em>Jatropha gossypifolia</em> L.</td>
<td>Leaves</td>
<td>Pulverised leaves are used as BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td><em>Manihot esculenta</em> Crantz (cited as <em>Manihot utilisima</em> Pohl)</td>
<td>Leaves</td>
<td>Paste of leaf or tuber used to bandage ulcer after washing ulcer with infusion of <em>Vernonia amygdalina</em> leaf</td>
<td>Ghana</td>
<td>Bankley</td>
<td>1</td>
<td>Sam et al. (2013)</td>
</tr>
<tr>
<td></td>
<td><em>Ricinus communis</em> L.</td>
<td>Leaves</td>
<td>The leaves are pressed in the palms and the substance obtained is applied to the wound twice a day (maceration).</td>
<td>Ivory Coast</td>
<td>Attéédé</td>
<td>1</td>
<td>Trébissou et al. (2014)</td>
</tr>
<tr>
<td>Humiriaceae</td>
<td><em>Sacoglotis gabonensis</em> (Baill.) Urh.</td>
<td>Stem bark</td>
<td>Stem bark decoction is taken orally to treat or disinfect the ulcer. Alternatively the ulcer is recovered with fine powder as bandage.</td>
<td>Ivory Coast</td>
<td>Unspecified</td>
<td>1</td>
<td>Kone et al. (2007)</td>
</tr>
<tr>
<td></td>
<td><em>Ocinum americanum</em> L. (cited as <em>Ocinum canum</em> Sims)</td>
<td>Leaves</td>
<td>Infusion used for BU treatment</td>
<td>Ghana, Benin</td>
<td>Ahame</td>
<td>2</td>
<td>Seefeld et al. (2013), Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td><em>Ocinum gratissimum</em> L. (cited as <em>Ocinum viride</em> Wild.)</td>
<td>Leaves</td>
<td>Infusion used for BU treatment</td>
<td>Ghana, Benin</td>
<td>Onunumu (Twi)</td>
<td>2</td>
<td>Seefeld et al. (2013), Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td><em>Holmliandia opposita</em> Vahl</td>
<td>Leaves</td>
<td>The juice of the fresh leaves is applied to wounds</td>
<td>Ghana</td>
<td>Abrewaninsu</td>
<td>1</td>
<td>Seefeld et al. (2013)</td>
</tr>
<tr>
<td>Leguminosae</td>
<td><em>Albizia zygia</em> (DC.) J.F.Macbr.</td>
<td>Seed</td>
<td>Roasted seed paste used to bandage the ulcer for treatment after washing ulcer with infusion of <em>Momordica charantia</em> L. leaf</td>
<td>Ghana</td>
<td>Nkroma</td>
<td>1</td>
<td>Sam et al. (2013)</td>
</tr>
<tr>
<td></td>
<td><em>Baushia thomningii</em> Schum. (cited as <em>Piloistigma thomningii</em> (Schum.) Milne-redh.)</td>
<td>Leaves</td>
<td>Decoction used in BU treatment. Leaves are also used as pomade or disinfectant</td>
<td>Benin, Ivory Coast</td>
<td>Djamla (baoulé)</td>
<td>2</td>
<td>Adjet et al. (2013), Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td><em>Erythrophleum suaveolens</em> (Guill. et Perr.) Brenan</td>
<td>Root or stem bark</td>
<td>Decoction or pulverisation of root or stem bark is used to wash the ulcer and powder apply 3 times per day during 3 to 4 days or more according to the size of the wound. In addition the decoction is administered as tea. The treatment can last from 2 weeks to many months in the BU treatment.</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td><em>Philenoptera cyanescens</em> (Schum. &amp; Thonn.) Roberty (cited as <em>Lonchorcarpus</em></td>
<td>Root</td>
<td>Maceration of root is used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td>Family</td>
<td>Species</td>
<td>Part used</td>
<td>Formulation and mode of usage</td>
<td>Country</td>
<td>Common / local name</td>
<td>Frequency of citation</td>
<td>References</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>---------------</td>
<td>---------------------</td>
<td>-----------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td><strong>Nyctaginaceae</strong></td>
<td>Mitracarpus villosus (Moure ex Baker)</td>
<td>Leaves</td>
<td>Leaf paste used to bandage ulcer for surgery.</td>
<td>Ghana</td>
<td>Yennua/ Sempe</td>
<td>2</td>
<td>Sam et al. (2013), Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus falcatum (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus affinis (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus berterianum (Baker)</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus brevius (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus evansii (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpusfortunei (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus fusca (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus glaber (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus hookeri (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus hypoleucus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus longifolius (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus myrtifolius (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus mucronatus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus paniculatus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus penicillus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus philippinus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus platycarpus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus praemorsus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus pseudopuertasus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus pulcher (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus quercifolius (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus robustus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus rotundifolius (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus semibaccatus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus sericeus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus subcordatus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus subpaniculatus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus subviridis (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus tetrasanguineus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus tenuifolius (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus tomentosus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus tortuosus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus trichopodus (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus vulcanensis (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus xerophyllum (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus yunnensis (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Mitracarpus zollingeri (L.) G. Don.</td>
<td>Whole plant</td>
<td>- Decoction used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Addo et al. (2007)</td>
</tr>
</tbody>
</table>

---

**References**

- Sam et al. (2013), Addo et al. (2007), Yemoa et al. (2008, 2011), Seefeld et al. (2013)
- Addo et al. (2007)

---

**Addendum**

- Yemoa et al. (2008, 2011)

---

**Additional Notes**

- Additional references and data not explicitly mentioned in the table may be found in the cited sources.

---

**Table 1 (continued)**

- For a complete list of references, please consult the original publication.
Ivory Coast. A total of 16 plants were individually reported in two countries consisting of 11 in Benin and Ghana and 5 in Benin and Ivory Coast. Only 3 plants were reported concomitantly in Benin, Ivory Coast, and Ghana (Fig. 1).

**Table 1** (continued)

<table>
<thead>
<tr>
<th>Family</th>
<th>Species</th>
<th>Part used</th>
<th>Formulation and mode of usage</th>
<th>Country</th>
<th>Common /local name</th>
<th>Frequency of citation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sapindaceae</td>
<td><em>Clausena anisata</em> (Wild.) Hook. f. ex Benth.</td>
<td>Root</td>
<td>Infusion of root used for BU treatment</td>
<td>Benin,</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td><em>Zanthoxylum zanthoxyloides</em> (Lam.) Zepern. &amp; Timler</td>
<td>Leaves</td>
<td>Decoction/trituration of leaves used for BU treatment</td>
<td>Benin, Ghana</td>
<td>Towantin</td>
<td>2</td>
<td>Yemoa et al. (2008, 2011), Seefeld et al. (2013)</td>
</tr>
<tr>
<td></td>
<td><em>Paullinia pinnata</em> L.</td>
<td>Leaves</td>
<td>Decoction of leaves used for BU treatment</td>
<td>Benin, Ghana</td>
<td>N’gouhin</td>
<td>2</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td><em>Solanum erianthum</em> D. Don</td>
<td>Leaves</td>
<td>Leaf paste used to bandage ulcer</td>
<td>Ghana</td>
<td>Pepediewuo</td>
<td>1</td>
<td>Sam et al. (2013)</td>
</tr>
<tr>
<td></td>
<td><em>Solanum rugosum</em> Dunal</td>
<td>Leaves</td>
<td>Leaves are dried under shade for two weeks.</td>
<td>Ghana,</td>
<td>Ivory</td>
<td>1</td>
<td>Trébissou et al. (2014)</td>
</tr>
<tr>
<td></td>
<td><em>Solanum torvum</em> Sw.</td>
<td>Leaves</td>
<td>Ground leaves are directly applied on the ulcer</td>
<td>Ghana</td>
<td>Abedru</td>
<td>1</td>
<td>Seefeld et al. (2013)</td>
</tr>
<tr>
<td>Talinaceae</td>
<td><em>Talinum fruticosum</em> (L.) Juss. (cited as <em>Talinum triangulare</em> (Jacq.) Willd.)</td>
<td>Leaves</td>
<td>Ground leaves are directly applied on the ulcer</td>
<td>Ghana</td>
<td>Bro-bro</td>
<td>1</td>
<td>Seefeld et al. (2013)</td>
</tr>
<tr>
<td>Vitaceae</td>
<td><em>Leea guineensis</em> G. Don</td>
<td>Root</td>
<td>The pounded root is used for BU treatment</td>
<td>Ghana</td>
<td>Agyaben</td>
<td>1</td>
<td>Owusu-Sekyere (2012)</td>
</tr>
<tr>
<td>Xanthorrhoeaceae</td>
<td><em>Aloe buettneri</em> A. Berger</td>
<td>Leaves</td>
<td>Maceration for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
<tr>
<td></td>
<td><em>Aloe vera</em> (L.) Burm.f.</td>
<td>Leaves</td>
<td>BU treatment, accelerates wound healing, burns, sores, ulcers, inflammation</td>
<td>Ghana</td>
<td>Unspecified</td>
<td>2</td>
<td>Addo et al. (2007), Seefeld et al. (2013)</td>
</tr>
<tr>
<td></td>
<td><em>Curcuma longa</em> L.</td>
<td>Leaves</td>
<td>Leaves decoction is used for BU treatment</td>
<td>Benin</td>
<td>Unspecified</td>
<td>1</td>
<td>Yemoa et al. (2008, 2011)</td>
</tr>
</tbody>
</table>

BU—Buruli ulcer.

Cassia alata L., Bauhinia thonningii (cited as Piliostigma thonningii), Ocimum gratissimum (cited as Ocimum viride), Vernonia amygdalina, Chromolaena odorata, Carica papaya, Periploca nigrescens (cited as P. nigrescens), Alstonia boonei, Mangifera indica, and

![Fig. 1. Repartition of plants used to treat Buruli ulcer per country.](image-url)
Dysphania ambrosioides (cited as Chenopodium ambrosioides) (2) Many others were cited only once.

The plant families with more cited species included Apocynaceae and Euphorbiaceae (7), Leguminosae (6), Solanaceae (5), Phyllanthaceae (4), Anacardiaceae, Annonaceae, Bignoniaceae, Compositae, Lamiaceae, Meliaceae, Poaceae, and Rutaceae (3), Araceae, Arecaceae, Capparaceae, Combretaceae, Malvaceae, Moraceae, Musaceae, Rubiaceae, Xanthorrhoeaceae and Zingiberaceae (2). The other plant families were represented by only one species as shown in Table 1.

Cultural believes are comparable in West Africa, especially between Ivory Coast and Ghana who are neighbouring countries, and Benin. It should also be emphasized that diversity of floras is shared by these nations. Plants citation frequency was therefore expected to corroborate this pattern. The observed disparities highlight a concern about the reports contents that might indicate a lack of credibility, or otherwise a rich biodiversity of medicinal plants with anti-BU potential. This latter option might underline a concern about the reports contents that might indicate a lack of credibility, or otherwise a rich biodiversity of medicinal plants with anti-BU potential. This latter option might underline a poor documentation of plants of interest for BU control, and therefore indicates that more interest and emphasis should be developed in this line, especially by local governments and scientists.

2.1.6. Recipes reports

2.1.6.1. Preparation of ethnopharmacological recipes for BU control. The ethnopharmacological data including plant parts used, methods of preparation and administration of potions are shown in Table 1. The repartition of forms of herbal preparations and routes of administration and dosage of prescribed herbal remedies are shown in Figs. 2 and 3, respectively. The preparation of the medicines employed several methods, decoction (27%), followed by trituration (20%), infusion (15%), powders (12%), pomade and maceration (10%). Of note, decoction and trituration are the fastest approaches when it comes to potions taken orally or applied to wounds.

Some of these preparations were made from mixtures of different plant species and used for the treatment of BU: Manihot esculenta and V. amygdalina; Gossypium hirsutum, Physalis angulata, Delonix regia and Jatropha curcas; C. papaya and Xylopia aethiopica; Citrus aurantifolia and Spathodea campanulata; Gossypium barbadense, Albizia zygia and Momordica charantia; and Spigelia anthelmia and Zea mays (Addo et al., 2007; Sam et al., 2013; Adjet et al., 2013; Seefeld et al., 2013; Trébissou et al., 2014).

Leaves were the most frequently used plant part (53), followed by root (22), fruit/seed (12), and stem bark/bark (11).

2.1.7. Routes of administration and dosage prescription of herbal remedies

Bandage or dermal administration (42 citations) was the predominant route of administration followed by oral administrations (5 citations). The choice for bandage or dermal administration is consistent given that BU usually starts with painless, raised skin lesion or papule that may extend from the skin into the subcutaneous tissue. Therefore, it becomes a serious concern for rural populations when the oedema breaks down to form an ulcerated wound that needs bandage and healing. Decoction, infusion, or maceration were reported as taken orally or used to wash or disinfect the wound while powders, trituration, and ointments were applied on the ulcer as bandages (Table 1).

Very few reports described dosage prescriptions and generally recommendations were to administer the herbal remedies twice or thrice daily during 3 days to many months or continued until recovery. The problems associated with dosage used in herbal remedies prescription have been repeatedly highlighted (Tsabang et al., 2012; Asase et al., 2010). In fact, the inadequate knowledge about herbs and their likely contribution to health makes the herbal dosage concept difficult to understand. It is generally believed in settings where traditional herbal medicine is keen that the pharmacological effect of herbs is due to their pretended active and “safe” components that will only exert quick effect when taken in large amounts. Almost all the reports made no mention of possible side effects. But this could be anticipated as most traditional healers do not, broadly speaking, know of the probable and significance of side effects of their herbal remedies.

Overall, plant potions are mainly used during necrosis ablation and wound healing phases of treatment (Johnson et al., 2004).
Different plant parts are used under various recipes administered by oral or topical route. The survey reports identified many recipes, the most cited including decoction, maceration, powder, carbonisation, triturum, pomade, and infusion (Table 1). Many other plants that are not described in this review have been reported in BU treatment and against skin ulcers without any description of recipes. In many occasions, detailed information about herbal remedies dosage were not specified, but only the plant name and route of administration and the outcome were mentioned.

2.1.8. Potency of herbal remedies in patients with Buruli ulcer and toxicity

A total of 7 species: *Ricinus communis*, *Nicotiana tabacum*, *M. indica*, *C. papaya*, *Solanum rugosum*, *Cyperus cypereoides* (cited as *Mariscus alternifolius*), and *Moringa oleifera* have been administered to patients and the outcome followed up. The first clinical study based on 6 plants used to treat BU was conducted in three Buruli ulcer caring and management centers in Ivory Coast. Three preparations were used, including maceration of *R. communis* and *N. tabacum*, infusion of *M. indica* and *C. papaya*, and powder for *S. rugosum* and *C. cypereoides* that were applied twice or thrice a day on the ulcer. Of a study population of 273 patients, 219 (80%) were healed (with *N. tabacum*, *M. indica*, *S. rugosum* and *C. papaya*), while 41 (15%) had their ulcer stabilized (with *R. communis* and *C. cypereoides*) and 13 (5%) felt no effect after treatment. This study highlighted the beneficial potential of the used herbs remedies (Trébissou et al., 2014). In the second study, a trial in two groups of 15 children (2–15 years) attending the Centre St Pio Padio, Ivory Coast and each having clinical forms of BU showed that after six weeks of treatment, children receiving normal diet supplemented with 330 mL of aqueous extract of *M. oleifera* leaves per meal, had a higher rate of healing compared to children under normal non supplemented diet (Kodia et al., 2014). The results achieved by the authors emphasize the added value of supplementation of the diet with *M. oleifera* extract. Meanwhile, understanding the mechanism of efficacy of this medicine could be helpful in the therapy of BU. Moreover, such beneficial effect should be validated through more detailed investigations of the added extract, specifically its action against the causative mycobacterial agent or other values such as anti-oedematous, anti-inflammatory, sedative, wound healing, immune inhibition, and inhibition enzymes involve mycolatone production.

On another hand, close collaboration between herbal practitioners and modern physicians and other health professionals should be effective to help tackle the impact of the disease in endemic regions (Johnson et al., 2004; Renzaho et al., 2007). However, no detailed safety studies were conducted prior to these trials.

To a certain extent, these plants that were reportedly used in clinical settings to treat BU have undergone safety studies. *Ricinus communis* intoxications in humans and animals have been known for centuries and it is attributed mainly to the toxicity of ricin, haemagglutinin and ricicine (Worbs et al., 2011). The seeds are the most toxic part of the plant although the leaves are also poisonous. The inhalational toxicity (in estimated LD50), for two different *R. communis* cultivars in rats has been reported to be between 3.7 \( \mu g/kg \) and 9.8 \( \mu g/kg \) body weight. In non-human primates, the LD50 after inhalational application was found to be 5.8 \( \mu g/kg \) for African green monkeys and 15 \( \mu g/kg \) for rhesus monkeys. The least toxic route is oral uptake or intra-gastric delivery and is about 1000 times less toxic than parenteral injection or inhalation. For mice, LD50 values of 21.5 mg/kg and 30 mg/kg were reported (Worbs et al., 2011). In clinical reports, the number of seeds ingested causing mild to severe symptoms, including a fatal outcome, range from uptake of only single seed to up to 30 seeds (Worbs et al., 2011).

Crushed leaves of *N. tabacum* that are applied on wounds contain nicotine, malic and citric acids, phenolic acids, flavonoids, coumarins and enzymes (Lans et al., 2001). An oral LD50 of 50 mg/kg body weight was observed in rats with no significant effects on hematoctit and bleeding time following 6 weeks of oral administration (Ukoha et al., 2012). Meanwhile, the increase in biochemical parameters such as: transaminases and alkaline phosphatase activities suggested that it may be associated with liver toxicity at up to 600 mg/kg (Nweze et al., 2015).

The administration of the aqueous decoction from leaves of *M. indica* up to a dose of 5000 mg/kg (per os) did not produce any signs or symptoms of toxicity in treated male Swiss albino mice (Severi et al., 2009). At this dose range, the extract can be categorized as safe. It is also documented that the acute toxicity (LD50) of *M. oleifera* aqueous extract of 16,100 mg/kg and ethanol extract of 39,800 mg/kg are within the safe range (Kasolo et al., 2012a). The oral daily administration of LD50 dose of *M. oleifera* leaves aqueous extract for 30 days shows features of mild sub-acute toxicity and indicates safer outcomes (Kasolo et al., 2012b). In another study, acute toxicity studies of *M. oleifera* leaves extract in rats showed no mortality at doses range of up to 2000 mg/kg. However, *M. oleifera* is genotoxic at supra-supplementation levels of 3000 mg/kg. In a sub-acute toxicity study, oral treatments in rats for 21 days with this extract at 400, 800 and 1600 mg/kg caused varied significant changes in haematological parameters that could be attributable to the presence of isothiocyanate producing glycosides (Adedapo et al., 2009). However this results have little scientific significance given the contradiction with the previously mention findings. The subchronic treatment of Sprague Dawley rats for 13 weeks with the leaf extract of *C. papaya* showed no significant toxicity effect at doses up to 2000 mg/kg. However, many orders of magnitude above the levels employed in traditional medicine (Ismail et al., 2014). Within the framework of this literature survey, no report on toxicity study on *C. cypereoides* and *S. rugosum* was found.

2.2. Anti-BU plants: In vitro potency, phytochemistry, and toxicity

Many plants with claimed anti-BU potential have undergone various degrees of scientific investigations as evidenced in this review. Briefly, reported scientific investigations include botanical identification and plant collection, aqueous/organic extraction and *in vitro* testing against *M. ulcerans*, the causative agent of BU. Generally, active extracts are further fractionated on a bio-guided basis using chromatographic techniques to isolate the bioactive natural products. In the following subsections, data reported on *in vitro* potency against *M. ulcerans* of 13 species (including a mixture of two species; tonic 1) used in traditional treatment of BU are presented (Table 2). In addition, reported phytochemical and toxicological data on plants as well as isolated active compounds are presented.

2.2.1. Aglaonema commutatum Schott.

*A. commutatum* is an erect herbaceous common ornamental plant that is used to treat BU. Extract from this plant showed anti- *M. ulcerans* activity with MIC value of 40 \( \mu g/mL \) (Table 1) (Addo et al., 2007). Leaves juice was reported to be used to heal wounds. It was also shown to exhibit inhibitory effects on *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* commonly involved in burns and wound infections that can account for its anti-BU potential. Very few studies have been reported on this plant. The main report referred to its poisonous crystals and its use as ornamental plant. All parts of the plant contain calcium oxalate crystals that can cause inflammation and irritation of the gastrointestinal tract with some fatalities reported (Fuller and McClintock, 1986).
2.2.2. Aloe vera (L.) Burm. f.

A. vera is a perennial plant widely used for the treatment of various ailments including BU (Addo et al., 2007; Seefeld et al., 2013). Leaf extract showed MIC value of 40 μg/mL (Table 2) (Addo et al., 2007) on M. ulcerans. Numbers of its chemical has been identified such as carbohydrate polymers; glucosamnans, phenolic compounds such as chrome and anthraquinone. Naturally the gel is used for its wound healing potential as its high content in water can keep the wound moist and promote epithelial cell migration. In addition, the main carbohydrate, mannose 6-phosphate, has been suggested to play a significant role in the wound healing potential of A. vera gel (Davis et al., 1994; Bruneton, 1995). In fact, the binding of mannose 6-phosphate to the growth factor receptors on the surface of the fibroblasts increases both collagen and proteoglycan synthesis that directly stimulates macrophages and fibroblasts resulting in tissue repair. Similarly, acemannan purified from leaves, has showed to accelerate wound healing and reduce radiation induced skin reactions through macrophage activation and consequently may stimulate the release of fibrogenic cytokines otherwise growth factors may directly bind to acemannan and promote their stability and extend the stimulation of granulation tissue. Genin, a saponin contained in A. vera, has also been reported as involved in wound healing activity (Mukherjee et al., 2014; Davis et al., 1994; Bruneton, 1995). Studies of the growth of normal human cells in vitro demonstrated that cell growth and attachment were promoted by exposure to fresh A. vera leaves, whereas a stable gel preparation was shown to be cytotoxic to both normal and cancer cells. However, the cytotoxic effects of the gel were thought to be due to the addition of other substances to the gel during processing (Winters et al., 1981). Treatment over 6 months with A. vera in rats did not induce tolerance in the sense of a reduced laxative effect. Meanwhile, prolonged use or overdosage may cause nephritis, vomiting, bloody, mucus, or watery diarrhoea leading to electrolyte imbalance and hemorrhagic gastritis. A. vera gel has been reported to cause contact and photo dermatitis or erythema with papulous when administered on the skin, despite its anti-inflammatory potential and ability to heal wounds. In ten control trials involving 803 subjects no withdrawals or significant side reactions was observed, and the benign adverse reactions mainly involved burning after topical application, contact dermatitis and mild itching. All adverse effects were reversible and A. vera was generally well tolerated (Mukherjee et al., 2014).

2.2.3. Alstonia boonei De Wild.

Alstonia is a widespread genus of evergreen trees and shrubs. The leaves paste of A. boonei is used for daily bandage of washed ulcer in BU treatment. Addo et al. (2007) reported it to have activity in vitro against M. ulcerans with MIC value of 40 μg/mL (Table 1). This plant known for its wound healing properties contains complex polysaccharides in abundance, mainly mucilages but also alkaloids, tannins, steroids, saponins, glycosides, flavonoids, triterpenoids, and terpenoids (Chime et al., 2013; Igbinaduwa and Obasuyi, 2012). This diversity of bioactive secondary metabolites found in this plant might sustain its effect against BU. The acute toxicity dose of the ethanolic and methanolic extracts (root & bark) of A. boonei was shown to be above 5000 mg/kg body weight (Iyiola et al., 2011; Onwusonye et al., 2014). Histological examination of liver sections of mice also showed relatively normal histological features (Onwusonye et al., 2014). The stem bark hydroethanolic extract showed no effect in guinea-pigs kidney at 50 and 200 mg/kg following 2 weeks of treatment. On another hand, extract dose of 200 mg/kg significantly raised blood urea, creatinine, potassium, and chloride ions levels by the 4th week and the kidney cells showed obvious histological signs of potential toxicity (Oze et al., 2006), indicating that A. boonei potions should be taken with caution.

2.2.4. Capsicum annum L.

C. annum is a perennial shrub, with woody trunk which bears green fruits that ripen to red. The fruits are widely known in tropical Africa where they are largely used as spices for pepperish taste. The maceration of fruit is used for BU treatment and has shown MIC value of 40 μg/mL on 7 M. ulcerans isolates (Table 2) (Addo et al., 2007). A phytochemical study of C. annum established the presence of reducing compounds, saponins, alkaloid salts, alkaloids, quaternary bases, anthracenosides, flavanoids, etc. and other compounds such as chromone and anthraquinones. Naturally identified such as carbohydrate polymers; glucomannans, phenolic compounds such as chrome and anthraquinone. These compounds are known to promote their stability and extend the stimulation of granulation tissue. Genin, a saponin contained in A. vera, has also been reported as involved in wound healing activity (Mukherjee et al., 2014; Davis et al., 1994; Bruneton, 1995). Studies of the growth of normal human cells in vitro demonstrated that cell growth and attachment were promoted by exposure to fresh A. vera leaves, whereas a stable gel preparation was shown to be cytotoxic to both normal and cancer cells. However, the cytotoxic effects of the gel were thought to be due to the addition of other substances to the gel during processing (Winters et al., 1981). Treatment over 6 months with A. vera in rats did not induce tolerance in the sense of a reduced laxative effect. Meanwhile, prolonged use or overdosage may cause nephritis, vomiting, bloody, mucus, or watery diarrhoea leading to electrolyte imbalance and hemorrhagic gastritis. A. vera gel has been reported to cause contact and photo dermatitis or erythema with papulous when administered on the skin, despite its anti-inflammatory potential and ability to heal wounds. In ten control trials involving 803 subjects no withdrawals or significant side reactions was observed, and the benign adverse reactions mainly involved burning after topical application, contact dermatitis and mild itching. All adverse effects were reversible and A. vera was generally well tolerated (Mukherjee et al., 2014).
flavonoids, coumarin derivatives, steroid glycosides and anthocya-
nosides (Lagu and Kayanja, 2013). C. annuum also contains a 
complex mixture of essential oils, waxes, coloured materials 
(mainly capsanthin, capsorubin, zeaxanthin, cryptoxanthin, 
and lutein), and several capsaicinoids (Wesołowska et al., 2011). Study 
by Lagu and Kayanja (2013) indicated a LD₅₀ of 12,043 mg/kg for 
aqueous extracts of C. annuum and 5492 mg/kg for 70% ethanolic 
extracts and concluded that the aqueous and 70% ethanolic 
extracts are safe to use and are classified as basically non-toxic (5000–15,000 mg/kg body weight). Indeed the complex chemical 
composition of C. annuum fruit appears to be an advantage in 
exerting beneficial biological activities. However, other studies 
have demonstrated that a capsaicinoid derivative, capsaincisin 
oral LD₅₀ values as low as 161.2 mg/kg in rats and 118.8 mg/kg in 
mites. In addition, haemorrhage of the gastric fundus was observed 
in some of the animals that died. Intravenous, intraperitoneal, 
and subcutaneous LD₅₀ values were lower. In subchronic oral toxicity 
uses studies using mice, capsaincisin produced statistically significant 
differences in the growth rate as the liver/body weight increased 
(Cosmetic Ingredient Review Expert Panel, 2007). Capsaincin is an 
active component of chili peppers, which are plants belonging to 
the genus Capsicum. It is an irritant for mammals, including 
humans, and produces a sensation of burning in any tissue with 
which it comes into contact. Capsaincin is used as an analgesic in 
topical ointments, nasal sprays, and dermal patches to relieve pain. 
These beneficial features of capsaincin if well managed, could add 
value to the use of medicinal plants to control BU.

2.2.5. *Jatropha curcas* L.

*J. curcas* is a tree that is reportedly used in traditional medicine to 
cure BU. Its leaf ethanolic extract inhibited the growth of *M. ulcerans* 
with MIC value of 250 µg/mL. Numerous biologically 
active compounds have been isolated and characterized from all 
parts of this plant including flavonoids, apigenin, vitezin, isovex-
tin, sterol, stigmasterol, β-sitosterol, β-glucoside, sapogen-
ins, alkaloids, triterpenae alcohol and 1-triacetantol (Prasad et al., 
2012). The latex contains proteolytic enzymes that have been 
suggested to provide significant wound healing activity (Lans et al., 
2001). Although fatalities with *Jatropha* poisoning are rare, 
Abudu-Agyue et al. (1986) demonstrated that oral seeds adminis-
tered to mice can cause macroscopic anal haemorrhage and death. They 
also found that extract of the seed administered intraper-
itoneally in mice can cause death in doses as low as 1 mg/kg 
(Adudu-Agyue et al., 1986). Singhal et al. (2013) studied the clinical 
and biochemical profiles of eight children with *J. curcas* poisoning 
and observed lethargy, severe abdominal pain, inability to ingest, 
and intense thirst amongst the most prominent complaints in all 
children (Singhal et al., 2013).

2.2.6. *Holarrhena floribunda* (G.Don) T. Durand

*H. floribunda* grows as a shrub or tree (Yemoa et al., 2008) and 
is used to treat BU. Yemoa et al. (2011) reported that *H. floribunda* 
root ethanol extract inhibited the growth of *M. ulcerans* with MIC 
value of 125 µg/mL. The methylene chloride fraction of this extract 
containing alkaloids also inhibited the growth of *M. ulcerans* with 
an MIC value of 125 µg/mL as well as the alkaloid-rich extract 
(MIC=62.5 µg/mL). Chemical compounds isolated from *H. flor-
ibunda* include holaphylline, holaphyllamine, holamine, holaphylli-
nol, holaphyllidine, holadysamine, holarrhines, conessine, and 
progesterone (Yemoa et al., 2015). Holamine, holaphyllamine and 
holaphylline showed significant anti-inflammatory properties that 
can add value to the anti-BU properties. They cause sodium 
retention and act as diuretics in rats. Aqueous extracts of root 
bark, stem bark and leaves showed relatively low toxicity 
(Schmelzer, 2006). Overall, the bioactive components isolated 
from this plant support its use in traditional medicine to treat BU.

2.2.7. *Sacoglottis gabonensis* (Baill.) Urb.

*S. gabonensis* is a tropical rain forest tree used in traditional 
medicine to treat BU. The stem bark decoction is taken orally or used 
for disinfecction of ulcer or covered with fine powder as bandage. Its 
aqueous extract showed promising activity against *M. ulcerans* 
in vitro (MIC=780 µg/mL) (Kone et al., 2007) (Table 2). The phyto-
chemical screening of its stem bark extract showed the presence of 
sterols, polyterpenes, polyphenols, flavonoids, tannins, saponins and 
alkaloids. Sofowora (1996) also reported that these compounds are 
responsible for the biological activities of a plant. The acute and 
sucutate toxicity studies of the aqueous extract of this plant showed 
a LD₅₀ value of 5000 mg/kg in mice per os whereas a 28 day 
administration of up to 350 mg/kg/day did not significantly influence 
haematological and biochemical parameters (Kone et al., 2009).

2.2.8. *Solanum torvum* Sw.

*S. torvum* is a commonly used herb in traditional medicine that 
possesses antitumor activity (Agrawal et al., 2010). The antimicro-
bial properties of its leaves have been reported in Gabon for cuts 
and wounds (Schippers, 2004). Its leaf decoction that is used to 
treat BU has been reported to act against *M. ulcerans* with MIC 
value of 40 µg/mL (Table 1) (Addo et al., 2007). *S. torvum* revealed 
the presence of flavanoids, alkaloids, sterols and triterpenes which 
may be responsible for anti-ulcer property (Agrawal et al., 2010). 
This plant also contains number of steroideal glycosides among 
which torvoside A–H are considered to be furostanol glycosides. 
Torvoside M and N have antimicrobial activity and cytotoxic effect 
on PC-12 and HCT-116 cell lines. Non alkaloidal constituents like 
tetrahydrocannabinolic acid, sitosterol, stigmasterol and campesterol 
have also been isolated and identified from *S. torvum* leaves 
(Agrawal et al., 2010). Acute intoxication with poisonous *S. torvum* 
berries appears to cause toxic myopathy. The constituents directly 
responsible for this effect remain unknown; however, there is a 
higher likelihood of the class of solanaceous steroideal glycoalk-
aloïds. Indeed, steroideal glycoalkaloïds inhibit serum and erythro-
cyte acetycholinesterase and butyrylcholinesterase and lead to 
clinical manifestations including gastrointestinal distress, cranial 
nerve abnormalities, and respiratory weakness. Electrophysiologi-
cal findings have never been described in affected patients (Glover 
et al., 2014). Solasonine, larger amounts of solamargine, and other 
steroideal glycoalkaloïds have been isolated in the toxic berry 
strains. *S. torvum* poisoning can produce significant neurological 
and gastrointestinal effects which appear to be mediated by 
steroideal glycoalkaloïds present in the berries (Smith et al., 
2008). Given this toxicity scale, use of this plant part in patients 
should therefore be avoided.

2.2.9. *Spathodea campanulata* P. Beauv.

The used of *S. campanulata* has been reported in the treatment of 
BU and relief for skin conditions, swollen cheeks, and body 
rashes. The leaves and stem bark paste are used to bandage ulcers 
while infusions of the leaves, root and bark are also used to clean 
ulcers (Adjet et al., 2013; Sam et al., 2013; Addo et al., 2007; Yemoa 
et al., 2008). Root decoction showed inhibitory potency on 7 *M. ulcerans* isolates with MIC value of 25 µg/mL (Table 1) (Addo et al., 
2007). Preliminary phytochemical screening revealed the presence 
of carboxydrates, alkaloids, tannins, and glycosides in extracts of 
flowers, and of steroids, carbohydrates, proteins, tannins glyco-
alds and alkaloids in the bark of the plant (Ilodigwe et al., 2010a). 
Tannins, saponins, anthraquinone glycosides, and flavonoids were 
also identified in leaves (Ilodigwe et al., 2010b). The acute toxicity 
potential in mice showed an estimated LD₅₀ of 4500 mg/kg with
the ethanolic leaf extract (Ilodigwe et al., 2010a) with no mortality during the period of study but the animals showed signs of anorexia, weakness, sluggishness and significant ($p < 0.05$) reduction in food and water intake and body weight. In the subchronic study, 750–3000 mg/kg of the extract were administered daily for 90 days and showed non-significant effect on haematological parameters while liver biochemical markers transaminases and alkaline phosphatase were increased followed by recovery 28 days post-treatment (Ilodigwe et al., 2010b).

### 2.2.10. *Syzygium aromaticum* (L.) Merr. & L.M. Perry

*S. aromaticum* is a tree commonly known as clove tree. It is widely used as analgesic and antiseptic primarily in dentistry for its main ingredient eugenol. Reports indicate that it is traditionally used externally or locally for the treatment of minor infections of the mouth and skin, dressing of minor wounds, and BU (Dalziel, 1956; Addo et al., 2007). *In vitro* screening of its seeds against *M. ulcerans* showed MIC value of 25 μg/mL (Table 1) (Addo et al., 2007). Besides, various studies have been carried out on the chemistry of *S. aromaticum* revealing that clove buds contain 15–20% essential oil, with high content in eugenol (70–85%), eugenyl acetate (15%) and β-caryophyllene (5–12%). Other reported compounds in clove buds include vanillin, crotegolic acid, tannins, gallotannic acid, methyl salicylate, flavonoids, eugenin, kaempferol, rhamnetin, eugenitin and triterpenoids like oleanolic acid (Mittal et al., 2014). The European Medicines Agency, (2011) reported that acute toxicity of a decoction of clove studied in 30 mice fasted overnight showed no respiratory, gastrointestinal tract, central nervous system symptoms, behavioural patterns and mortality and exhibited LD$_{50}$ of 263 mg/kg (i.p.) and 2500 mg/kg (oral). No signs of mortality or gross behavioural changes were observed either after administration of 500 mg/kg of ethanolic extract (DER app. 10:1, ethanol 50%) p.o. Also, a single oral dose of 140 mg/animal killed rats within a short period of time. Other studies also indicated that undiluted clove oil applied on the dorsal skin of hairless mice did not cause irritation. On intact or shaved rabbit skin clove essential oil acted under occlusive conditions as a weak irritant. Phototoxic effects were not observed with undiluted clove oil on hairless mice and pigs. Significant alterations in liver enzymes and haematological parameters were reported after 90 days of administration of a decoction of clove at doses of 300 mg/kg and 700 mg/kg in rats. Even at lower dose, histopathological modifications could be found in body organs. The authors concluded that a prolonged use of decoctions of clove should be avoided. Clove essential oil in oral dosages of 35 or 70 mg per animal (rat) over 8 weeks was tolerated without signs of toxicity. Higher doses led to inactivity and weight loss. About 105 mg/animal p.o. daily for 2 to 3 weeks led to serious liver and kidney damage and death of the animals (European Medicines Agency, 2011). On another hand, all animals died within 24 h after oral administration of 5000 mg/kg of the essential oil in rats and the autopsy showed bleeding in the stomach and intestines, and pleural effusion (European Medicines Agency, 2011). Essential oils are complex lipophilic mixtures that are highly diffusible across cell membranes and might exert significant toxicity effect on organs when taken orally or injected at high undiluted doses. Caution should therefore be paid while using these substances that are otherwise beneficial when used with moderation.

### 2.2.11. Tonic 1: Mixture of Spigelia anthelmia L. and Zea mays L.

The mixture of *Z. mays* grain and *S. anthelmia* leaves reported as used in traditional BU treatment showed growth inhibition of 7 *M. ulcerans* isolates with MIC values of 6.25–25 μg/mL (Table 1) (Addo et al., 2007).

*Spigelia anthelmia* L.

*S. anthelmia* is a common annual weed of cultivation in open re-growths, on unused land in towns (Jegede et al., 2006). Phytochemical investigation has described the isolation of the alkaloid spiganthine, volatile alkaloids, isoquinoline and acetylene isomer, and three quaternary alkaloids, choline, benzoylcholine and 2,3-dimethylacryloyl choline, phenolcarboxylic acids and flavonoids (Maia de Morais et al., 2002). The acute toxicity study by intraperitoneal administration of the aqueous extract of *S. anthelmia* showed a LD$_{50}$ value of 1140 mg/kg in rats (Jegede et al., 2006). The ethyl acetate extract also showed LD$_{50}$ values of 345.9 mg/kg and 60.8 mg/kg, respectively through oral and intraperitoneal administration in Swiss albino mice (Camurca-Vasconcelos et al., 2004).

**Zea mays** L.

*Z. mays* corn silk is rich in phenolic compounds, particularly flavonoids. It also contains proteins, vitamins, carbohydrates, calcium, potassium, magnesium and sodium salts, volatile oils and steroids such as sitosterol and stigmasterol, alkaloids, and saponins (Hasanudin et al., 2012). A 90 days toxicity study using male and female Wistar rats confirmed that *Z. mays* corn silk is non-toxic in nature with no histopathological and adverse effects observed at 9354 and 10,308 mg/day/kg body wt. respectively (Hasanudin et al., 2012).

### 2.2.12. *Zanthoxylum zanthoxyloides* (Lam.) Zepern. & Timler

*Z. zanthoxyloides* is an indigenous plant widespread in West Africa that is used to treat BU. Report indicates that it showed inhibitory activity against *M. ulcerans* (MIC values 12.5–25 μg/mL) (Table 1) (Addo et al., 2007). *Z. zanthoxyloides* contains essential oils, alkaloids, coumarins, sterols as well as several aliphatic and aromatic amides (Matu, 2011). Methanolic extract of *Z. zanthoxyloides* root-bark (cited Fagara zanthoxyloides) showed LD$_{50}$ at 5000 mg/kg body weight with signs of cerebral irritation before death and also congestion and focal necrosis of the liver and renal tubules after histopathological examinations of the viscera. Authors however declared the safety of the extract, even if the cerebral mechanism that led to death of the mice needed to be investigated (Ogwal-Ongk et al., 2003).

### 2.3. Compounds with potency on Mycobacterium ulcerans

Currently, there is only one study that attempted to use isolated active ingredients from plants to treat BU, highlighting the poor emphasis given to research into new chemotherapeutic agents against BU. The authors reported the isolation of four compounds including Holadysamine and three others compound A, B, and C for which chemical structures are yet to be confirmed according to the authors (Yemoa et al., 2015). Yet the authors tentatively suggested the compounds structures based on LC-MS data on *H. floribunda*. They could correspond respectively to holaphyllin (MW: 331.29), holamine, or holaphyllamine (MW: 315.26), N,N-diméthyl holamine or méthyl holaphylline (MW: 343.29). Further analysis of spectroscopic data on C showed the presence of a fragment at m/z 326 ([M – H$_2$O + H]$^+$) and the loss of a water molecule in its MS/MS fragmentations allowed them to propose an alcoholic and not a ketonic function on C20 (Fig. 4). Meanwhile Holadysamine showed MIC value of 50 μg/mL against the causative agent of BU, while compounds A, B and C were less active (125 μg/mL).
3. Conclusion and future perspectives

Among the 98 species reportedly used to treat BU, 7 species were validated through trials in BU patients. In addition, 13 were subjected to further studies supported by pharmacological investigations. Globally, it appears that ethnopharmacological data for this topic is scarce. Also, the reported results of pharmacological investigations highlighted some degree of inconsistency among findings, but also showed promise and indicated that more emphasis should be given to well-planned and coordinated validation studies on all the plants with claimed anti-BU potential. Furthermore, careful attention should be paid while diagnosing BU because it may be confounded with other causes of ulcers especially in rural communities. The gap in knowledge remains huge. Therefore further studies should clearly demonstrate the in vitro and in vivo activities of crude extracts and further characterized fractions, as well as safety in humans.

Acknowledgements

Patrick Valere Tsouh Fokou is a postdoctoral researcher at Noguchi Memorial Institute for Medical Research, University of Ghana. This integrated programme is developed with the support of Bill & Melinda Gates Foundation special programme for leadership research, capacity building and training in tropical diseases. The author would like to thank Mr. Kojo Agymang (Noguchi Memorial Institute for Medical Research, University of Ghana, Ghana) for critically reading through this manuscript.

References
