Review Article

Update on Medicinal Plants with Potency on Mycobacterium ulcerans

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Received 26 September 2015; Accepted 17 November 2015

Academic Editor: Adair Santos

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Mycobacterium ulcerans disease has been a serious threat for people living in rural remote areas. Due to poverty or availability of traditional medicine these populations rely on herbal remedies. Currently, data on the anti- Mycobacterium ulcerans activity of plants, so far considered community-based knowledge, have been scientifically confirmed, concomitantly with some medicinal plants used to treat infectious diseases in general. Products derived from plants usually responsible for the biological properties may potentially control Mycobacterium ulcerans disease; numerous studies have aimed to describe the chemical composition of these plant antimicrobials. Thus, the present work provides the first compilation of medicinal plants that demonstrated inhibitory potential on Mycobacterium ulcerans. This work shows that the natural products represent potential alternatives to standard therapies for use as curative medicine for Mycobacterium ulcerans disease.

1. Background

Mycobacterium ulcerans disease has been a serious threat for people living in rural remote areas. Due to cultural belief, convenience or inaccessibility of modern therapy, in many rural folk, usually relies on traditional medicine for ulcer management [1]. Besides, many people with M. ulcerans disease suffer mutilation and amputation because modern treatment seems to be expensive and also associated with side effects [2]. These traditional medicines are usually sold in markets and public places or administered by traditional healers in their clinics. Most remedies are mixtures of two or more plants species and solvents used including water, palm wine, or oils. Health problems are often treated through self-medication, first with the popular pharmacopoeia [3, 4] or specialized pharmacopoeia from traditional healers for difficult health problems.

Traditional treatment for Mycobacterium ulcerans disease is done in four steps that involve diagnosis, necrosis ablation, wound curing, and exorcism [1]. The use of medicinal plants takes place in the second and the third stages of the treatment process [1]. Although medicinal plants may play a significant role in Buruli ulcer case management and control of the disease at an affordable cost for the local population, no attempt has been made to document potent medicinal plants against Buruli ulcer. We previously compiled ethnopharmacological data on plants used traditionally to treat Buruli ulcer which addressed only the activities of ethnopharmacologically used medicinal plants excluding plants for which there was no report on their use against Buruli ulcer. In this review we
provide a comprehensive list of medicinal plants that show activity against *M. ulcerans*. The list includes plants that are traditionally used in Buruli ulcer treatment.

2. An Overview of the Assay Methods

2.1. Antimicrobial Assays. Several *M. ulcerans* strains and isolates have been successfully adapted to *in vitro* culture. They were employed in the activity screening described. Two different assays were used to determine the antimicrobial activity of the extracts, fractions, and pure compounds and where possible were compared to commercially available antimicrobial agents, such as rifampicin (MIC = 2 μg/mL) [20].

2.1.1. The Proportion Method. The proportion method, which is still the main method used for drug or products screening of *Mycobacterium ulcerans* by many researchers, applied Löwenstein-Jensen medium. This involved the use of a drug containing media associated with or without dilution of the drug and drug-free media. A standardized inoculum was applied to the drug containing and drug-free media and incubated. After numbering the colonies formed on drug containing medium and on drug-free medium, the MIC was defined as the minimum concentration that inhibited at least 99% mycobacteria [53]. From the studies reviewed, serial dilution of the plant extracts at concentration ranging from 0.4 μg/mL to 50 μg/mL (25% vol/vol to 0.20% vol/vol) [5] or 0.5 to 50 mg/mL [33, 43] was incorporated into Löwenstein-Jensen media. Thereafter, inocula size of $10^4$ to $10^5$ mycobacteria/mL was applied and incubated for 8 to 12 weeks at 30–33°C [5, 33, 43].

2.1.2. The Resazurin Microtiter Assays (REMA). Resazurin or alamar Blue-based assays are sensitive and powerful tools used to detect growth inhibition of a given substances in various concentration ranges on mammalian cell lines and microorganism including mycobacteria [66]. The resazurin microtiter assay was first proposed as a simple, rapid, and cheap alternative for *Mycobacterium tuberculosis* susceptibility testing by Martin et al. [67] and was then adapted by Yemoa et al. in 2011 [21] for *Mycobacterium ulcerans* susceptibility testing. This method is performed usually in the 96-well microplates and can be read with a spectrophotometer or spectrofluorometer or visually without any equipment. In the latter case, which is the one used in the review studies, the minimum inhibitory concentration (MIC) is defined as the lowest concentration of extract that prevents a color change of resazurin from blue to pink. In fact, viable mycobacteria will reduce the blue resazurin into the pink-coloured resorufin. In all cases, extracts or compounds were serially diluted in a 96-well plate and incubate with the inoculum of mycobacteria $10^5$ cfu/mL in Middlebrook 7H9 broth supplemented with oleic acid-albumin-dextrose-catalase with concentration ranging from 7.81 to 12,500 μg/mL. After 15 days of incubation, resazurin was added and a colour change was visible after additional 48 hours of incubation [11, 21].

2.2. Medicinal Species with Anti-Mycobacterium ulcerans Activities. Several authors have reported medicinal species with biological activity against *M. ulcerans in vitro*. In this work, we have reviewed 33 species either alone or in combination for their potential on *M. ulcerans in vitro* (Table 1).

2.2.1. Aloe vera (L.) Burm. f. *A. vera* is an evergreen perennial medicinal plant known for centuries for its beauty and medicinal and skin care properties [51]. Classically, *A. vera* has been used for its wound healing potential [51]. Recently Seefeld et al. [68] reported its use in the traditional treatment of Buruli ulcer while Addo et al. [5] have demonstrated its *in vitro* activities on 7 different *M. ulcerans* strains and isolates with MIC mean value of 40 μg/mL (Table 1). Phenolic compounds such as chromone, anthrone, anthraquinone [52], aloin, and emodin have been identified and are known for their antibacterials effect [51]. Also, its anti-inflammatory action through the inhibition of the cyclooxygenase pathway and reduction of prostaglandin E2 production from arachidonic acid was reported. Recently, the novel anti-inflammatory compound called C-glucosyl chrome was isolated from gel extracts [51] of *A. vera*. The anti-inflammatory activity combined with the antibacterial effect and the wound healing activity of *A. vera* support its use in Buruli ulcer case management. In fact, its high water content can keep the wound moist and increase epithelial cell migration. In addition, its content of glucosmannan, a mannose-rich polysaccharide, and gibberellin, a growth hormone interacts with growth factor receptors on fibroblasts and macrophages, thereby significantly increasing collagen and proteoglycan synthesis, and the degree of collagen cross linking after topical and oral administration resulting in accelerated tissue repair [51, 52]. Furthermore, acemannan, saponin, and genin isolated from *Aloe* leaves have been shown to accelerate wound healing [52, 69, 70].

2.2.2. Alstonia boonei De Wild. *Alstonia boonei* is a large deciduous evergreen tree, usually up to 45 m tall and 1.2 m in diameter, and is also called devil tree in tropical and subtropical Africa, Central America, and Australia [71]. The plant is used to treat various diseases across Africa and the stem bark has been listed as an agent useful for treatment of ulcer or wounds [72]. Addo et al. [5] reported *in vitro* activity of infusion of leaves on 7 *M. ulcerans* strains and isolates with MIC mean value of 40 μg/mL (Table 1). A wide array of chemical compounds, including alkaloids (echitamine, echitamidine, voacangine, akuammidine, N-formylechitamidine, N-formyl-12-methoxyechitamidine), tannins, iridoids (boonein, loganin), steroids, saponins, glycosides, flavonoids, and terpenoids and triterpenoids (lupeol, ursolic acid, and β-amyrin) [19, 71–73], have been isolated from the plant that might support its reported *Mycobacterium ulcerans* inhibitory effects.

2.2.3. Pupalia lappacea Juss. *Pupalia lappacea* is a widespread medicinal plant found in savannah and woodland localities
| Family          | Species                              | Part used                  | Extraction method | Solvent(s) used | Main components (or groups)                                                                 | Antimycobacterial assay methods | Activity/MIC (µg/mL) | Reference |
|----------------|--------------------------------------|----------------------------|-------------------|-----------------|--------------------------------------------------------------------------------------------|--------------------------------|----------------------|-----------|
| Amaranthaceae  | *Pupalia lappacea* Juss.             | Leaves                     | Hot water extraction | Water           | Alkaloids, amino acids, glycosides, flavonoids, glycosides, saponins, tannins, starch, coumarins, terpenoids, and sterols such as 1-docosanol, stearic acid, stigmasteryl, stigmasterol, N-benzyl-L-phenylalaninol acetate, seosteryl 3-O-D-glucopyranoside, stigmasterol 3-O-D-glucopyranoside, and 20-hydroxyl ecdyone | Proportion method             | 40 (cited as 1:5 (20% w/v)) | [5–8]    |
| Amaryllidaceae | *Allium sativum* L.                   | Bulb large/white cloves    | Cold maceration (juice) | Water           | Allin, γ-glutamylcysteine peptides, alllicin, ajoenes, vinyldithiins, and sulfides                | Proportion method             | 0.78–6.25 (cited as 0.39–3.13% (V/V)) | [5, 9, 10] |
|                |                                      | Bulb small/purple cloves  |                   | Water/juice     | 3.13–6.25 (cited as 1.56–3.13% (V/V))                                                          |                                |                      | [5]       |
| Anacardiaceae  | *Sorindeia juglandifolia* A. Rich.   | Fruit                      | Cold maceration, column chromatographies (Fractions SJfr 3.2 and SJfr 3.41) | Methanol, hexane, ethyl acetate, chloroform | C-glycosylflavone, 2',6'-di-O-acetyl-7-O-methyl vitexin, 2',6'-di-O-acetyl-7-O-methyl vitexin, marnnitrin, robustavonine, 3-O-galloyl catechin, tachioside, 3-O-D-glucopyranosyl-o-sigmaseryl, methyl gallate, 2,3,6-trihydroxybenzoic acid, 2,3,6-trihydroxymethyl benzate | REMA                            | 62.5                  | [11–13]   |
|                | *Lannea nigritana* (Sc. Elliot) Keay | Root                       | Decoction         | Water           | Tannins and phenolic compounds (Lanneaneol)                                                   | Proportion method             | 40 (cited as 1:5 (20% w/v)) | [5, 14]   |
| Annonaceae     | *Annickia chloranta* (Oliv.) Setten and Maas | Stem bark             | Maceration       | Ethanol         | Berberine and protoberberine alkaloids: palmatine, jatrorrhizine, columbamine                   | REMA                            | 1.95                  | [11, 15, 16]|
|                |                                      | Stem                      | Interface water-CH<sub>2</sub>Cl<sub>2</sub>/ACaat | Partitioned between water and dichloromethane | Polysin, greenwayodendrin-3-one, 3-O-acetyl greenwayodendrin, N-acetylpolysin, polysin, indole, squiterpenes, aporphines | REMA                            | 3125                  | [11, 17, 18]|
| Apocynaceae    | *Alstonia boonei* De Wild.           | Leaves                    | Hot water maceration | Water           | Alkaloids (echitamine, echitamine, voacangine, akuamidine, N-formylechitamine, Nα-formylechitamine, tannins, iridoids (boonein, loganin), triterpenoids (lupene, unsolcic acid, β-amyrin) | Proportion method             | 40 (cited as 1:5 (20% w/v)) | [5, 19]   |
|                | *Holarrhena floribunda* (G. Don) T. Durand et Schinz | Root                  | Maceration       | 70% ethanol     | Saponins, polar steroid glycosides, sterylal glycosides, alkaloids including helaphylamine, holaphylamine, holamine, holaphyllin, holaphylline, holadysamine, holarrhine, conessine, conamine, conamine, progesterone, norconamine (kurchine), conessimine, kurchamine, conamine, conamine, holarrhine, holarrhine, conarrhine | REMA                            | 125                  | [20–22]   |
|                |                                      | Liquid chromatography     |                   | 70% ethanol, 2% sulfuric acid, hexane, 10% NaOH, dichloromethane (alkaloid enriched fraction extract) |                                      | REMA                            | 62.5                  | [125]     |
| Araceae        | *Aglaonema commutatum* Schott        | Leaves                    | Hot water maceration | Water           | Calcium oxalate crystals                                                                       | Proportion method             | 40 (cited as 1:5 (20% w/v)) | [5, 23]   |
| Family        | Species                                      | Part used | Extraction method | Solvent(s) used | Main components (or groups)                                                                 | Antimycobacterial assay methods | Activity/MIC (µg/mL) | Reference |
|--------------|----------------------------------------------|-----------|-------------------|----------------|-------------------------------------------------------------------------------------------|---------------------------------|---------------------|-----------|
| Bignoniaceae | Spathodea campanulata P. Beauv.              | Root      | Decoction         | Water          | Carbohydrates, alkaloids, Tannin glycosides, steroids, saponins, anthraquinone glycosides | Proportion method               | 25 (cited as 12.50% (V/V)) | [5, 24–26] |
| Cleomaceae   | Cleome viscosa L.                            | Leaves    | Hot water maceration | Water          | Alkaloids, tannins, saponins, flavonoids, terpenes, carbohydrates                         | Proportion method               | 40 (cited as 1:5 (20% w/v))  | [5, 27, 28] |
| Compositae   | Ageratum conyzoides (L.) L.                  | Leaves    | Hot water maceration | Water          | Pyrrolizidine alkaloids lycozamine, dihydrolycozamine, acetyl-lycozamine, N-oxides, methoxylated flavonoids, chromones | Proportion method               | 40 (cited as 1:5 (20% w/v))  | [5, 29]   |
| Euphorbiaceae| Bridelia ferruginea Benth.                   | Stem bark | Decoction         | Water          | Polyphenols, steroids, saponins, tannins, terpenoids, alkaloids, quercetin derivatives such as rutin, myricetin derivatives gallicatechin-(4’-O-7)-epigallocatechin; 3,5-dicaffeoylquinic acid and 1,3,4,5-tetracaffeoylquinic acid; lignans deoxyepidophyllotoxin, β-peltatin, β-peltatin-5-O-β-D-gluopyranoside, 5’-demethoxy-β-peltatin-5-O-β-D-gluopyranoside; Flavonoids, apigenin, vitexin, isovitexin, sterol stigmastrol, β-D-sitosterol, β-D-glucoside, sapogenins, alkaloids, trierpen epoxide, 1-triacetinol | Proportion method               | 40 (cited as 1:5 (20% w/v))  | [5, 30, 31]|
|             | Jatropha curcas L.                           | Leaves    | Maceration         | 70% ethanol    |                                                                                           | REMA                            | 250                 | [21, 32] |
| Humiriaceae  | Sacoglottis gabonensis (Baill.) Unh.         | Stem bark | Cold maceration    | Water          | Bergenin, sterols, polyterpenes, polyphenols, flavonoids, tannins, saponins, alkaloids   | Proportion method               | Growth inhibition in vitro | [33–38]  |
| Leguminosae  | Senecio occidentalis (L.) Link (Syn. Cassia occidentalis L.) | Leaves    | Hot water maceration | Water          | Acrocin, aloes-emodin, emodin, anthraquinones, anthrones, apigenin, aurantiobutin, campesterol, cassiolin, chrysoberin, chrysophanic acid, chrysarobin, chrysophanol, chrysoeriol, emodin, essential oils, funiculosin, galactopyranosyl, helminthosporine, isodiscine, kaempferol, lignoceric acid, limoleic acid, linoleic acid, mannitol, manno-lyropyranoxy, matuecinol, obtusifolin, obtusin, oleic acid, phycsn, quercetin, rhamnoses, rhein, rubrofusarin, sitosterols, tannins, xanthosine | Proportion method               | 40 (cited as 1:5 (20% w/v))  | [5, 39]   |
| Family       | Species                                      | Part used | Extraction method       | Solvent(s) used | Main components (or groups)                                                                 | Antimycobacterial assay methods | Activity/MIC (µg/mL) | Reference |
|--------------|----------------------------------------------|-----------|-------------------------|-----------------|--------------------------------------------------------------------------------------------|-------------------------------|----------------------|-----------|
| Myrtaceae    | Psidium guajava L.                           | Leaves    | Hot water maceration    | Water           | Phenol, tannin (Amoroside; ellagic acid 4-gentobioside, Guavins A, B, C, and D, isooctostin (V), strictinin, pedunculin, (+)-gallicatechin), flavonoid (queretin and its glycosides, morin-3-O-β-L-lyxopyranoside, morin-3-O-α-L-arabinopyranoside, kaempferol, hureolin-7-O-glucoside, apigenin-7-O-glucoside), carotenoid, triterpenoid, isopropenyl, isopropenyl (monoterpens: caryophyllene oxide, β-selinene, 1,8-cineole, α-pinene, myrcene, δ-cembrene, d-limonene, caryophyllene, linalool, eugenol, β-bisabolol, β-bisabolene, β-sesquiphellandrene, δ-cadinene and β-cadinene, cardamomene, α- and β-humulene, benzaldehyde, methyl salicylate, α-cubebene, α-copaene, γ-cadinene and δ-cadinene, γ-cadinene and β-ylangene, chavicolvanillin, crategolic acid, tannins, gallotannic acid, flavonoids eugenin, kaempferol, rhamnetin, eugenitin, triterpenoids like oleanolic acid) | Proportion method            | 40 (cited as 1:5 (20% w/v)) | [5, 40]   |
| Plantaginaceae | Gratiola officinalis L.                     | Bark      | Decoction               | Water           | Alkaloids, flavonoids, saponins, coumarin derivatives, mannitol, glycoside-like substances, Gruitogenin, 1,6-hydroxygritogenin, cucubetin C and E, 1-lycosides triterpenoids, 3-beta-D-glucoside, triterpenoids, elastin, lignans                                     | Proportion method            | 1.56-25 (cited as 0.78-12.5% (V/V)) | [5, 42]  |
| Phyllanthaceae | Phyllanthus amarus Schumach. & Thonn.       | Leaves    | Maceration              | 70% ethanol     | Alkaloids, flavonoids, tannins (geraniin, corilagin, 1,6-digalloylgluopyranoside rutin, quercetin-3-O-glucopyranoside, amaranthone, phyllanthusin D and amarin), lignans (niranthin, nirnitratin, phyllethralin, hypophyllanthin, phyllanthin, demethylenediox-niranthin, 5-demethoxy-niranthin, iso-niranthin), polyphenolic compounds, tetracyclic triterpenoids | Proportion method            | 32,000                      | [43, 44] |
| Phyllanthaceae | Phyllanthus fraternus G.L. Webster          | Leaves    | Hot water maceration    | Water           | Alkaloids (phyllanthin, hypophyllanthin, phyllanthin, phyllanthin, rhamnopyranoside, phyllanthone, linetralin, astragalin, cymene, niranthin, niteralnin, niruicide, phyllochrysine, 6-methoxy-niruicurarine, 3-methoxy-niruicurarine, limone, niruicurine, niruicurine, phyllochrysine), steroids (β-sitosterol, cholesterol), flavonoids (quercetin, quercetin heteroside, quercetin, quercetin, 3, 4, 5-trimethoxy flavonone, 3,5,7-trihydroxy flavonol), other compounds (estradiol, corilagin, ellagic acid, gallic acid, rutin, germanine, rutinoside, lupa, lapse License, methyl salicylate), saponins (triaccontanal, tricantanol) | Proportion method            | 40 (cited as 1:5 (20% w/v)) | [5, 45]   |
| Family          | Species                     | Part used | Extraction method | Solvent(s) used | Main components (or groups)                                                                 | Antimycobacterial assay methods | Activity/MIC (μg/mL) | Reference |
|-----------------|-----------------------------|-----------|-------------------|-----------------|--------------------------------------------------------------------------------------------|--------------------------------|---------------------|-----------|
| Ranunculaceae   | *Hydrastis canadensis* L.   | Root      | Decoction         | Water           | Alkaloids (major: hydrastine, berberine, canadine; minor: hydrastine, canadine, isohydrastine, 1-β-hydrastine, 5-hydroxytetrahydroberberine, (S)-corypalmine, (S)-iso-corypalmine, (S)-tetrahydropalmatine, Berberastine, 8-oxotetrahydrothalifendine, Canadinic acid), flavonoids (6,8-C-dimethylflavolin 7-methyl ether, 6-C-methylflavolin 7-methyl ether, sauleoxyn, 8-deamethyl-sauleoxyn, 6-desmethyl-sideroxyl), organic acids (quinic acid derivatives, hycondinic acid esters, 5-O-(4'-[β-d-glucopyranosyl]-trans-feruloyl) quinic), Sterols (β-sitosterol 3-O-β-D-glucoside), volatile oil, resin, and fatty acids | Proportion method                | 0.39–6.25 (cited as 0.20–3.13% (V/V)) | [5, 46] |
| Rutaceae        | *Zanthoxylum zanthoxyloides* (Lam.) Zepern. & Timler | Roots     | Decoction         | Water           | Essential oils, benzophenanthridine, furoquinoline, aporphine alkaloids, fagaridine, diphrose, chelerythrine, oxeychelerythrine, skimmianine and 8-methoxydixamine, as well as the aporphines magnoflorine, berberine, tembutarine, N-methyl-corydine, N-isobutylycoca-2,4-dienamide, N-isobutylycoca-2,4-dienamide, antronanamide, fagaramide, piperlongumine, rubemarin, N-isopentyl-cinnamamide, umbelliferone, scopoletin, sorarine, xanthotoxin, imperatorin, bergapten, marmesin, pimpinellin, lignan sesamin, C-7 epimer asarin, sterols zanthoxyl, dioxim, fagrol, hesperidin, luteol, β-strosterol, stigmasterol, campesterol, β-amyrin, vanillyl acid, hydroxybenzoic acid, parahydroxybenzoic acid, 2-hydroxymethyl benzoic acid, parfluorobenzoic acid, divanillylquinic acids burkinabin A, burkinabin B, and burkinabin C. | Proportion method                | 12.5–25 (cited as 6.25–12.5% (V/V)) | [5, 47] |
| Solanaceae      | *Capsicum annum* L.         | Fruit     | Cold maceration   | Water           | Saponins, alkaloids, quaternary bases, anthracenosides, flavanones, flavonoids, oumarin derivatives, steroid glycosides, arylaminoxydases, essential oils, waxes, capsunbin, capsorubin, zeaxanthin, cryptoxanthin, lutin, capsicinoids | Proportion method                | 40 (cited as 1:5 (20% w/v)) | [5, 48, 49] |
|                 | *Solanum torvum* Sw.       | Leaves    | Hot water         | Water           | Isolavanoid sulfate, steroidal glycosides, chlorogenone, neochlorogenone, triacantone derivatives, 22-β-O-spirostanol oligoglycosides, 26-O-β-glucosidase | Proportion method                | 40 (cited as 1:5 (20% w/v)) | [5, 50] |
| Xanthorrhoeaceae| *Aloe vera* (L.) Burm. f.   | Leaves    | Cold maceration   | Water           | Chromone, anthraquinone, anthrone derivatives, anthraquinones, saponins, salicylic acids, amino acids, vitamins, enzymes, minerals, sugars, lignin | Proportion method                | 40 (cited as 1:5 (20% w/v)) | [5, 51, 52] |
| Tonic 1         | Mixture of *Spigelia anthelmia* L. and *Zea mays* L. | Leaves, grain | Hot water         | Water           | Sanguinaria alkaloids, spiganthine, ryanodine, volatile alkaloids, isoquinoline, actinide isoer, quaternary alkaloids, choline, benzoylcholine, 2,3-dimethylacetyl chloride, phenyllactic acid, flavonoids *Zea mays* proteins, vitamin, carbohydrates, volatile oils, sterols such as stigmasterol and stigmasterol, alkaloids, saponins | Proportion method                | 6.25–25 (cited as 3.13–12.5% (V/V)) | [5, 53–56] |
| Family | Species | Part used | Extraction method | Solvent(s) used | Main components (or groups) | Antimycobacterial assay methods | Activity/MIC (µg/mL) | Reference |
|--------|---------|-----------|------------------|----------------|-----------------------------|-------------------------------|----------------------|----------|
| **Tonic 2** | Mixture of *Citrus aurantium* (Christm.) Swingle and *Gossypium barbadense* L. | Leaves | Hot water maceration | Water | *Citrus aurantium*: alkaloids, flavonoids, tannins, saponins, sterols, cardiac glycosides, reducing sugar, 5-geranyloxypsoralen, 5-geranyloxy-7-methoxy coumarin, 5,7-dimethoxy xanthone, 5-methoxy xyp-soralen, 5,8-dimethoxy xyp-soralen, 3-methyl-1,2-cyclopentanedione, 1-methoxy-cicloe hexene, corylone, palmitic acid α-terpineol, umbelliferone
*Gossypium barbadense*: gossypol, L1-dimethylbutanol, (3-ethyl-2-oxiranyl) ethanone, (3-ethyl-2-oxiranyl) ethanone, 4,1L11-trimethyl-1,8-methylene bicycle (7.2.0) under-4-ene, 9-octadecene, hexadecene, 1-(1.5-dimethyl-4-hexanoyl)-4-methyl-3-cyclohexen-1-ol, 9-eicosene, hexadecanoic acid, methyl ester palmitic acid, 3-eicosene, 9,12,15-octadecatrienoic acid, methyl ester linolenic acid, phylol-2-hexadecen-1-ol, oleic acid, 9-octadecanoic acid, 1-tricosene, hexadecanoic acid, pentadecanopropionic acid heptadecyl ester, 13-octadecenal, di-n-ocytphthalate 1,2-benzene carboxylic acid, squalene 2,6,10,15,19,23-hexamethyl | Proportion method | 12.5–25 (cited as 6.25–12.5% (V/V)) | [5, 57, 58] |
| **Tonic 3** | Mixture of *Jatropha curcas* L., *Gossypium hirsutum* L., *Physalis angulata* L., and *Delonix regia* (Hook.) Raf. | Leaves | Hot water maceration | Water | *Jatropha curcas*: flavonoids, apigenin, vitexin, isovitexin, sterol stigmasterol, β-D-sitosterol, β-D-gluco side, sapogenins, alkaloids, triterpene alcohol, 1-triacontanol
*Gossypium hirsutum*: gossypol and cyclopropenoic fatty acids including dihydrosterculic, sterolic, and malvolic acids
*Physalis angulata*: flavonoids (A flavonol glycoside, myricetin 3-O-neohesperidoside), alkaloids (phygrine) and many different types of plant steroids (physalins) A–W, withanolides, physagulins A, B, C, and D, withano lides, withangulatins B, C, D, E, F, G, H, and I, withangulatin I, physangulidines A, B, and C, carotenoids, and oleanolic acid
*Delonix regia*: sterols, triterpenoids, phenolic compounds, saponins, alkaloids, flavonoids, sugars, tannins, steroids, β-D-stereol, carotene, hydrocarbons phytophins, carotenoids, lupeol, euphuleol, stigmasterol, p-hydroxy benzaldehyde, kaempferol 3-rhamnoside 1, quercetin 3-rhamnoside 2, kaempferol 3-glucoside 3, kaempferol 3-rutinoside 4, kaempferol 3-neohesperidoside 5, quercetin 3-rutinoside 6 and quercetin 3-glucoside 7, anthocyanins, cyanidin 3-glucoside, cyanidin 3-o-rutinoside, pelargonidin 3-o-rutinoside | Proportion method | 6.25–25 (cited as 3.13–12.5% (V/V)) | [5, 32, 59–65] |

w/v = 20% w/v (200 µg/mL) of herbal preparations (infusions, decoctions and juices) were each incorporated at 1:5 dilution into L-J medium corresponding to a final concentration of 40 µg/mL. V/V = The herbal preparations (infusions, decoctions and juices) at 20% w/v were incorporated into L-J media at final concentrations ranging from 25% vol/vol to 0.20% vol/vol corresponding to 50 µg/mL to 0.4 µg/mL.
as well as forests in the tropical Africa and in Asia [74]. It has been used in the management of wound [5, 6] and its leaves extracts have shown inhibitory activity on 7 𝑀. ulcerans strains and isolates with MIC mean value of 40 𝜇g/mL (cited as 1:5 (20% w/v)) (Table 1) [5]. Chemical investigations show that 𝑃. lappacea leaf extract contains alkaloids, glycosides, flavonoids, saponins, tannins, coumarins, terpenoids, and steroids such as 1-docosanol, stearic acid, stigmasterol, sitosterol, N-benzoyl-L-phenylalaninol acetate, setosterol-3-O-D-glucopyranoside, stigmasterol-3-O-D-glucopyranoside, and 20-hydroxyl ecodyrone. These compounds have been shown to promote the wound healing process in animals and humans. Stigmasterol found in the plant has been shown to exhibit haemostatic and anti-inflammatory activities. Similarly, 20-hydroxyl ecodyrone also present in the plant promotes protein synthesis and wound healing in animals and humans. Since some of the compounds contained in 𝑃. lappacea leaves extract have antibacterial activities and also promote the wound healing process, the plant extract may exhibit wound healing activities as claimed by the traditional practitioners [6–8].

2.2.4. Lannea nigritana (Sc. Elliot) Keay. Lannea nigritana is a small tree of 3–6 m of height found in the tropical rain forest [14]. It is used in traditional medicine for the treatment of various infectious diseases [14] including wounds [5]. The leaves of the plant showed activity on 7 𝑀. ulcerans strains and isolates with MIC mean values of 40 𝜇g/mL. Phytochemical studies on this plant are scanty. Meanwhile the plant is known to contain tannins and phenolic compounds (Lanneanol) [5].

2.2.5. Aglaonema commutatum Schott. Aglaonema commutatum is a common ornamental plant used to treat BU that showed MIC mean value of 40 𝜇g/mL on 7 𝑀. ulcerans isolates (Table 1) [5]. Besides, solution from washings of leaves showed inhibitory effects on growth of bacteria such as 𝑃. aeruginosa, and 𝑆. aureus [75] which are commonly involved in wound infection. All parts of the plant contain the active constituent calcium oxalate crystals [23].

2.2.6. Ageratum conyzoides (L.) L. Ageratum conyzoides is an annual herbaceous plant used in African traditional medicine for the treatment of wounds, burns, and ulcer [76]. Addo et al. [5] demonstrated the leaves activity on 7 𝑀. ulcerans strains and isolates with MIC mean value of 40 𝜇g/mL (Table 1). A. conyzoides contains phenolic compounds, methoxylated flavonoids and chromenes, and pyrrolizidine alkaloids, pyrrolizidine alkaloids lycopsisamine, dihydrolycopsamine, and acetyl-lycopsamine, and their N-oxides [29].

2.2.7. Cleome viscosa L. Cleome viscosa is commonly known as tickweed, wild mustard, or spider plant that occurs in woodland and grassland. It is a weed found in fallow land, fields, roadsides, and wasteland. It often grows on sandy soils but sometimes grows on calcareous and rocky soils. It is a widely distributed herb with yellow flowers and long slender pods containing seeds [77]. The leaves and whole plant of 𝐶. viscosa are used as a folk remedy to cure wounds, ulcers, inflammations, and skin infections [27]. Its leaves have shown MIC mean value of 40 𝜇g/mL (cited as 1:5 (20% w/v)) on 7 𝑀. ulcerans isolates (Table 1) [5]. Methanolic extract of the aerial parts of the plant is also reported to have significant wound healing properties on experimentally induced excision and incision wound models in rats in addition to its previously reported analgesic, antimicrobial, and antiulcer activities [77]. All of this supports the traditional use of the plant. Its content of alkaloids, tannins, saponins, flavonoids, terpenes, and carbohydrates [27, 28] may be probably responsible for the observed wound healing activity.

2.2.8. Phyllanthus fraternus G. L. Webster. Phyllanthus fraternus is commonly a small, erect, annual herb that grows 30–40 cm in height [78] indigenous to the rainforests of the Amazon and other tropical areas throughout the world [79]. The plant has numerous uses by indigenous peoples to treat blemorrhagia, colic, diabetes, dysentery, fever, flu, tumors, jaundice, vaginitis, dyspepsia, and pain [80]. P. fraternus has previously demonstrated an MIC mean value of 40 𝜇g/mL (cited as 1:5 (20% w/v)) on 7 𝑀. ulcerans (Table 1) [5] isolates and strains. It has been shown to contain alkaloids, steroids, glycosides, tannins, saponin, flavonoids, other compounds (estradiol, corilagin, ellagic acid, gallic acid, rutin, gernanine, rutinoside, lupa, lupeol, and methyl salicylate), and saponins (tricdontanal, tricotonantol) [45, 79]. The reported antimicrobial activity may be attributed to the presence of some of the reported secondary metabolites. However, the active compound(s) known to give this observed activity need to be identified.

2.2.9. Bridelia ferruginea Benth. Bridelia ferruginea Benth. is a gnarled shrub which can reach the sizes of a tree in suitable condition [30]. B. ferruginea bark is used for treatment of bacterial infections on wound [81] and has been shown to inhibit the growth of 7 𝑀. ulcerans strains and isolates with an MIC mean value of 40 𝜇g/mL (cited as 1:5 (20% w/v)) (Table 1) [5]. The presence of phytochemical such as polyphenols, steroids, saponins, tannins, terpenoids, and alkaloids [30, 31] may support the demonstrated antimicrobial activity against mycobacteria.

2.2.10. Senna occidentalis (L.) Link. Senna occidentalis (syn. Cassia occidentalis) is an annual or perennial plant [39] that has been used as natural medicine in rainforests and tropical regions as laxative, analgesic, febrifuge, diuretic, hepatoprotective, vermifuge, and cholagogue [82]. Leaf paste is externally applied for wound healing [39]. S. occidentalis leaf extracts were found to be active against different microbes [39] and inhibit the growth of 7 𝑀. ulcerans strains and isolates with MIC mean value of 40 𝜇g/mL (cited as 1:5 (20% w/v)) (Table 1) [5]. The presence of compounds such as acrosin, aloe-emodin, emodin, anthraquinones, anthrones, sitosterols, tannins, and xanthosine [39] can justify its reported antimycobacterial activity.
2.2.11. *Psidium guajava* L. *Psidium guajava*, commonly known as guava, is a native plant of tropical America and has been used in indigenous system of medicine for the treatment of various human ailments such as wounds, ulcers, bowels, and cholera [40, 83]. In Central and West Africa, its decoctions are used externally for skin ulcers [84]. *P. guajava* also possesses antibacterial and anti-inflammatory properties and also inhibited the growth of *7 M. ulcerans* strains and isolates with MIC mean value of 40 μg/mL (cited as 1:5 (20% w/v)) (Table 1) [5]. A number of secondary metabolites in good yield have been isolated and some, which are mainly phenolic, flavonoid, carotenoid, volatile oil, tannins, terpenoid, and triterpene, have been shown to possess useful biological activities [40].

2.2.12. *Capsicum annum* L. *Capsicum annum* is a perennial shrub, with woody trunk, which bears green fruits that ripen to red. The active ingredient in the plant is capsaicin that is used for the management of various medical conditions [48]. This plant possesses antibacterial and wound healing properties. It is used often in combination with *Pothis scandens* L. and *Allium sativum* to heal wounds [85]. The maceration of fruit, used to treat Buruli ulcer, has showed MIC mean value of 40 μg/mL (cited as 1:5 (20% w/v)) on 7 *M. ulcerans* strains and isolates (Table 1) [5]. Bioactive chemical compounds against bacteria involved in wound infection found in *C. Annun* included saponins, alkaloids, quaternary bases, anthracenosides, flavanoses, flavones, coumarin derivatives, steroid glycosides, anthocyanosides, essential oils, waxes, coloured materials (mainly capsanthin, capsorubin, zeaxanthin, cryptoxanthin, and lutein), and several capsaicinoids [48, 49].

2.2.13. *Solanum torvum* Sw. *Solanum torvum*, commonly known as Turkey berry, is an erect spiny shrub about 4 m tall, evergreen and widely branched found in Africa and West Indies. The fruits and leaves are widely used in Cameroonian folk medicine. Agrawal et al. [86] have reported the traditional use of this plant as an antulcer agent while its antimicrobial properties of the leaves are known and are used to manage cuts and wounds [87]. Its leaf decoction inhibits the growth of 7 *M. ulcerans* strains and isolate with MIC mean value of 40 μg/mL (cited as 1:5 (20% w/v)) (Table 1) [5]. *S. torvum* contains a number of potentially pharmacologically active chemicals like stigmastanol involved in the wound healing process and isoflavonoid sulfate and steroidal glycosides, chlorogenone and neochlorogenone, triacontane derivatives, 22-β-O-spirostanol oligoglycosides, 26-O-β-glucosidase, tetrahydroactoic acid, sitosterol, stigmastanol, campesterol, and C-22 steroidal lactone saponins [50, 86].

2.2.14. *Spathodea campanulata* P. Beauv. *Spathodea campanulata* is a tree that grows between 7 and 25 meters (23–82 feet) tall. It is native to tropical Africa and Southern Asia. *S. campanulata* flowers and bark are used traditionally in the treatment of mental disorders, malaria, hemorrhoids, bacterial infections, HIV, poor blood circulation, gastrointestinal diseases, respiratory ailments, and genital-urinary system disorders [24] as well as relief for skin conditions, swollen cheeks, and body rashes and Buruli ulcer. 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 [4, 5, 20, 88, 89]. The decoction of the root showed inhibitory activity on 7 *M. ulcerans* strains isolates with MIC mean value of 25 μg/mL (cited as 12.50% (V/V)) (Table 1) [5]. Biologically active phytochemicals have been identified such as alkaloids, tannins, saponins, glycosides, anthraquinone glycosides, steroids, flavonoids, tannins, and glycosides [24–26].

2.2.15. *Allium sativum* L. *Allium sativum* has been widely recognized as a valuable spice and a popular remedy for various ailments and physiological disorders. The plant appears to have originated from Central Asia and then spread to China, the Near East, and the Mediterranean region before moving west to Central and Southern Europe, Northern Africa, and Mexico [90]. The juice of *A. sativum* cloves is used to treat Buruli ulcer conditions [5]. It has been shown experimentally to accelerate the wound healing process in mice [91]. Besides, aqueous extract of *A. sativum* in combination with honey has shown acceleration of wound healing in rats [92]. It has shown growth inhibition on 7 *M. ulcerans* strains and isolates with MIC mean values of 0.78–6.25 μg/mL (cited as 0.39–3.13% (V/V)) (Table 1) [5]. Active constituents such as alliin, allicin and γ-glutamylcysteine, ajoenes, and vinyldithiins have been identified [9, 10]. Allicin has antimicrobial effects against many bacteria and fungi [90] usually found in ulcers. Its activity on *M. ulcerans* combined with its antibacterial, antifungal and anti-inflammatory, antioxidant, [90, 93], and wound healing potency supports its traditional use in Buruli ulcer treatment.

2.2.16. *Syzygium aromaticum* (L.) Merr. & L. Perry. *Syzygium aromaticum* is an evergreen tree found worldwide [41]. It is a natural analgesic and antiseptic used primarily in dentistry because of its main ingredient eugenol. It has been traditionally used externally or locally for the treatment of minor infections of the mouth and skin, dressing of minor wounds, and Buruli ulcer [5]. Its seeds have showed MIC mean value of 25 μg/mL (cited as 12.50% (V/V)) on 7 *M. ulcerans* isolates (Table 1) [5]. Many active ingredients have been identified from *S. aromaticum* including essential oils, tannins, gallo-tannic acid, methyl salicylate, flavonoids eugenin, and triterpenoids like oleanolic acid [41].

2.2.17. *Hydrastis canadensis* L. *Hydrastis canadensis* is an herbaceous perennial growing short yellowish rhizome [94]. *H. canadensis* is widely used to treat many ailments, including arrow wounds [46]. It inhibited the growth of 7 *M. ulcerans* strains and isolates with MIC values of 0.39–6.25 μg/mL (cited as 0.20–3.13% (V/V)) on (Table 1) [5]. In an antimicrobial screening program, *H. canadensis* extract also exhibited significant activity against multiple drug resistant strains of *M. tuberculosis* and other *Mycobacterium* species as well as other human pathogens [95]. *H. canadensis* is found
to contain alkaloids, flavonoids, organic acids, sterols (β-sitosterol 3-O-β-D-glucoside), volatile oil, resin, and fatty acids [46]. Bioassay-guided fractionation revealed berberine to be the active constituent on mycobacteria [95]. This in combination with its wound healing properties can explain the higher activity observed against M. ulcerans and support the indigenous treatment of Buruli ulcer.

2.2.18. Zanthoxylum zanthoxyloides (Lam.) Zepern. & Timler. Zanthoxylum zanthoxyloides is widely distributed in many African countries. It is well known for its use in treating elephantiasis, toothache, sexual impotence, gonorrhoea, malaria, dysmenorrhoea abdominal pain [96], and Buruli ulcer [5]. It showed inhibitory activity with MIC values 12.5–25-μg/mL (cited as 6.25–12.5% (V/V)) on 7 M. ulcerans strains and isolates (Table 1) [5] in addition to its antimicrobial activity [5, 96]. Antibacterial and anti-inflammatory amides have also been isolated from the plant [96] as well. The presence of a diversity of essential oils, alkaloids, and several aliphatic and aromatic amides [47] strengthens claims of effectiveness of this plant in its traditional use for treatment of Buruli ulcer.

2.2.19. Gratiola officinalis L. Gratiola officinalis Linn. is a glabrous perennial herb and is native to the south of Europe, and its favourable habitat is damp grounds. Gratiola officinalis L., commonly known as common Hedgehyssop or “Herb of Grace” is well known for its pharmacological properties. Various parts of this plant (root and herb) are used in phytomedicines to treat skin diseases [42]. This may explain the observed good inhibitory activity on 7 M. ulcerans strains and isolates with MIC values 1.56–25-μg/mL (cited as 0.78–12.5% (V/V)) (Table 1) [5]. The active constituents found in G. officinalis include gratiogenin, 16-hydroxygratiogenin, cucurbitacins E and I, glycosides gratiogenin-3beta-D-glucoside, gratoside, elaterinide, flavonoids, alkaloids, lignans, coumarin, and saponins which have many biological properties [42].

2.2.20. Jatropha curcas L. Jatropha curcas Linn belonging to the family Euphorbiaceae is a drought-resistant shrub originating in Central and South America but now thrives in many parts of the tropics and subtropics in Africa and Asia [97]. J. curcas has been used as traditional medicine to cure Buruli ulcer [4]. Its leaf ethanolic extract inhibited the growth of M. ulcerans ATCC 19423 with MIC value of 250 μg/mL and the crude bark extract of Jatropha curcas has been shown to be very effective in accelerating wound healing process in rat [98]. Researchers have isolated and characterized a number of biologically active constituents such as flavonoids, apigenin, vitexin, isovitexin, stigmasterol, β-D-sitosterol, β-D-glucoside, sapogenins, alkaloids, triterpene alcohol, and 1-triacontanols from all parts of this plant [32].

2.2.21. Holarrhena floribunda (G. Don) T. Durand. Holarrhena floribunda grows as a shrub or tree up to 25 m tall, with a stem diameter of up to 30 cm [4, 21]. Bark is used as an enema or in baths to treat skin infections and the leaf sap is sprinkled on wounds as a haemostatic. A sap extracted from its leaves is sprinkled onto wounds to act as a haemostatic [22]. Yemoa et al. [4] report its use in the traditional treatment of Buruli ulcer and hydroethanolic extract and CH2Cl2 fraction of root inhibited the growth of M. ulcerans ATCC 19423 with MIC value of 125 μg/mL [20] while that of the alkaloid enriched fraction had an MIC of 62.5 μg/mL. These give some support to the use of this plant in traditional medicine (Table 1) [21]. It contains active compounds such as saponins, polar steroidal glycosides, steroidal glycosides, and alkaloids including holaphylline, holaphyllamine, holamine, holaphyllinol, holaphyllidine, holadysamine, holarrhines, conessine, and progesterone [21, 22].

2.2.22. Sorindeia juglandifolia (A. Rich.) Planch. ex Oliv. Sorindeia juglandifolia is a shrub or small tree that grows to 23 m tall and 40 cm in diameter. It is widespread in the West and Central Africa subregion. This plant is found on the edges of dry deciduous forest and regrowth in humid forest and in the galleryd Sudanian forest of Senegal to Dahomey and also in Ubangi-Shari, Angola, and Zambia. Its common English name is “damson” [99, 100]. In Senegal pulped leaves are applied to sores and ulcers [101]. Fruit fractions and a purified compound (2,3,6-trihydroxymethyl benzoate) from S. juglandifolia is reported to have an antimycobacterial activity against M. ulcerans strain 1615 with MIC value of 62.5 μg/mL and minimal bactericidal concentration (MBC) values of 250 and 125 μg/mL, respectively [11].

2.2.23. Annickia chlorantha (Oliv.) Setten & Maas. Annickia chlorantha is a tree up to 30 m tall commonly known as “Yello Wood” found in dense forests in Cameroon, Nigeria, and Gabon. In the southern forest zone of Cameroon, it is used for the traditional treatment of stomach problems, jaundice, urinary tract infections, malaria, tuberculosis, hepatitis, and some forms of ulcer [3, 15]. The stem bark and stem preparations of A. chlorantha have been shown to have high inhibition against the growth of M. ulcerans strain 1615 with respective MIC values of 1.95 and 7.81 μg/mL (Table I). The chemistry of A. chlorantha formally Enantia chlorantha has been extensively studied. Berberine and protoberberine alkaloids [15] with antibacterial [102] properties have been isolated from the stem bark of A. chlorantha. A mixture of protoberberine alkaloids from A. chlorantha containing palmitine, jatrhorzine, and cumbamine was shown to prevent liver injury from chemically induced traumatization and also promoted the healing process after injury in experimental mice [16].

2.2.24. Greenwayodendron suaveolens (Engl. & Diels) Verdc. Greenwayodendron suaveolens is a deciduous, medium-sized to fairly large tree up to 35 (to 45) m tall that is widespread from Southern Nigeria, East to Western Uganda, Northern Tanzania, and Southern Democratic Republic of Congo and Cabinda (Angola) and commonly known in English as “Molina.” Various plant parts are used in traditional
medicine to treat stomach ache and other pains, gonorrhoea, psychosis, rheumatism, epilepsy and toothache, malaria, liver complaints and headache, helminths, oedema and swollen glands, and hepatitis; it is used to manage infertility, as diuretic, purgative, an aphrodisiac, and to facilitate childbirth [17]. Extracts and fractions from *G. Suaveolens* (cited as *Polyalthia suaveolens*) have been shown to inhibit *M. ulcerans* with moderate MIC and MBC values of 3,125 μg/mL (Table 1) [11]. Many compounds such as polysin, greenwayodendrin-3-one, 3-O-acetyl greenwayodendrin, N-acetylpolyveoline, polyvineolone [18], and several alkaloids including indolos-esterpenes and aporphines have been isolated from the plant [17].

2.2.25 Phyllanthus amarus Schumach. & Thonn. Phyllanthus amarus is a small herb well known for its medicinal properties and widely used worldwide [44]. It is useful in gastropathy, diarrhoea, dysentery, intermittent fevers, ophthalmopathy, scabies, ulcers, and wounds [44]. The aqueous extract of *P. amarus*, used in traditional medicine in Ivory Coast to treat incurable wounds, has demonstrated in vitro activity against *M. ulcerans* strain 02003 with IC50 and IC50 values, respectively, of 3.5 mg/mL and 19.8 mg/mL and was bactericidal at concentrations of 64 mg/mL [103]. Coulibaly et al. [43] have demonstrated the growth inhibition activity of aqueous and ethanolic extracts of *P. amarus* on 7 *M. ulcerans* isolates in vitro with similar MIC of 32 μg/mL (Table 1). *P. amarus* has numerous active phytocompounds such as alkaloids, flavonoids, tannins, lignans, polyphenolic compounds, and tetracyclic triterpenoids [44]. Though the main use of *P. amarus* traditionally is to treat tuberculosis [104] rather than Buruli ulcer, its in vitro effect on *M. ulcerans* supports its traditional use against Buruli ulcer [43].

2.2.26 Sacoglottis gabonensis (Baill.) Urb. Sacoglottis gabonensis is a large, evergreen tree up to 40 m tall and it is used to cure many ailments, namely, difficult cases of dermatitis [34] and Buruli ulcer. A decoction of the stem bark of the plant is administered orally or used topically to disinfect the ulcer or the ulcer is covered with fine powder of the stem bark and bandaged [33]. The aqueous extract of *S. gabonensis* showed promising activity against *M. ulcerans* in vitro (MIC = 780 μg/mL) [33] (Table 1). Bergenin, an isocoumarin, was identified as the main active compound of the main active compound of the stem bark extract of *S. gabonensis* [34]. Further analyses of stem bark extract have shown tannins, sterols, polyterpenes, polyphenols, flavonoids, and alkaloids in appreciable amounts with a trace of saponins. The stem bark also contains 2 cis/trans isomers of lignans (calopiptin and galagrin) [34]. Sofowora [35] has also reported that these compounds are responsible for the biological activities of the plant. Kamanzi [105] also argued that plants show antibacterial activity when they contain flavonoids, tannins, saponins, and alkaloids.

2.2.27 Tonic 1: Mixture of Zea mays L. and Spigelia anthelmia L. Mixture of *S. anthelmia* leaves and *Z. mays* (tonic 1) used in traditional BU treatment [5] showed growth inhibition of *M. ulcerans* with MIC values of 6.25–25 μg/mL (cited as 3.13–12.5% (V/V)) (Table 1) [5].

(i) Spigelia anthelmia *L.* Spigelia anthelmia is a common annual weed that grows in open regrowths, on unused land in towns and on road sides [106]. The plant is reputed to be useful in wound healing. A decoction of leaves and twigs is used to wash the wound, which is then dressed with a powder of the bark of the plant [107]. Phytochemical investigation has described the isolation of the alkaloid spiganthine, volatile alkaloids, isoquinoline and actinide isomer, three quaternary alkaloids, choline, benzoylcholine and 2,3-dimethylacrolyl choline, phenylcarboxylic acids, and flavonoids [54, 55] from the plant.

(ii) Zea mays *L.* Zea mays is a robust annual grass up to 4 (~6) m tall [108] that possesses wound healing activity [109]. *Z. mays* corn silk is rich in phenolic compounds, particularly flavonoids. It also consists of proteins, vitamins, carbohydrates, calcium, potassium, magnesium and sodium salts, volatiles oils, and steroids such as sitosterol and stigmastanol, alkaloids, and saponins [56] that might promote the wound healing and antibacterial activities of the mixture.

2.2.28 Tonic 2: Mixture of Citrus aurantifolia (Christm.) Swingle and Gossypium barbadense L. It consists of *C. aurantifolia* mixed with *G. barbadense* and inhibits the growth of *M. ulcerans* isolates with MIC values of 12.5–25 μg/mL (cited as 6.25–12.5% (V/V)) (Table 1) [5].

(i) Citrus aurantifolia (Christm.) Swingle. Citrus aurantiolifa is widespread in tropical and subtropical regions around the world and it is known for its nutritional values and flavour [110]. The plant and fruit of *C. aurantiolifa* have been commonly used in traditional medicine to treat various diseases [110] including Buruli ulcer. It is used either alone as decoction or mixed with *G. barbadense* leaves or *S. campa-nulata* as a bandage for ulcer [4, 5, 20, 68, 88]. The essential oil of *C. aurantiolifa* fruits contain mainly limonene, betapinene, gamma-terpinene, and citral [111]. The methanolic extract of *C. aurantiolifa* contains alkaloids, flavonoids, tannins, saponins, steroids, cardiac glycosides, and reducing sugar [57]. The hexane extract of the fruit peels fractionated by column chromatography yielded the following major compounds: 5-geranyloxypsoralen, 5-geranyloxy-7-methoxycoumarin, 5,7-dimethoxyxycoumarin, 5-methoxyxpsoralen, and 5,8-dimethoxyxpsoralen. In addition, GC-MS analysis of the hexane extract allowed for the identification of 44 volatile compounds, where 5,7-dimethoxyxycoumarin, 3-methyl-1,2-cyclopentanedione, 1-methoxy-cyclohexene, corylone, palmitic acid, 5,8-dimethoxyxpsoralen, α-terpineol, and umbelliferone are the major constituents. Some constituents that have shown activity against *Mycobacterium tuberculosis* strains were 5,8-dimethoxyxpsoralen (MICs = 25–50 μg/mL), 5-geranyloxypsoralen (MICs = 50–100 μg/mL), palmitic acid (MICs = 25–50 μg/mL), linoleic acid (MICs = 50–100 μg/mL), oleic acid (MICs = 100 μg/mL), 4-hexen-3-one (MICs = 50–100 μg/mL), and citral (MICs = 50–100 μg/mL) [110]. The antimycobacterial activity of *C. aurantiolifia* against
The MICs for Holadysamine and 2,3,6-Trihydroxymethyl benzoate are 50 µg/mL and 62.5 µg/mL, respectively. Holaphyllinol has an MIC of 125 µg/mL. The proposed chemical structure for compound C has a chemical formula of C_{23}H_{37}NO, with an exact mass of 343.28751.

Figure 1: Potent anti-Mycobacterium ulcerans compounds isolated from plants.

*M. ulcerans* could be attributed to these compounds and might have significantly contributed to the observed potency of the mixture.

(ii) *Gossypium barbadense* L. *G. barbadense* is an annual herb that has been reported to have many therapeutic effects including treatment of cutaneous and subcutaneous parasitic infections are mostly attributed to its active constituent gossypol [58].

2.2.29. Tonic 3: Mixture of *Jatropha curcas*, *Gossypium hirsutum*, *Physalis angulata*, and *Delonix regia*. Tonic 3 consisting of *J. curcas* mixed with *G. hirsutum*, *P. angulata*, and *D. regia* inhibits the growth of 7 *M. ulcerans* isolates with MIC value of 6.25–25 µg/mL (reported as 3.13–12.5% (V/V)) (Table 1) [5].

(i) *Jatropha curcas*. See the above.

(ii) *Physalis angulata* L. *Physalis angulata* is a much branched annual shrub, perennial in subtropical zones, and can grow until it reaches 1.0 m. It is used in several countries of tropical and subtropical regions of the world as medicinal and fruit tree. Recent ethnopharmacological studies show that *P. angulata* leaf paste is used as an external application for wounds [59]. The major identifiable phytochemical constituents of medicinal importance are physalins and withanolides [59, 60]. The anti-inflammatory, antimycobacterial, antinociceptive, and antitumor activities together with the inhibitory effect on *M. Ulcerans* support its traditional uses for Buruli ulcer treatment.

(iii) *Gossypium hirsutum* L. *Gossypium hirsutum* is a perennial shrubs also known as upland cotton or Mexican cotton. It is native to Mexico. Extract from cotton plant, which would be primarily gossypol, has been used as traditional medicine. Cotton leaves have been used as a treatment for nausea during pregnancy, for “proud flesh” (swollen tissue around a wound) or for fungal infections. Cotton tissue, particularly the seeds, can be toxic if ingested in excessive quantities because of the presence of anti-nutritional and toxic factors including gossypol and cyclopropenoid fatty acids (including dihydrosterculic, sterlicul, and malvacous acids) [61, 62].

(iv) *Delonix regia* (Hook.) Raf. *Delonix regia* is broad, spreading, flat crowned deciduous tree found in tropical areas. Phytochemical studies of *D. Regia* have shown the presence of sterols, triterpenoids, phenolic compounds, flavonoids, sugars, tannins, steroids, β-sitosterol, lupeol, hydrocarbons, glycosides, saponins [63, 64], and an aromatic compound, p-methoxybenzaldehyde. Adje et al. [65] characterized three major anthocyanins: cyanidin 3-O-glucoside, cyanidin 3-O-rutinoside, and pelargonidin 3-O-rutinoside; three sterols (stigmasterol, β-sitosterol, and its 3-O-glucoside); a triterpene (ursolic acid) and four flavonoids (quercetin, quercitrin, isoquercitrin, and rutin) [112]. Ethanolic and aqueous extracts of *D. regia* flowers containing β-sitosterol and stigmasteryl...
significantly promoted the healing process in rat [113] supporting its usage in the treatment of Buruli ulcer.

2.3. Anti-Mycobacterium ulcerans Compounds Isolated from Plants. Five active compounds with MICs ranging from 50 to 125 μg/mL have been isolated from two plants: one from Sorindeia juglandifolia (2,3,6-trihydroxymethyl benzote) [11] and four from Holarrhena floribunda (holadysamine, holaphyllinol, holamine/holaphyllamine, compound C required further analysis to confirm the structure) [21] (see Figure 1).

3. Conclusion and Future Perspectives

In this review, we have discussed medicinally significant plant species from Sub-Saharan Africa and showed that many have activity against M. ulcerans. Currently, there are only two studies that have reported the purification of active compounds against M. ulcerans. This highlights the poor emphasis given to research into new chemotherapeutic agents against one of the world most neglected diseases: Mycobacterium ulcerans disease. The present review can be used to validate ethnomedicinal knowledge and bioactivities. Unfortunately, most of the species that are claimed to contain antitymocobacterial activities have not been studied in vivo. Screening with in vitro assays has little meaning if there is no clear evidence of effectiveness of the extracts in vivo. Therefore, further in vivo studies of preparations from the identified plant species are required. This should be followed by systematic phytochemical studies of plants that contain bioactive antitymocobacterial activities, isolation, and characterization of the anti-M. ulcerans chemical entities. These can provide the needed validation before such chemical entities can be used as sustainable cheaper/alternative medicines for management of Buruli ulcer disease.

Conflict of Interests

The authors declare that they have no conflict of interests regarding the publication of this paper.

Acknowledgment

The authors are grateful to Noguchi Memorial Institute for Medical Research, University of Ghana, for hosting Patrick Valere Tsouf Fokou under a Postdoctoral Research Fellowship financially supported by the Bill and Melinda Gates Foundation.

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