



## Review

# Morinda lucida Benth (Rubiaceae): A review of its ethnomedicine, phytochemistry and pharmacology

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## ABSTRACT

**Ethnomedicinal relevance:** Natural products derived from plants have served the primary healthcare needs of millions of indigenous people for centuries, many of which have been documented and scientifically validated. *Morinda lucida* Benth (Rubiaceae), also referred to as brimstone tree, is an ethnomedicinal plant which has been widely used in traditional medicine for several decades, particularly in the African continent. Various parts of the plant, including stem bark, leaves and root, have been applied in traditional medicine for the management of various pathological conditions such as malaria, diabetes, hypertension, inflammation, typhoid fever, cancer, cognitive disorders, sickle cell disease, trypanosomiasis, onchocerciasis and various fevers. In this review, we critically evaluated the relationship between traditional uses, laboratory pharmacological activities and clinical studies on *M. lucida* so as to unveil opportunities for the development of relevant therapeutic agents against diseases that threaten mankind.

**Materials and methods:** A search for relevant data on *M. lucida* was done using scientific databases (Google Scholar, Mendeley, ScienceDirect, PubMed, Asian Science Citation Database, Chinese Biomedical Literature Database, Chinese National Knowledge Infrastructure, Chinese Scientific Journal Database, Chinese Science Citation Database, other web sources (such as The Plant List and PROTA), books and other literature sources.

**Results:** A hundred compounds have been isolated from *M. lucida*. Many of the reported secondary metabolites include alkaloids, tannins, anthraquinones, sterols, saponins, polyphenols, terpenoids, phenols and cardiac glycosides. The *in vitro* and *in vivo* experimental studies on various extracts, fractions and isolated compounds of *M. lucida* support the acclaimed pharmacological activities of the plant, such as antimalarial, antidiabetic, hypotensive, anti-inflammatory, immunostimulatory, antioxidant, antimicrobial, antiproliferative, cognitive-enhancement, anti-sickling, anti-trypanosomal, anti-onchocercal, muscle relaxant, antifungal and anti-leishmanial activities. These evidence-based scientific reports lend credence to their traditional uses. However, the safety of extracts of *M. lucida* is a cause for concern following reported toxicities such as anti-spermatogenic effect, genotoxicity and *in vitro* inhibition of human cytochrome P450 3A subfamily.

**Conclusion:** Documented evidence suggests that *M. lucida* remains a rich source of extracts and chemical compounds with diverse bioactivities that are of therapeutic benefit to man and this justifies its traditional uses for the primary healthcare needs of indigenous populations across tropical Africa. Due to the fact that *M. lucida* extracts may not be safe at some reported doses, more in-depth studies on their toxicities are required to better understand safer approaches to their traditional uses. In addition, mechanistic studies on the isolated compounds with known pharmacological activities are quite limited, thus necessitating future research efforts to be focused on the mechanisms of action of these active principles in order to facilitate their potential enlistment for rational drug design.

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## 1. Introduction

Plants have long history of extensive use in traditional medicine for the management of various diseases. The traditional claims on the healing properties of plants are most often tied to cultural reasons, long-term use, affordability, safety and efficacy. Ethnomedicinal plants have also played significant role in drug discovery, development and production (Farnsworth et al., 1985). Accumulating evidence indicates that 60% of current cancer drugs and 75% of anti-infectious drugs are nature-derived (Newman et al., 2003). The World Health Organization (WHO) estimated that about 65% of the global population and about 80% of populations in developing countries depend on plants and their products for their primary health care needs, while plant-based products also play significant but indirect role in the health care systems of developed countries (Farnsworth et al., 1985). One of such important and widely used ethnomedicinal plants in sub-Saharan Africa is *Morinda lucida* Benth which belongs to the Rubiaceae family. Recently, Mabberly (2017) described the Rubiaceae family to be made up of 576 genera and 12,000 species and based on phylogenetic approach to plant systematics, this family appear to represent the fourth largest angiosperm family after Asteraceae (23,000 species), Orchidaceae (19,500 species) and Fabaceae. (18,000 species) (Judd et al., 1999; APG IV). Based on molecular phylogenetic studies, the Rubiaceae family has been subdivided into three subfamilies namely Cinchonoideae, Ixoroideae and Rubioideae (Moreira et al., 2015). In sub-Saharan Africa, there are 1900 species of the Rubiaceae family belonging to 164 genera, with over half of them documented to be native to the continent (Robbrecht, 1996). *M. lucida* belongs to the Rubioideae subfamily, Morindeae tribe and genus *Morinda*.

*M. lucida*, also called brimstone tree, is an ever-green medium-sized tree with dark-shiny leaves on the upper surface (Kwofie et al., 2016; Lawal et al., 2012). It is called brimstone tree because the wood is yellow. It is one of the commonly collected and administered medicinal plants in African traditional medicine, growing around the tropical regions of Central and West Africa (Lawal et al., 2012; Rath et al., 1995; Suzuki et al., 2015). The Yorubas in Western Nigeria call it Oruwo; the Igbos of South East Nigeria call it Nfia or Eze Ogu; the Hausas in Northern Nigeria call it Njisi; the Igede in Benue State, North Central Nigeria, call it Ufu Ogile (Nweze, 2012; Saalu, 2016); the Tivs also in Benue State, Nigeria, call it Kpan ligom (Tor-anyiin et al., 2003); the Ebiras in Kogi State, North-Central Nigeria, call it Ugigo (Umar et al., 2013); and the Esan People of Southern Nigeria call it Egbogo ([www.projectshelve.com](http://www.projectshelve.com)). In Cote d'Ivoire, the Baoule people call it Koya while other tribes call it Sangogo, or Bondoukou alongua; it is called Twi, Ewe amake or Kon kroma in Ghana while the Togolese call it Atak ake (Ashafa and Olunu, 2011). In Cameroon, it is called Akeng in Yaounde, Heuheun in Bafia (Noumi and Dibakto, 2000) and Ewoka in Bakweri, South West Cameroon (Jiofack et al., 2010). It is called Gligo in Diogo Vaz, São Tomé and Príncipe (Madureira et al., 2002) and N'siki in Kinshasa DR Congo (Mpiana et al., 2007). Although *M. lucida* has always been reported to be native and growing only in Africa, a recent report has revealed its existence in the Coastal Regions of Tamil Nadu, India (Vijayakumar et al., 2017). Considering the wide use of *M. lucida* in African traditional medicine, which is based on cultural and historical beliefs, there is the need to juxtapose the acclaimed medicinal properties of this plant with the empirical findings on the pharmacological activities of the plant. Thus, the aim of this review was to critically evaluate the relationship between traditional uses, laboratory-based pharmacological activities and clinical studies on *M. lucida* so as to unveil opportunities for drug discovery and development.

## 2. Methodology

To achieve this aim, a search for relevant data on *M. lucida* was carried out. This was done using scientific databases (Google Scholar, Mendeley, ScienceDirect, PubMed, Asian Science Citation Database,

Chinese Biomedical Literature Database, Chinese National Knowledge Infrastructure, Chinese Scientific Journal Database, Chinese Science Citation Database, other web sources (such as The Plant List and PROTA), books and other literature sources. For the antimalarial activity of *Morinda lucida* leaf decoction, the Research Initiative on Traditional Antimalarial Methods (RITAM) score was calculated and compared with those of other plant remedies (the calculations are shown in the supplementary file).

## 3. Traditional uses

Different parts of *M. lucida* are indigenously used for the treatment/management of various diseases in Africa. For example, in malaria endemic tropical Africa, *M. lucida* has found a wide application in malaria treatment (Adebayo and Krettli, 2011; Chinsebu, 2015; Kayode, 2006). Practitioners in West African traditional medicine apply the leaves, stem bark and roots of *M. lucida*, using different indigenous methods, as antimalarial remedies (Iwu, 1993). *M. lucida* has been used to treat malaria in the Dangme West District of Ghana (Asase et al., 2010), the Eastern Region of Ghana (Ameyaw and Duker-eshun, 2009), Togo (Koudouvo et al., 2011), Ivory Coast (Okpekon et al., 2004) and Nigeria (Ishola et al., 2014). It has been employed for the treatment of hypertension in Ghana (Abbiw, 1990), Togo (Karou et al., 2011), Nigeria (Ajayi, 2012; Olaniyan and Babatunde, 2014) and other parts of Africa (Ajayi, 2013; Iwu, 1993; Owolabi et al., 2014; Zimudzi and Cardon, 2005). The plant is also used for the treatment of sickle cell disease in Togo (Joppa et al., 2008). The Forestry Research Institute of Ghana (FORIG) also reported that the root, bark and leaves of *M. lucida* are used to treat typhoid fever, gonorrhea, bone fracture, rheumatism, high blood pressure and candidiasis (Ofori et al., 2011). Additionally, the plant is used in many African countries by traditional medical practitioners for the treatment of bacterial diseases (Umeh et al., 2016). For instance, it is used by the Igalas in North Central Nigeria for the treatment of typhoid fever (Musa et al., 2014). In Ivory Coast, it has found application in helminthiasis and trypanosomiasis (Okpekon et al., 2004). Also, the plant is found in recipes given by traditional medical practitioners in South West Nigeria either as memory enhancers or anti-aging agents (Elufioye et al., 2013; Elufioye and Hameed, 2017). *M. lucida* has been reported to be used for managing diabetes in Nigeria (Gbolade, 2009; Kayode, 2006). It is also used in Nigeria as an astringent and antiseptic agent for ulcerating abscess (Adomi and Umukoro, 2010). A summary of the ethnomedicinal uses of *M. lucida* is presented in Table 1.

### 3.1. Traditional uses of the leaves

Leaves and twigs of *M. lucida* are sold in markets as a medicinal tonic for young children in West Africa (Zimudzi and Cardon, 2005). In Nigeria, *M. lucida* is one of the most widely used traditional medicines against fever (Dalziel, 1937; Zimudzi and Cardon, 2005). Decoction of *M. lucida* leaf is used for the treatment of malaria in Ogun and Lagos States, South West Nigeria (Idowu et al., 2010; Ishola et al., 2014) and Kogi State, North Central Nigeria (Umar et al., 2013). In Côte d'Ivoire, leaf decoction is applied against jaundice ([https://uses.plantnet-project.org/en/Morinda\\_lucida\\_\(PROTA\)](https://uses.plantnet-project.org/en/Morinda_lucida_(PROTA))). Furthermore, *M. lucida* leaves are used to manage sickle cell disease (Kunle and Egharevba, 2013). For example, the *M. lucida* leaves are prescribed by traditional medical practitioners for their potentials against sickle cell disease in DR Congo (Mpiana et al., 2007, 2010). Extract of the leaves of *M. lucida* has been recommended for the prevention and treatment of hypertension and its cerebral complications (Iwu, 1993). Ethanolic infusion of *M. lucida* leaf is used as an anti-inflammatory agent in managing rheumatic disorders in Nigerian traditional medical system (Akah and Nwambie, 1994). In Gabon, the leaf decoction is taken orally for the treatment of abdominal pain (Akendengue and Louis, 1994) and as an antidiabetic remedy (Taika et al., 2017). From these reports, the solvents used traditionally for the preparation of the extracts are water and ethanol.

**Table 1**  
Ethnomedicinal uses of *Morinda lucida* Benth (Rubiaceae)

| Country (Region or State)                 | Disease condition                               | Plant parts used                 | Ethnomedicinal recipes                                                                                                                                                                                                                     | References                                         |
|-------------------------------------------|-------------------------------------------------|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| Ghana (Dangme West, Greater Accra Region) | Malaria                                         | Leaves                           | Whole plants with leaves of <i>M. lucida</i> are boiled and decoction taken orally as desired until recovery.                                                                                                                              | Asase et al. (2010)                                |
| Ghana (Eastern Region)                    | Malaria                                         | Roots                            | Decoction                                                                                                                                                                                                                                  | Ameyaw and Duker-eshun (2009)                      |
| Nigeria (not specified)                   | Malaria                                         | Leaves                           | Aqueous extract                                                                                                                                                                                                                            | Nworu et al. (2012); Unekwujo et al. (2011)        |
| Nigeria (Ogbomoso, South West)            | Malaria                                         | Leaves                           | Boiled in water for an hour in combination with other plants to make antimalarial concoction, one cup of the concoction is taken orally twice daily after meals                                                                            | Olorunnisola et al. (2013)                         |
| Nigeria (Lagos State, Southwest)          | Malaria                                         | Stem bark, Leaves                | Decoction                                                                                                                                                                                                                                  | Ishola et al. (2014)                               |
| Nigeria (Benue State, North Central)      | Malaria                                         | Leaves                           | Aqueous decoction in addition with <i>Crossopteryx febrifuga</i> , and <i>Newbouldia laevis</i> P. beauf. (Bignoniaceae). Concoction (300 mL) is taken 4 times daily for 5 days as a cure for malaria infection.                           | Tor-anyiin et al. (2003)                           |
| Nigeria (Okeigbo Ondo State, South West)  | Malaria                                         | Leaves, roots                    | Tincture and infusion                                                                                                                                                                                                                      | Odugbemi et al. (2007)                             |
| Nigeria (Ogun State)                      | Malaria                                         | Stem bark, Leaves                | Decoction                                                                                                                                                                                                                                  | Idowu et al. (2010)                                |
| Nigeria (Kogi State, North Central)       | Malaria                                         | Leaves, roots                    | Not specified                                                                                                                                                                                                                              | Umar et al. (2013)                                 |
| Nigeria (Ibadan, Oyo State)               | Malaria                                         | Roots                            | Not specified                                                                                                                                                                                                                              | Gbadamosi et al. (2011)                            |
| Ivory Coast                               | Malaria                                         | Leaves, roots, stem, trunk barks | Not specified                                                                                                                                                                                                                              | Okpekon et al. (2004)                              |
| Togo (Maritime region)                    | Malaria                                         | Not specified                    | Decoction                                                                                                                                                                                                                                  | Koudouvo et al. (2011)                             |
| Central and West Africa                   | Malaria                                         | Bark, Leaves, roots              | Infusion, decoction                                                                                                                                                                                                                        | Chithambo et al. (2017).                           |
| Cameroon                                  | Malaria/fever                                   | Leaves, stem bark, roots         | Decoction                                                                                                                                                                                                                                  | Dalziel (1937), Titanji et al. (2008)              |
| Sao Tome and Principe islands             | Malaria/fever                                   | Bark, Leaves                     | Not specified                                                                                                                                                                                                                              | Madureira et al. (2002)                            |
| Nigeria (Benue State, North Central)      | Diarrhoea                                       | Leaves                           | Decoction of <i>M. lucida</i> stem bark and <i>Zanthoxylum zanthoxyloides</i> (Lam) Waterm (Rutaceae) Leaves                                                                                                                               | Igoli et al. (2005)                                |
| Cameroon                                  | Stomach wounds                                  | Leaves, roots, stem bark         | Decoction                                                                                                                                                                                                                                  | Jiofack et al. (2010)                              |
| Cameroon                                  | Abdominal pains, dysmenorrhoea and splenomegaly | Bark                             | Decoction                                                                                                                                                                                                                                  | Jiofack et al. (2009)                              |
| Gabon                                     | Abdominal pains                                 | Leaves, bark                     | Decoction is used in a bath or drank                                                                                                                                                                                                       | Akendengue and Louis (1994)                        |
| Togo                                      | Hypertension                                    | Roots                            | Decoction                                                                                                                                                                                                                                  | Karou et al. (2011)                                |
| Nigeria                                   | Hypertension                                    | Leaves, stem bark                | Not specified                                                                                                                                                                                                                              | Ajayi (2012), Iwu (1993)                           |
| Ivory Coast                               | Helminthiasis, trypanosomiasis                  | Leaves, roots, stem, trunk bark  | Not specified                                                                                                                                                                                                                              | Okpekon et al. (2004)                              |
| Nigeria (South West)                      | Memory enhancer/anti-aging                      | Leaves                           | Not specified                                                                                                                                                                                                                              | Elufioye et al. (2013); Elufioye and Hameed (2017) |
| Nigeria (Lagos State, South West)         | Diabetes                                        | Leaves                           | The leaves of <i>M. lucida</i> and <i>Saccharum officinarum</i> are squeezed till the juice comes out, then mixed with water and a glassful is taken twice daily                                                                           | Gbolade (2009)                                     |
| Gabon                                     | Diabetes                                        | Bark, Leaves                     | Decoction                                                                                                                                                                                                                                  | Taika et al. (2017)                                |
| Democratic Republic of Congo              | Sickle cell disease                             | Leaves                           | Decoction                                                                                                                                                                                                                                  | Mpiana et al. (2007)                               |
| Benin Republic                            | Sickle cell disease                             | Roots                            | Roots of <i>M. lucida</i> , <i>Uvaria chamae</i> , <i>Lonchocarpus cyanescens</i> , the leaves of <i>Croton zambesicus</i> , the fruits of <i>Xylopia aethiopica</i> and the stems of <i>Raphiostylis beninensis</i> in a single decoction | Avaligbe et al. (2012b)                            |
| Togo                                      | Sickle cell disease                             | Leaves                           | Decoction                                                                                                                                                                                                                                  | Joppa et al. (2008)                                |
| Nigeria                                   | Inflammation                                    | Leaves                           | Ethanol infusion                                                                                                                                                                                                                           | Akah and Nwambie (1994)                            |
| Nigeria (Kogi State, North Central)       | Typhoid fever                                   | Leaves                           | Not specified                                                                                                                                                                                                                              | Musa et al. (2014)                                 |

### 3.2. Traditional uses of the stem bark

It has been reported that the Europeans use the decoction of *M. lucida* stem to make “bitters” (Dalziel, 1937). Decoction of *M. lucida* stem bark is used for the treatment of malaria in Ogun State, South West Nigeria (Idowu et al., 2010). Stem bark decoction is applied against jaundice in Côte d’Ivoire ([https://uses.plantnet-project.org/en/Morinda\\_lucida](https://uses.plantnet-project.org/en/Morinda_lucida)

(PROTA)). Apart from the leaves, extracts of *M. lucida* stem bark are also used for the prevention and treatment of hypertension and its cerebral complications (Iwu, 1993). *M. lucida* stem bark decoction is used for the treatment of abdominal pain in Gabon (Akendengue and Louis, 1994) and Cameroon (Jiofack et al., 2009). The stem bark is also used as an antidiabetic remedy (Taika et al., 2017) and for the treatment of dysmenorrhoea and splenomegaly in Cameroon (Jiofack et al., 2009).

### 3.3. Traditional uses of the roots

In Democratic Republic of Congo, a dressing of powdered *M. lucida* root bark is used against itching and ringworm ([https://uses.plantnet-project.org/en/Morinda\\_lucida\\_\(PROTA\)](https://uses.plantnet-project.org/en/Morinda_lucida_(PROTA))). The Tem people in the Central Region of Togo use the root decoction as an antihypertensive agent (Karou et al., 2011) while it is used for the production of bitters by the Europeans (Dalziel, 1937). The root is used for the treatment of malaria in Kogi State, North Central Nigeria (Umar et al., 2013). The decoction of the root bark is used as enema (Noumi and Dibakto, 2000).

### 3.4. Traditional uses of combination of different parts

Tincture and infusion of the root and leaf of *M. lucida* are used for malaria therapy in Okeigbo, Ondo State, South West Nigeria (Odugbemi et al., 2007). The indigenous people of São Tomé and Príncipe use the bark and leaf of this plant to treat malaria (Silva et al., 2011). The bitter decoction of the bark, leaf and root is taken as bitter tonic and for the management of dysentery, abdominal colic and intestinal worm infestation in West Africa (Dalziel, 1937). Decoction of the bark, leaf, stem and root is used for the treatment of stomach wounds (Jiofack et al., 2010).

From literature search, it was noticed that the leaves of the plant have found more uses in traditional medicine than other parts of the plant while the seed and flowers had no documented record of application in traditional medicine. Also, aqueous extract was the predominant traditional preparation of the herbal remedies produced from the plant. While myriads of pathological conditions are treated with the aqueous extracts of the plant, malaria was the predominantly mentioned disease for which the plant has been widely used in African traditional medicine.

### 3.5. Traditional uses in combination with other plants

In Nigeria, the decoction obtained from the roots of *M. lucida* and the leaves of *Carica papaya* Linn., *Mangifera indica* L. and *Cassia podocarpa* Guill & Perr. is taken two times daily for the treatment of malaria (Gbile, 1986). In Ogbomoso, South West Nigeria, *M. lucida* is used in combination with other plants to make antimalarial concoction. Specifically, the bark of *Enantia chlorantha* Oliver (Annonaceae) and the leaves of *M. lucida*, *Picralima nitida* Th. & H. Dur., *Physalis angulata* L and *Piper guineense* Thonn. are usually boiled together in water for an hour; then, one cup is taken twice daily after meals for the treatment of malaria (Olorunnisola et al., 2013). The Tivs in Benue State, North Central Nigeria, make aqueous decoction of mixed fresh leaves of *Crossopteryx febrifuga*, *Newbouldia laevis* P. beauv. and *M. lucida*. The decoction (300 mL) is taken orally 4 times daily for 5 days as a cure for malaria infection (Tor-anyiin et al., 2003). *M. lucida* is one of the ingredients of MAMA, a commercial herbal remedy in Nigeria. MAMA decoction is made up of *Mangifera indica* L. (Anacardiaceae), *Alstonia boonei* De Wild (Apocynaceae), *M. lucida* and *Azadirachta indica* A. Juss (Meliaceae) leaves, commonly prepared in ratio 1:1:1:1 (Odediran et al., 2014). The inclusion of various parts of *M. lucida* in herbal mixtures for malaria treatment suggests the significant contribution of the plant to such mixtures because each of the parts of the plant used in the mixtures is used singly for the treatment of malaria in African traditional medicine. Due to the fact that some of these plants are well established antimalarial plants, it is expected that the herbal mixture will exhibit higher antimalarial activity than *M. lucida* alone, with the potential of getting rid of the resistant strains of the parasite due to an array of various antimalarial compounds with different mechanisms of action. However, the increased adverse effects of such preparations cannot be overruled.

A decoction of *M. lucida* stem bark and *Zanthoxylum zanthoxyloides* (Lam) Waterm (Rutaceae) leaf is used for the treatment of diarrhoea among the Igede people of Benue State, North Central Nigeria (Igoli et al., 2005). However, the actual contribution of *M. lucida* stem bark to

the antidiarrhoeal activity of the herbal mixture is yet to be verified because there are no reports of it being used alone for the treatment of diarrhoea in African traditional medicine. In Lagos State, Nigeria, leaves of *M. lucida* and *Saccharum officinarum* are used as herbal recipes for the management of diabetes mellitus (Gbolade, 2009). The leaves of the two plants are squeezed till the juice comes out; the juice is then mixed with water and a glassful is taken twice daily (Gbolade, 2009). The traditional use of *M. lucida* leaf for the treatment/management of diabetes mellitus singly suggests its significant contribution to the antidiabetic activity of the herbal mixture. In Benin Republic, traditional herbal preparation of the roots of *Uvaria chamae*, *Lonchocarpus cyanescens* and *M. lucida*, the leaves of *Croton zambesicus*, the fruits of *Xylopia aethiopica* and the stem of *Raphiostylis beninensis*, in a single decoction, are used as a traditional remedy for sickle cell disease (Avaligbe et al., 2012b). However, the actual contribution of *M. lucida* root to the antisickling activity of the herbal mixture is yet to be verified due to lack of reports of its use singly for the management of sickle cell disease in African traditional medicine.

## 4. Chemical constituents

Chemotaxonomic markers of the Rubiaceae family include biologically active alkaloids (indole alkaloids), anthraquinones, phenolic compounds, terpenes (most commonly iridoids) and fatty acid glycosides (Bolzani et al., 2001; Cardoso et al., 2008; Mongrand et al., 2005). Anthraquinones have been reported to be the main chemical markers common to the plants in the subfamily Rubioideae and, thus, the genus *Morinda* (Inouye et al., 1988; Rath et al., 1995). Evidence from several studies suggests anthraquinones, monoterpenes, sesquiterpenes and fatty acids are important chemotaxonomic markers of *M. lucida* and may be useful in the standardization of the plant.

### 4.1. Classes of phytochemicals identified

Phytochemical screening of *M. lucida* leaf has shown the presence of alkaloids (Adeyemi et al., 2014; Chukwuemeka et al., 2013; Osuntokun et al., 2016a), tannins (Adeyemi et al., 2014; Chukwuemeka et al., 2013; Okeniyi et al., 2015; Osuntokun et al., 2016a), anthraquinones (Adeyemi et al., 2014), sterols (Addy et al., 2013; Adeyemi et al., 2014), phlobatannins (Okeniyi et al., 2015), cardenolides (Addy et al., 2013), saponins (Okeniyi et al., 2015; Osuntokun et al., 2016a; Chukwuemeka et al., 2013), polyphenols (Okeniyi et al., 2015; Osuntokun et al., 2016a), terpenoids (Addy et al., 2013; Okeniyi et al., 2015) and phenols (Osuntokun et al., 2016a). Phytochemical analyses of the root of *M. lucida* have confirmed the presence of alkaloids (Ameyaw and Duker-eshun, 2009; Gbadamosi et al., 2011), tannins (Gbadamosi et al., 2011), anthraquinones (Gbadamosi et al., 2011; Sittie et al., 1999), saponins (Gbadamosi et al., 2011) and cardiac glycosides (Gbadamosi et al., 2011). The presence of phlobatannins, terpenoids, alkaloids, tannins, phenols, saponins and polyphenols in the stem bark of *M. lucida* has been documented (Adeneye et al., 2017; Osuntokun et al., 2016a). The specific compounds that have been isolated from various parts of *M. lucida* (Table 2) are further discussed in the following subsections. However, many of the documented phytochemical data lack in-depth analysis of the constituents of various classes of phytochemicals identified, particularly the alkaloids. Also, some parts of the plant, i.e. the seed and flower, have not been screened for bioactive secondary metabolites. This further confirms the paucity of information on the traditional uses of the seed and flower of the plant.

### 4.2. Isolated phytochemicals

#### 4.2.1. Anthraquinones and derivatives

The anthraquinols, oruwal (1) and oruwalol (2), and the anthraquinones, damnacanthol (3), nordamnacanthol (4), soranjidiol (5), alizarin-l-methyl ether (6), rubiadin (7), rubiadin-l-methyl ether (8), 2-

**Table 2**  
Chemical constituents isolated from *Morinda lucida* Benth (Rubiaceae)

| SN | Chemical constituents                                                  | Class                      | Plant part(s)            | References                                                                               |
|----|------------------------------------------------------------------------|----------------------------|--------------------------|------------------------------------------------------------------------------------------|
| 1  | Oruwal (1)                                                             | Anthraquinone              | Stem                     | Adesida and Adesogan (1972); Adesogan (1973)                                             |
| 2  | Oruwalol (2)                                                           | Anthraquinone              | Stem/leaf                | Adesida and Adesogan (1972); Adesogan (1973); Kwofie et al. (2016)                       |
| 3  | Damnacanthol (3)                                                       | Anthraquinone              | Stem/root                | Adesida and Adesogan (1972); Adesogan (1973); Koumaglo et al. (1992); Rath et al. (1995) |
| 4  | Nordamnacanthol (4)                                                    | Anthraquinone              | Stem/root                | Adesida and Adesogan (1972); Adesogan (1973); Rath et al. (1995)                         |
| 5  | Alizarin-1-methyl ether (5)                                            | Anthraquinone              | Stem/root                | Adesida and Adesogan (1972); Adesogan (1973); Rath et al. (1995)                         |
| 6  | Soranjidiol (6)                                                        | Anthraquinone              | stem                     | Adesida and Adesogan (1972); Adesogan (1973)                                             |
| 7  | Rubiadin (7)                                                           | Anthraquinone              | Stem/bark                | Adesida and Adesogan (1972); Adesogan (1973); Zimudzi and Cardon (2005)                  |
| 8  | Rubiadin-1-methyl ether (8)                                            | Anthraquinone              | Stem/root                | Adesida and Adesogan (1972); Adesogan (1973); Koumaglo et al. (1992); Rath et al. (1995) |
| 9  | 2-Methyl-anthraquinone (9)                                             | Anthraquinone              | Stem/root                | Adesida and Adesogan (1972); Adesogan (1973); Rath et al. (1995)                         |
| 10 | Anthraquinone-2-aldehyde (10)                                          | Anthraquinone              | stem                     |                                                                                          |
| 11 | 1-Hydroxy-2-methyl anthraquinone (11)                                  | Anthraquinone              | Stem/root                | Rath et al. (1995)                                                                       |
| 12 | 1-Methoxy-2-methyl-anthraquinone (12)                                  | Anthraquinone              | Trunk heartwood          | Demagos et al. (1981)                                                                    |
| 13 | 3-Hydroxyanthraquinone-2-carbaldehyde (13)                             | Anthraquinone              | Trunk heartwood/<br>root | Demagos et al. (1981); Rath et al. (1995)                                                |
| 14 | Morindone-5-methyl ether (14)                                          | Anthraquinone              | Trunk heartwood          | Demagos et al. (1981)                                                                    |
| 15 | Munjistin methyl ester (15)                                            | Anthraquinone              | Trunk heartwood          | Demagos et al. (1981)                                                                    |
| 16 | Damnacanthol- $\omega$ -methyl ether (16)                              | Anthraquinone              | Trunk heartwood          | Demagos et al. (1981)                                                                    |
| 17 | Soranjidiol- 6-O- $\beta$ -primveroside (17)                           | Anthraquinone              | Trunk heartwood          | Demagos et al. (1981)                                                                    |
| 18 | Lucidin 3-O- $\beta$ -primveroside (18)                                | Anthraquinone              | Trunk heartwood          | Demagos et al. (1981)                                                                    |
| 19 | Lucidin (19)                                                           | Anthraquinone              | Wood/bark                | Zimudzi and Cardon (2005)                                                                |
| 20 | Morindin (20)                                                          | Anthraquinone              | Root/bark                | Rath et al. (1995); Zimudzi and Cardon (2005)                                            |
| 21 | Munjistin (21)                                                         | Anthraquinone              | Wood/bark                | Zimudzi and Cardon (2005)                                                                |
| 22 | Purpuroxanthin (22)                                                    | Anthraquinone              | Wood/bark                | Zimudzi and Cardon (2005)                                                                |
| 23 | 5,15-O- dimethylmorindol (23)                                          | Anthraquinone              | Stem                     | Chithambo et al. (2017)                                                                  |
| 24 | 3-Hydroxy-2-hydroxymethyl anthraquinone (24)                           | Anthraquinone              | Root                     | Rath et al. (1995)                                                                       |
| 25 | Damnacanthol (25)                                                      | Anthraquinone              | Root                     | Rath et al. (1995)                                                                       |
| 26 | 1,5,6-Trihydroxy-2-methyl anthraquinone (morindon) (26)                | Anthraquinone              | Root                     | Rath et al. (1995)                                                                       |
| 27 | 1,5,6-Trimethoxy-2-methyl anthraquinone (morindon trimethylether) (27) | Anthraquinone              | Root                     | Rath et al. (1995)                                                                       |
| 28 | Digitolutein (28)                                                      | Anthraquinone              | Stem/root                | Koumaglo et al. (1992)                                                                   |
| 29 | $\beta$ -sitosterol (29)                                               | Phytosterol                | Leaf/bark                | Chithambo et al. (2017); Nweze (2012)                                                    |
| 30 | Stigmasterol (30)                                                      | Phytosterol                | Leaf/bark                | Chithambo et al. (2017); Nweze (2012)                                                    |
| 31 | Campesterol (31)                                                       | Phytosterol                | Bark                     | Chithambo et al. (2017)                                                                  |
| 32 | (+)-catechin (32)                                                      | Polyphenols                | Leaf                     | Okeniyi et al. (2015)                                                                    |
| 33 | (+)-catechin hydrate (33)                                              | Polyphenols                | Leaf                     | Okeniyi et al. (2015)                                                                    |
| 34 | (-)-epicatechin (34)                                                   | Polyphenols                | Leaf                     | Okeniyi et al. (2015)                                                                    |
| 35 | Phytol (35)                                                            | Diterpene                  | Leaf                     | Elufioye et al. (2015)                                                                   |
| 36 | Cycloartenol (36)                                                      | Triterpene                 | Bark                     | Chithambo et al. (2017)                                                                  |
| 37 | Ursolic acid (37)                                                      | Triterpene                 | Leaf                     | Cimanga et al. (2006); Kwofie et al. (2016)                                              |
| 38 | Oleanolic acid (38)                                                    | Triterpene                 | Leaf                     | Cimanga et al. (2006); Kwofie et al. (2016)                                              |
| 39 | Oruwacin (39)                                                          | Monoterpenoids             | Leaf                     | Adesogan (1979)                                                                          |
| 40 | Molucidin (40)                                                         | Monoterpenoids             | Leaf                     | Kwofie et al. (2016); Suzuki et al. (2015),                                              |
| 41 | Asperuloside (41)                                                      | Monoterpenoids             | Bark                     | Chithambo et al. (2017)                                                                  |
| 42 | Asperulosidic acid (42)                                                | Monoterpenoids             | Bark                     | Chithambo et al. (2017)                                                                  |
| 43 | Cis-Sabinene hydrate (43)                                              | Monoterpenoid              | Leaf oil                 | Owolabi et al. (2014)                                                                    |
| 44 | Cis-p-Menth-2-en-1-ol (44)                                             | Monoterpenoid              | Leaf oil                 | Owolabi et al. (2014)                                                                    |
| 45 | Trans-p -Menth-2-en-1-ol (45)                                          | Monoterpenoid              | Leaf oil                 | Owolabi et al. (2014)                                                                    |
| 46 | Borneol (46)                                                           | Monoterpenoid              | Leaf oil<br>Root oil     | Owolabi et al. (2014); Okoh et al. (2011)                                                |
| 47 | Neryl acetate (47)                                                     | Monoterpenoid              | Leaf oil                 | Owolabi et al. (2014)                                                                    |
| 48 | $\beta$ -Fenchyl alcohol (48)                                          | Monoterpenoid<br>(Alcohol) | Leaf oil                 | Okoh et al. (2011)                                                                       |
| 49 | Carvacrol (49)                                                         | Monoterpenoid              | Root oil                 | Okoh et al. (2011)                                                                       |
| 50 | $\alpha$ -terpinene (50)                                               | Monoterpene                | Leaf oil                 | Okoh et al. (2011)                                                                       |
| 51 | $\beta$ -bisabolene (51)                                               | Monoterpene                | Leaf oil                 | Okoh et al. (2011)                                                                       |
| 52 | $\alpha$ -Thujene (52)                                                 | Monoterpene                | Leaf oil                 | Okoh et al. (2011)                                                                       |
| 53 | Camphene (53)                                                          | Monoterpene                | Leaf oil                 | Okoh et al. (2011)                                                                       |
| 54 | 1,8-cineole (54)                                                       | Monoterpene                | Leaf oil                 | Owolabi et al. (2014)                                                                    |
| 55 | $\alpha$ -terpinyl acetate (55)                                        | Monoterpene                | Leaf oil                 | Owolabi et al. (2014)                                                                    |
| 56 | Sabinene (56)                                                          | Monoterpene                | Leaf oil                 | Owolabi et al. (2014)                                                                    |
| 57 | $\beta$ -pinene (57)                                                   | Monoterpene                | Leaf oil                 | Owolabi et al. (2014)                                                                    |
| 58 | Myrcene (58)                                                           | Monoterpene                | Leaf oil                 | Owolabi et al. (2014)                                                                    |
| 59 | $\alpha$ -phellandrene (59)                                            | Monoterpene                | Leaf oil                 | Owolabi et al. (2014)                                                                    |
| 60 | $\alpha$ -3-Carene (60)                                                | Monoterpene                | Leaf oil                 | Owolabi et al. (2014)                                                                    |
| 61 | g-Terpinene (61)                                                       | Monoterpene                | Leaf oil                 | Owolabi et al. (2014)                                                                    |
| 62 | p-Cymene (62)                                                          | Monoterpene                | Leaf oil                 | Owolabi et al. (2014)                                                                    |

(continued on next page)

Table 2 (continued)

| SN  | Chemical constituents                  | Class                     | Plant part(s) | References                                   |
|-----|----------------------------------------|---------------------------|---------------|----------------------------------------------|
| 63  | Limonene (63)                          | Monoterpene               | Leaf oil      | Owolabi et al. (2014)                        |
| 64  | $\delta$ -Terpineol (64)               | Monoterpene               | Leaf oil      | Owolabi et al. (2014)                        |
| 65  | $p$ -Terpineol (65)                    | Monoterpene               | Leaf oil      | Owolabi et al. (2014)                        |
| 66  | Nerol (66)                             | Monoterpene               | Leaf oil      | Owolabi et al. (2014)                        |
| 67  | Linalool (67)                          | Monoterpene               | Leaf oil      | Okoh et al. (2011); Owolabi et al. (2014)    |
| 68  | Terpinen-4-ol (68)                     | Monoterpene               | Leaf oil      | Okoh et al. (2011); Owolabi et al. (2014)    |
| 69  | Trans-Sabinyl acetate (69)             | Monoterpene               | Leaf oil      | Owolabi et al. (2014)                        |
| 70  | Spathulenol (70)                       | Sesquiterpene             | Leaf oil      | Owolabi et al. (2014)                        |
| 71  | Caryophyllene oxide (71)               | Sesquiterpene             | Leaf oil      | Owolabi et al. (2014)                        |
| 72  | $\beta$ -Eudesmol (72)                 | Sesquiterpene             | Leaf oil      | Owolabi et al. (2014)                        |
| 73  | Germacrene (73)                        | Sesquiterpene             | Leaf oil      | Okoh et al. (2011)                           |
| 74  | Cadinene (74)                          | Sesquiterpene             | Leaf oil      | Okoh et al. (2011)                           |
| 75  | $\beta$ -Elemene (75)                  | Sesquiterpene             | Leaf oil      | Okoh et al. (2011)                           |
| 76  | $\beta$ -Caryophyllene (76)            | Sesquiterpenoid           | Root oil      | Okoh et al. (2011)                           |
| 77  | Neryl acetone (77)                     | Sesquiterpenoid           | Root oil      | Okoh et al. (2011)                           |
| 78  | Guanidine carbonate (78)               | Guanidines                | Leaf          | Okeniyi et al. (2015)                        |
| 79  | <i>N</i> -methylmercaptoacetamide (79) | Monocarboxylic acid amide | Leaf          | Okeniyi et al. (2015)                        |
| 80  | Pyridine hydrobromide perbromide (80)  | Pyridine                  | Leaf          | Okeniyi et al. (2015)                        |
| 81  | 1-formylpyrrolidine (81)               | Carbaldehyde              | Leaf          | Okeniyi et al. (2015)                        |
| 82  | <i>N</i> -phenylthiourea (82)          | Thiourea                  | Leaf          | Okeniyi et al. (2015)                        |
| 83  | 3-fluoro- <i>p</i> -anidine (83)       | Benzeneamine              | Root oil      | Okoh et al. (2011)                           |
| 84  | 2-Hydroxy-methyl benzoic acid (84)     | Benzoic acid              | Root oil      | Okoh et al. (2011)                           |
| 85  | 1,2-Benzedicarboxylic acid (85)        | Dicarboxylic acid         | Root oil      | Okoh et al. (2011)                           |
| 86  | Terpinolene (86)                       | Cannabis terpene          | Leaf oil      | Okoh et al. (2011); Owolabi et al. (2014)    |
| 87  | Eugenol (87)                           | Allylbenzene              | Leaf oil      | Owolabi et al. (2014)                        |
| 88  | Methyl eugenol (88)                    | Phenylpropanoid           | Leaf oil      | Owolabi et al. (2014)                        |
| 89  | Cis-Verbenyl acetate (89)              | Monoterpene               | Leaf oil      | Owolabi et al. (2014)                        |
| 90  | Isobornyl acetate (90)                 | Monoterpene               | Leaf oil      | Owolabi et al. (2014)                        |
| 91  | Trans-Pinocaryyl acetate (91)          | Monoterpene               | Leaf oil      | Owolabi et al. (2014)                        |
| 92  | Hexacosanoic acid (92)                 | Fatty acid                | Stem          | Adesida and Adesogan (1972); Adesogan (1973) |
| 93  | Hexadecanoic acid (93)                 | Fatty acid                | Root oil      | Okoh et al. (2011)                           |
| 94  | Dodecanoic acid (94)                   | Fatty acid                | Root oil      | Okoh et al. (2011)                           |
| 95  | Tetradecanoic acid (95)                | Fatty acid                | Root oil      | Okoh et al. (2011)                           |
| 96  | 9-Octadecanoic acid (96)               | Fatty acid                | Root oil      | Okoh et al. (2011)                           |
| 97  | Tetradecanal (97)                      | Aliphatic hydrocarbon     | Root oil      | Okoh et al. (2011)                           |
| 98  | 9, 17-Octadecadienal (98)              | Aliphatic hydrocarbon     | Root oil      | Okoh et al. (2011)                           |
| 99  | Tetradecane (99)                       | Aliphatic hydrocarbon     | Root oil      | Okoh et al. (2011)                           |
| 100 | Nonanal (100)                          | Aliphatic hydrocarbon     | Leaf oil      | Okoh et al. (2011)                           |

methyl- anthraquinone/tectoquinone (9), anthraquinone-2-aldehyde (10), 1-hydroxy-2-methyl anthraquinone (11) and 1-methoxy-2-methyl-anthraquinone (12) were isolated from *M. lucida* stem (Adesida and Adesogan, 1972; Adesogan, 1973). The anthraquinones, 3-hydroxyanthraquinone-2-carbaldehyde (13), morindone-5-methyl ether (14), munjistin methyl ester (15), Damnacanthol- $\omega$ -methyl ether (16), sornjidiol- 6-*O*- $\beta$ -primveroside (17) and lucidin 3-*O*- $\beta$ -primveroside (18) were isolated from the trunk heartwood of *M. lucida* (Demagos et al., 1981). Other anthraquinones isolated from the wood and stem bark of *M. lucida* include lucidin (19), morindin (20), munjistin (21), purpur-oxanthin (22), rubiadin (7) (Zimudzi and Cardon, 2005) and 5,15-*O*-dimethylmorindol (23) (Chithambo et al., 2017).

Some antifungal anthraquinones isolated from *M. lucida* root include 3-hydroxyanthraquinone-2-carbaldehyde (13), nordamnacanthol (4), damnacanthol (3), 3-hydroxy-2-hydroxymethyl anthraquinone (24), damnacanthol (25), 2-methyl-anthraquinone (9), 1-hydroxy-2-methyl anthraquinone (12), rubiadin-1-methyl ether (8), morindin (20), 1,5,6-trihydroxy-2-methyl anthraquinone (morindon) (26), 1,5,6-trimethoxy-2-methyl anthraquinone (morindon trimethylether) (27) and alizarin-1-methyl ether (6) (Rath et al., 1995). Three antiplasmodial anthraquinones, digitolitein (28), rubiadin-1-methyl ether (8) and damnacanthol (3) have also been isolated from the stem bark and the roots of *M. lucida* (Koumaglo et al., 1992). Structures of selected anthraquinones and their derivatives are shown in Fig. 1. Since anthraquinones are chemical markers for this genus (Moreira et al., 2015), further phytochemical screening of various parts of the plant could yield new compounds with novel pharmacological activities. Also, there were no documented anthraquinols and anthraquinones isolated from the seed and flower of the plant. This suggests that the studies carried out on

the isolation of phytochemicals from various parts of the plant were mainly informed by their traditional uses (Fabricant and Farnsworth, 2001), which were authenticated by experimental pharmacological activities. No traditional uses have been reported for the seed and flower; therefore, no attention has been given to the isolation of phytochemicals from them.

#### 4.2.2. Phytosterols and polyphenols

$\beta$ -sitosterol (29) and stigmasterol (30) have been isolated from *M. lucida* leaf and stem bark (Chithambo et al., 2017; Nweze, 2012) while campesterol (31) has been isolated from the stem bark (Chithambo et al., 2017). The presence of some important polyphenols, such as catechin (32), catechin hydrate (33) and epicatechin (34) have also been confirmed in *M. lucida* leaf (Okeniyi et al., 2015). Structures of these phytosterols and polyphenols are shown in Fig. 2.

#### 4.2.3. Terpenes and terpenoids

A lot of terpenes (monoterpenes, diterpenes, and triterpenes) and terpenoids have been isolated from the stem bark, leaf and root oils of this plant. An example of diterpenes isolated from the leaf is phytol (35) (Elufioye et al., 2015) while triterpenes isolated from the plant include cycloartenol (36) from the stem bark (Chithambo et al., 2017) as well as ursolic acid (37) and oleanolic acid (38) from the leaf (Cimanga et al., 2006; Kwofie et al., 2016). Monoterpenoids isolated from the plant include an iridoid ferulate, Oruwacin (39) (Adesogan, 1979) and tetracyclic iridoids, molucidin (40) from the leaf (Kwofie et al., 2016; Suzuki et al., 2015), asperuloside (41) and asperulosidic acid (42) from the stem bark (Chithambo et al., 2017) as well as cis-sabinene hydrate (43), cis- $p$ -menth-2-en-1-ol (44), trans- $p$ -menth-2-en-1-ol (45), borneol

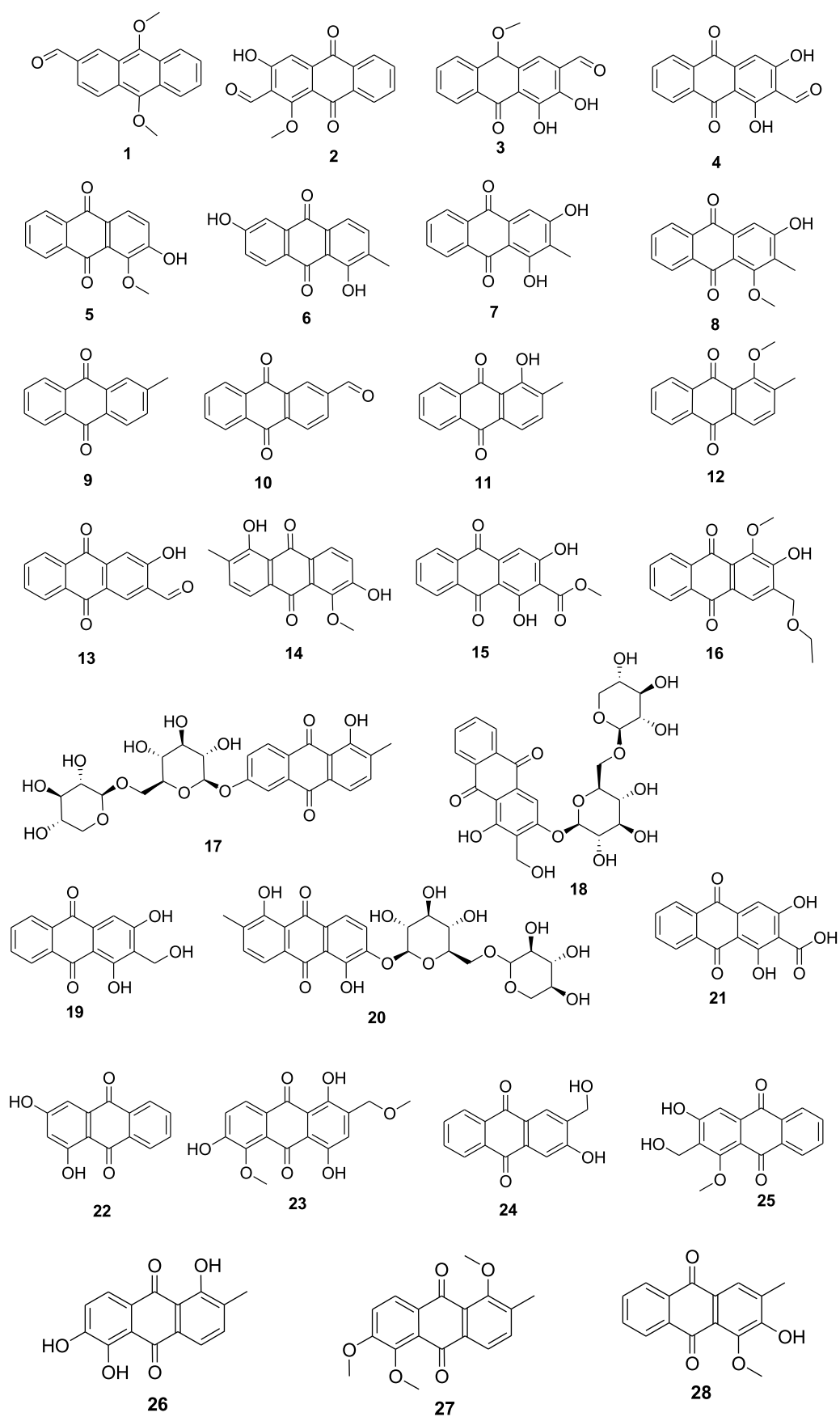


Fig. 1. Anthraquinones and their derivatives isolated from *Morinda lucida*.

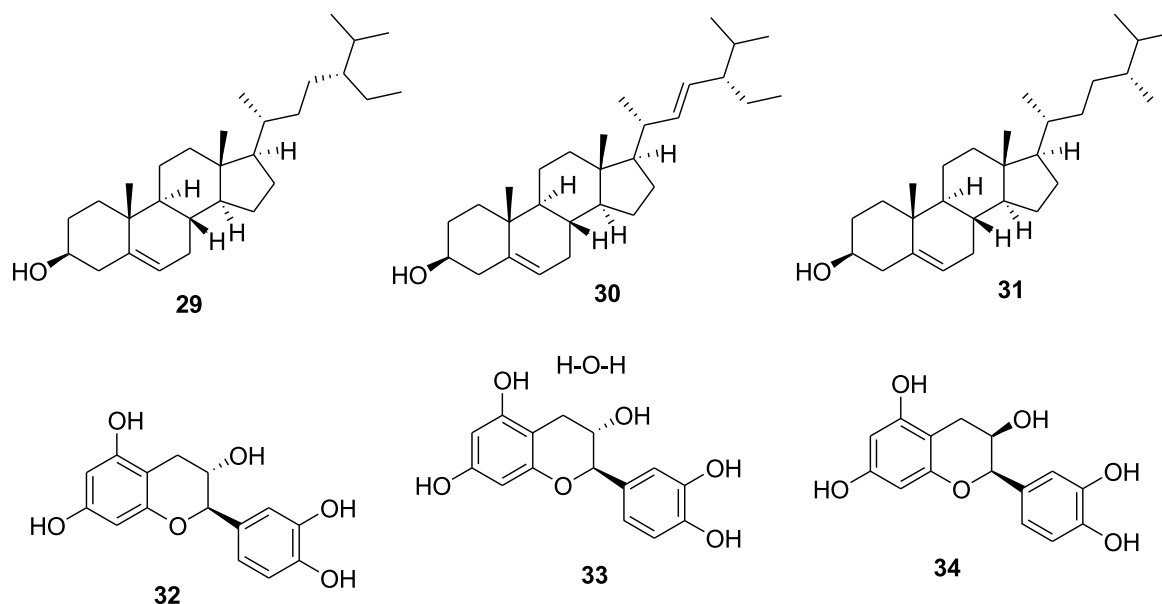


Fig. 2. Phytosterols and polyphenols isolated from *Morinda lucida*.

(46), neryl acetate (47),  $\beta$ -fenchyl alcohol (48) from the leaf oil, and carvacrol (49) and borneol from the root oil (Okoh et al., 2011; Owolabi et al., 2014). Monoterpenes isolated from the leaf oil include  $\alpha$ -terpinene (50),  $\beta$ -bisabolene (51),  $\alpha$ -thujene (52), camphene (53) (Okoh et al., 2011), 1,8-cineole (54),  $\alpha$ -terpinyl acetate (55), sabinene (56),  $\beta$ -pinene (57), myrcene (58),  $\alpha$ -phellandrene (59),  $\alpha$ -3-carene (60),  $\gamma$ -terpinene (61),  $\rho$ -cymene (62), limonene (63),  $\delta$ -terpineol (64),  $\rho$ -terpineol (65), nerol (66), linalool (67), terpinen-4-ol (68) and trans-sabinyl acetate (69) (Okoh et al., 2011; Owolabi et al., 2014). Sesquiterpenes isolated from the leaf oil include spathulenol (70), caryophyllene oxide (71),  $\beta$ -eudesmol (72), germacrene (73), cadinene (74),  $\beta$ -elemene (75) while those isolated from the root oil include  $\beta$ -caryophyllene (76) and neryl acetone (77) (Okoh et al., 2011; Owolabi et al., 2014). Structures of selected terpenes and terpenoids are shown in Fig. 3. The leaf of the plant, which is the most widely used part in traditional medicine, is particularly rich in terpenes, some of which have been reported to possess antimalarial activities (Bekono et al., 2020). Generally, terpenoids have been reported to be present in three parts of the plant – stem bark, leaf and root, with no report of such in the seeds and flowers. Of all the reported isolated phytochemicals, terpenes and terpenoids have the highest percentage.

#### 4.2.4. Other compounds

The presence of other classes of compounds in different parts of *M. lucida* (Fig. 4) has also been reported; these compounds from the leaf include guanidine carbonate (78), N-methylmercaptoacetamide (79), pyridine hydrobromide perbromide (80), 1-formylpyrrolidine (81) and N-phenylthiourea (82) (Okeniyi et al., 2015) and 3-fluoro- $\rho$ -anidine (83), 2-hydroxy-methyl benzoic acid (84) and 1,2-benzedicarboxylic acid (85) isolated from the root oil (Okoh et al., 2011). From the leaf oil, terpinolene (86), eugenol (87), methyl eugenol (88), cis-verbenyl acetate (89), isobornyl acetate (90) and trans-pinocarvyl acetate (91) were isolated (Okoh et al., 2011; Owolabi et al., 2014). Cysteine-stabilised peptides have also been identified in the aqueous extract of *M. lucida* leaf (Adewole et al., 2018).

#### 4.3. Fatty acids and aliphatic hydrocarbons of oils of *M. lucida*

Some fatty acid constituents of the oils of this plant have been reported (Fig. 5); these include hexacosanoic acid (92) from the stem (Adesida and Adesogan, 1972; Adesogan, 1973), hexadecanoic acid

(93), dodecanoic acid (94), tetradecanoic acid (95) and 9-octadecanoic acid (96) from the root oil (Okoh et al., 2011). Some aliphatic hydrocarbons, including tetradecanal (97), 9, 17-octadecadienal (98) and tetradecane (99) have been identified in the root oil while nonanal (100) was identified in the leaf oil (Okoh et al., 2011). However, thus far, there are no reports on the fatty acid constituents of oils of the seed and flower of the plant.

### 5. Experimental pharmacological activities

#### 5.1. Antimalarial activity

Malaria is a major public health concern with an estimated 228 million cases in 2018, of which 93% occurred in Africa (WHO, 2019). It is caused by *Plasmodium* species transmitted by mosquitoes. Numerous studies have confirmed the antiplasmodial and antimalarial activities of different extracts of *M. lucida* obtained from different parts of the plant (Table 3). In a study, partially purified cysteine-stabilised peptide extract (PPCPE) of *M. lucida* leaf was evaluated for its activity against *P. falciparum* W2 *in vitro* and *P. berghei* NK65 *in vivo*. Findings from the investigation showed that PPCPE was not active against *P. falciparum* W2 *in vitro* (IC<sub>50</sub>: >50  $\mu$ g/mL) but was active against *P. berghei* NK65 *in vivo* (using Peters' 4-day suppressive test), causing 75.8% reduction in parasitaemia at 125 mg/kg body weight on day 4 post-inoculation. The results suggested that PPCPE isolated from *M. lucida* leaf had antimalarial activity *in vivo* (Adebayo et al., 2017). However, further purification of the extract is required in order to obtain the specific cysteine-stabilised peptide responsible for the antimalarial activity in order to reduce the dose required to achieve the desired effect. Makinde and Obih (1985) confirmed the schizontocidal activity of the leaf extract of *M. lucida* in Swiss albino mice infected with *P. berghei berghei*. Chloroquine (standard drug) or *M. lucida* leaf extract as a single daily dose was administered to infected mice for evaluation against early infection; the repository action of pyrimethamine with *M. lucida* extract was also evaluated (Makinde and Obih, 1985). For the early infection, the chloroquine equivalent of *M. lucida* leaf extract was found to be 1.0 mg/kg body weight. In established infection, there was a sharp fall in parasitaemia from the second day of treatment in the groups administered chloroquine (5 mg/kg body weight) and *M. lucida* extract (administered subcutaneously) whereas a daily increase in parasitaemia was observed in the control group (distilled water) (Makinde and Obih, 1985). For the

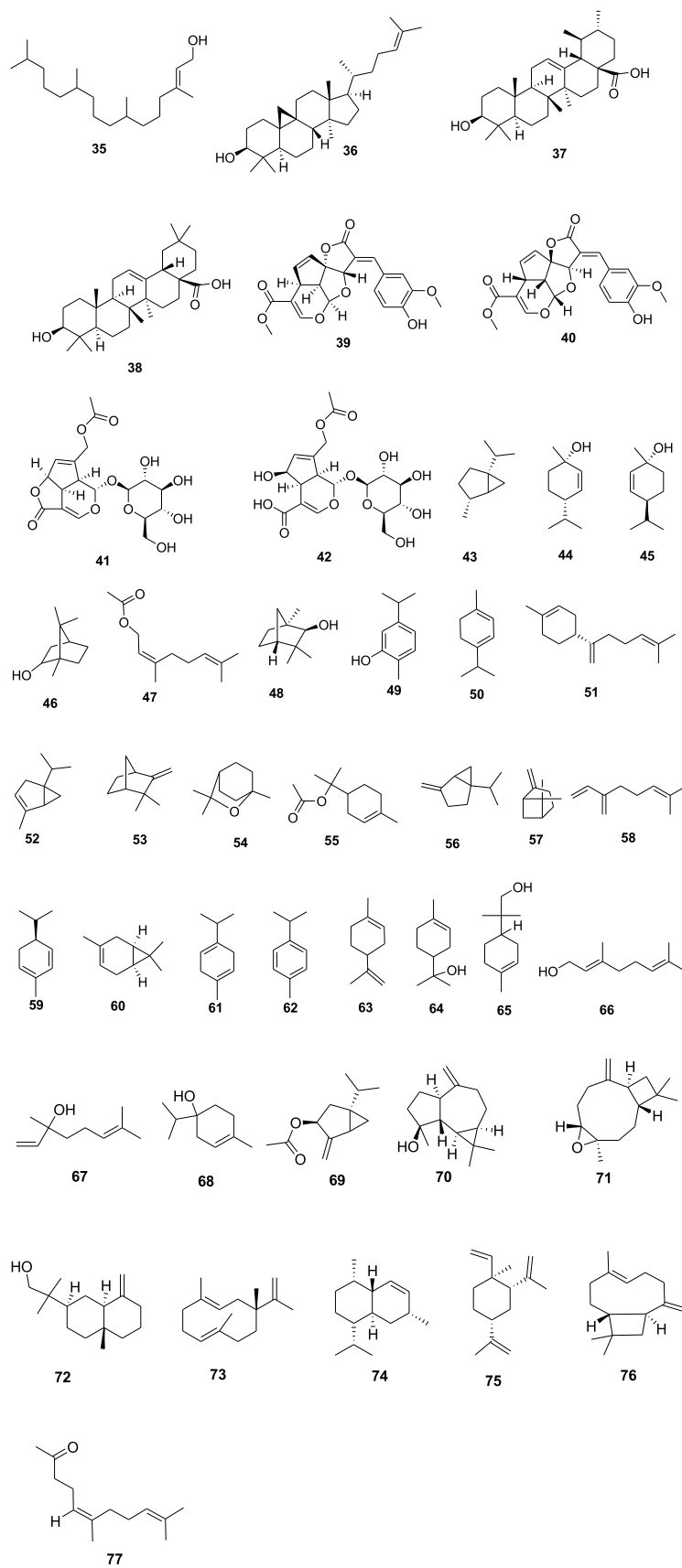
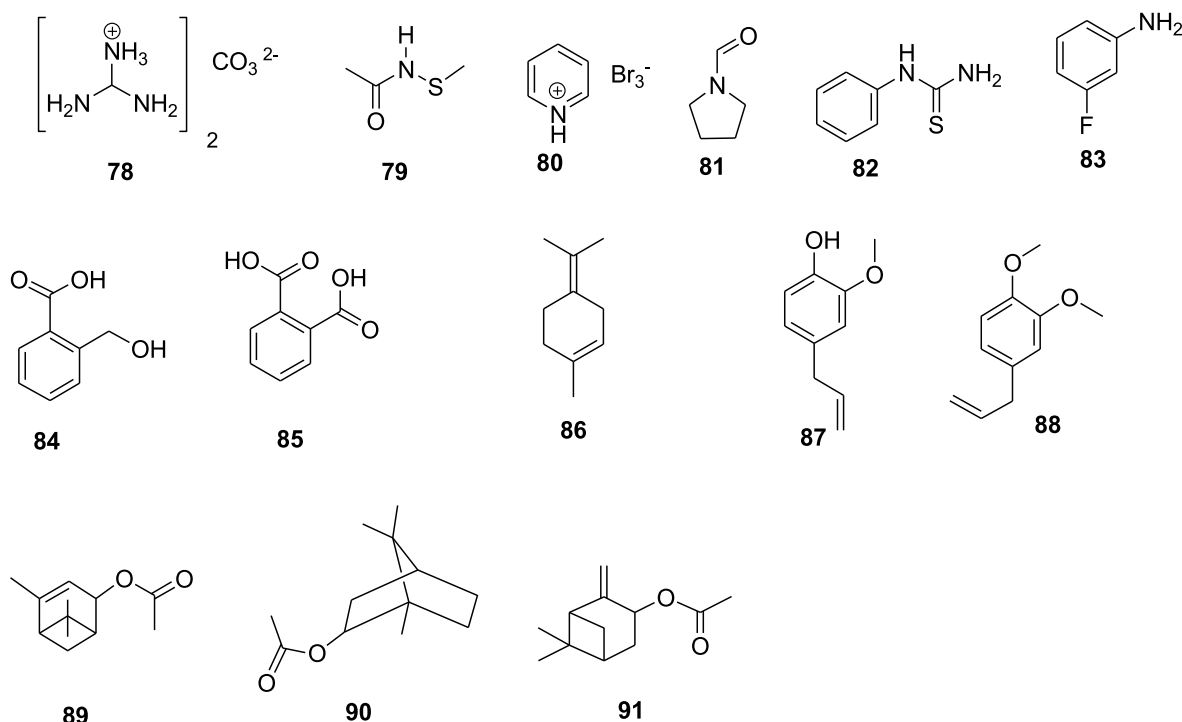
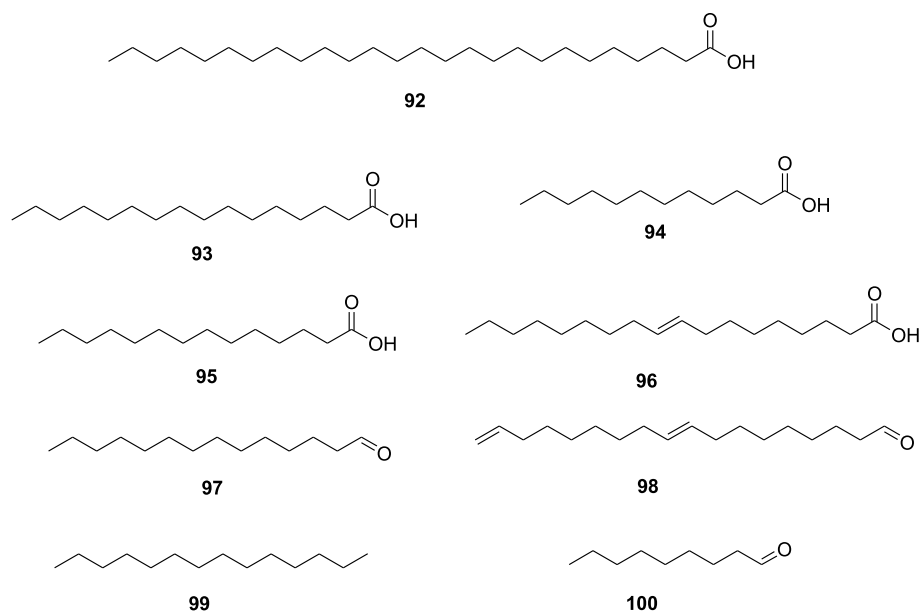


Fig. 3. Terpenes and Terpenoids isolated from *Morinda lucida*.

Fig. 4. Other compounds isolated from *Morinda lucida*.Fig. 5. Fatty acids and aliphatic hydrocarbons isolated *Morinda lucida* oils.

prophylactic test, 1.2 mg/kg body weight of pyrimethamine and 1/6 dilution of stock of extract produced 80.5% and 70.0% chemosuppression respectively (Makinde and Obih, 1985). These results showed that *M. lucida* leaf extract had schizontocidal and repository effects in mice infected with *P. berghei berghei*. Obih et al. (1985) screened extracts of the leaves, stem bark and the root bark of *M. lucida* for antimalarial activity in a '4-day schizontocidal test' against a chloroquine-sensitive strain of *P. berghei berghei* in mice. Each extract produced a degree of chemosuppression of parasitaemia, with the most promising being the chromatographic fractions of the stem bark extract and the highest dose producing 96.4% chemosuppression of parasitaemia. Therapeutic effects of the methanolic root extract and a

combination of leaf and root extracts of *M. lucida* were evaluated in mice with *P. berghei* infection (Umar et al., 2013). Results from this study showed that *M. lucida* methanolic root extract displayed dose-dependent inhibition of parasite growth (Umar et al., 2013). In the combination study, it was observed that the antimalarial activity of the combined leaf and root extract was slightly higher compared to that of each of the extracts. The study concluded that the methanolic root and leaf extracts of *M. lucida* are potentially useful for the development of antimalarial drug (Umar et al., 2013). The increased activity of the extract combination compared to the extract of each part suggests the synergistic effect of the different phytochemicals of the constituent extracts in the combination. Such combination may also delay the emergence of

**Table 3**  
The RITAM score for *Morinda lucida* leaf decoction

| Component of Score | Parameter                                | Value                     | Reference                  | Score |
|--------------------|------------------------------------------|---------------------------|----------------------------|-------|
| Ethnobotanical     | Citation scores                          |                           | Asase et al. (2010)        | 1     |
|                    |                                          |                           | Olorunnisola et al. (2013) | 1     |
|                    |                                          |                           | Ishola et al. (2014)       | 0.7   |
|                    |                                          |                           | Tor-anyiin et al. (2003)   | 0.7   |
|                    |                                          |                           | Odugbemi et al. (2007)     | 0.7   |
|                    |                                          |                           | Idowu et al. (2010)        | 0.6   |
|                    |                                          |                           | Koudouvo et al. (2011)     | 1     |
|                    |                                          |                           |                            |       |
| Efficacy           | IC <sub>50</sub> <i>in vitro</i>         | >20 µg/mL                 |                            | 0     |
|                    | <sup>a</sup> % inhibition <i>in vivo</i> | 50.17%                    | Unekwujo et al. (2011)     | 5     |
| Safety             |                                          | >16,265 mg/kg body weight | Saganuwan et al. (2014)    | 6     |
|                    | <sup>b</sup> LD <sub>50</sub>            | >5000 mg/kg body weight   | Adejo and Atawodi (2014)   |       |
|                    |                                          |                           |                            |       |
| TOTAL              |                                          |                           |                            | 16.7  |

<sup>a</sup> Priority was given to extracts which mimicked most closely the traditional preparation (Willcox et al., 2011). Extracts which are different from the highly polar and predominantly aqueous traditional preparations were excluded (e.g. extracts obtained from organic solvents, such as dichloromethane and petroleum ether). In addition, only results of the preparation tested *in vivo* by the Peters' 4-day suppressive test in animal models (and administered orally) were included. Results of extracts tested by the intra-peritoneal route were excluded. Moreso, only results applied by oral administration were used.

<sup>b</sup> Only studies that used rats and extracts administered orally were considered; studies using mice were excluded (Willcox et al., 2011).

drug-resistant strains.

The antiparasmodial activities of fractions of petroleum ether extract of *M. lucida* leaves have been confirmed *in vitro* (Awe and Makinde, 1998a), as well as *in vivo* against *P. berghei berghei* (Awe and Makinde, 1998b), though the solvent used in this study is not used traditionally. The fractions demonstrated schizontocidal activity against early and established infections but showed less activity when evaluated for repository effect (Awe and Makinde, 1998b). In another study, the ethanolic and dichloromethane extracts of *M. lucida* leaves produced more than 60.0% inhibition of *P. falciparum* growth *in vitro* at a concentration of 6 µg/mL (Tona et al., 1999). Another study investigated the antimalarial activities of aqueous leaf extract of *M. lucida* against early, established and residual infections in *P. berghei* NK65-infected mice. The extract at all doses administered produced significant dose-dependent activity against the parasite in the suppressive, curative and prophylactic studies, showing that the *M. lucida* aqueous leaf extract had potent antimalarial effects. The extract caused 50.2% inhibition of parasite growth at 200 mg/kg body weight on day 4 post-inoculation (Unekwujo et al., 2011). An *in vitro* study by Bello et al. (2009) also confirmed the antiparasmodial activities of the crude ethanolic extract of *M. lucida* leaf and the n-hexane and chloroform fractions of the extract. A study on the effect of the raw liquid content of *M. lucida* leaf on parasite density in human subjects has been reported (Olaniyan and Babatunde, 2014). The study employed sixty-four *Plasmodium*-infected patients visiting traditional homes in Oke-Ogun, the Northern part of Oyo State, Nigeria, for traditional malaria treatment. Results from this study showed that the raw liquid extract of *M. lucida* leaf caused 92.7% reduction in parasite density after one week of treatment (Olaniyan and Babatunde, 2014). However, the researchers did not monitor the patients till complete clearance of the parasite. This may lead to the emergence of drug-resistant strains of the parasite, which may be a threat to the communities that mainly rely on the use of this herbal remedy for the

treatment of malaria. Also, the 3-hydroxy-2-hydroxymethyl anthraquinone (24) and damnacanthol (25), isolated from the root, have been reported to exhibit significant antiparasmodial activity against chloroquine-susceptible (3D7) and chloroquine-resistant (K1) strains of *P. falciparum* with 20–45 µM range of IC<sub>50</sub> values (Sittie et al., 1999).

The Research Initiative on Traditional Antimalarial Methods (RITAM) further developed a scoring system for the evaluation of the antimalarial efficacy of plants (Willcox et al., 2011), which will enhance more effective, evidence-informed applications of traditional medicines that have the potential to trigger malaria-control policy decisions. RITAM scoring system is meant for comparison of efficacies of herbal remedies and standard remedies from which very potent antimalarial compounds currently in use clinically have been isolated, e.g. *Artemisia annua*, from which artemisinin was isolated. This scoring system incorporates *in vitro*, *in vivo*, clinical and ethnobotanical studies, as well as toxicity studies. The RITAM scoring system has been used in this study to assess the antimalarial efficacy of *M. lucida* as well as to unveil future research priorities on the plant, and by extension, prevent research duplication. Studies on the antiparasmodial activity of *M. lucida* extracts have revealed the use of non-polar extracts which have been extracted using organic solvents, such as dichloromethane and petroleum ether. Since extracts obtained from solvents of medium polarity or non-polar solvents are not commonly used in traditional preparations, such deserve to be excluded from RITAM scoring system. In this study, preference was accorded to extracts which mimicked most closely the traditional preparations (Willcox et al., 2011). For example, if a methanolic extract was more active than an aqueous decoction, but the decoction was the traditional preparation, preference was given to the score for the decoction. Therefore, there is the need to scientifically investigate the antiparasmodial activities of the rather neglected aqueous extracts of different parts of *M. lucida* since this is the dosage form used in traditional medicine, i.e. decoction. On few occasions, extracts reported in this review were administered via intraperitoneal (i.p) route, and many have shown interesting efficacy due to an enhanced bioavailability as compared to the oral route. However, such results were excluded because the intra-peritoneal route is never used traditionally and findings from i. p administration cannot be applied to oral administration. Based on the RITAM scoring system, the calculated overall antimalarial efficacy score for *M. lucida* leaf decoction was 16.7 compared to 19.9, 17 and 14 for *Artemisia annua* L. (Asteraceae) aerial parts infusion, *Vernonia amygdalina* Delile (Asteraceae) leaf decoction and *Argemone mexicana* L. (Papaveraceae) leaf decoction respectively (Tables 3 and 4). Hence, using the RITAM scores as a yardstick, *Artemisia annua* L. (Asteraceae) (which is the source of the antimalarial drug artemisinin) may be considered to show more efficacy than *M. lucida* leaf decoction. However, this may not be the case in reality considering the higher *M. lucida* RITAM score for the ethnobotanical component (5.7) and parasite clearance (93%) compared to 0.9 and 74% respectively for *Artemisia annua* (Tables 3 and 4). Moreover, more scientific studies have been documented for *Artemisia annua*, in particular clinical studies, than *M. lucida*, which favoured a higher total RITAM score for the Asian plant. In addition, the RITAM scores for the ethnobotanical component (5.7) and the safety component (6.0) suggest that *M. lucida* may be moderately safe. Nonetheless, more clinical studies on the efficacy and safety of the aqueous extract of *M. lucida* are needed to permit a more realistic comparative analysis of the two antimalarial plants – *Artemisia annua* and *M. lucida*.

## 5.2. Antidiabetic activity

*M. lucida* is highly valued in the traditional management of diabetes mellitus among the African traditional medical practitioners (Adejuwon, 2013; Ojewunmi et al., 2013). Adejuwon (2013) reported the antihyperglycaemic and antihyperlipidaemic activities of chloroform and butanol fractions of *M. lucida* extract in an alloxan-induced diabetic rat model (Table 5). The antidiabetic, antihyperlipidaemic and antioxidant

**Table 4**  
RITAM Scores for selected medicinal plants and results of clinical evaluation in uncomplicated *falciparum* malaria patients

| Plant Remedy                                                  | RITAM scores |                          | Clinical results   |                  |                           |                        | Study characteristics |             |                | Reference  |                  |                                     |
|---------------------------------------------------------------|--------------|--------------------------|--------------------|------------------|---------------------------|------------------------|-----------------------|-------------|----------------|------------|------------------|-------------------------------------|
|                                                               | Overall      | Ethnobotanical component | Efficacy component | Safety component | Parasite clearance d7 (%) | Fever clearance d7 (%) | Side-effects (%)      | ACR d14 (%) | No of patients |            | Mean age (years) | Geometric mean parasitaemia d0      |
| <i>Artemisia annua</i> L. (Asteraceae) aerial parts infusion  | 19.9         | 0.9                      | 13                 | 6                | 74                        | 86                     |                       |             | 72             |            |                  | Willcox et al. (2011)               |
| <i>Vernonia amygdalina</i> Delile (Asteraceae) leaf decoction | 17           | 5                        | 6                  | 6                | 32                        | 67                     | 65                    | 67          | 33             | 29         | 5393             | Willcox et al. (2011)               |
| <i>Morinda lucida</i> Benth (Rubiaceae)leaf decoction         | 16.7         | 5.7                      | 5                  | 6                | 93                        |                        |                       |             | 64             | 5-73 years |                  | Calculated in this review (Table 3) |
| <i>Argemone mexicana</i> L. (Papaveraceae) leaf decoction     | 14.9         | 1.9                      | 7                  | 6                | 21                        | 74                     | 17                    | 73          | 231            | 10         | 1746             | Willcox et al. (2011)               |

activities of aqueous extracts of *M. lucida* leaves have also been confirmed in alloxan-induced diabetic male rat (Ojewunmi et al., 2013). In an *in vitro* study, aqueous extract of *M. lucida* leaf exhibited inhibitory activities against  $\alpha$ -amylase ( $IC_{50} = 2.30$  mg/mL) and  $\alpha$ -glucosidase ( $IC_{50} = 2.00$  mg/mL), suggesting the antidiabetic activity of the extract (Kazeem et al., 2013). The aqueous and 50% methanolic extracts of *M. lucida* leaf have also been investigated for their antihyperglycemic effects on alloxan-induced hyperglycemia in rats (Bamisaye et al., 2013). The results obtained revealed that the extracts significantly lowered blood glucose level in rats with alloxan-induced hyperglycemia. However, the aqueous extract was more effective than the 50% methanolic extract (Bamisaye et al., 2013).

Adeneye and Agbaje (2008) reported that 50% ethanolic extract of the fresh leaves of *M. lucida* displayed hypoglycemic and antidiabetic effects in adult normal and alloxan-induced diabetic male rats, with the extract having higher effect in lowering fasting blood glucose than tolbutamide. The study concluded that the extract could be mediating its hypoglycemic effect via enhanced peripheral glucose utilization (Adeneye and Agbaje, 2008). These results give some caution with respect to the use of ethanolic extract of leaves. Since 50% ethanol caused hypoglycemia and both ethanolic and aqueous extracts are traditionally used as herbal remedies, the use of the ethanolic extract in treating patients with other diseases should be discouraged so as to prevent hypoglycaemia in such patients. In a study on the hypoglycaemic and anti-hyperglycaemic activities of methanolic extract of *M. lucida* leaves in normal and streptozotocin-induced diabetic rats, the extract demonstrated a significant antidiabetic effect from the third day after oral administration which compared favourably with glibenclamide (Olajide et al., 1999a).

The antihyperglycemic effects of aqueous extract and methanolic extract of *M. lucida* stem bark in alloxan-induced hyperglycaemic rats have been reported (Odutuga et al., 2010). The antidiabetic activities of aqueous extracts of the stem bark of *M. lucida* in an acute oral glucose tolerance test and subchronic (streptozotocin-induced) diabetic models have been reported. The extracts at 500 mg/kg body weight produced better blood sugar lowering effect than glibenclamide (25 mg/kg body weight) (Domekouo et al., 2016). In another study, the aqueous extract of *M. lucida* stem bark administered for eight days exhibited antihyperglycemic and antihyperlipidemic effects in alloxan-induced diabetic rats (Adeneye et al., 2017). Kamanyi et al. (1994) also reported that the aqueous root extract of *M. lucida* exhibited potent hypoglycemic and antihyperglycemic effects in normoglycemic and alloxan-induced diabetic mice respectively, with the extract being more active than chlorpropamide. Thus, the use of the aqueous extract of the root for other diseases in non-diabetic patient should be discouraged in order to prevent hypoglycemia in such patients, especially when it involves prolonged administration of the extract.

### 5.3. Antisickling activity and effects on haematology

Mpiana et al. (2007) reported a significant antidrepanocytary activity (anti-sickling activity) of ethanolic extract of *M. lucida* leaves and the aqueous and ethanolic extracts of the combination of the leaves and stem bark (Table 5). The ability of the extracts to normalize the SS blood erythrocytes may offer a rational explanation for the use of this plant in treating drepanocytosis by Congolese traditional healers (Mpiana et al., 2007). Mpiana et al. (2010, 2012) reported the *in vitro* anti-sickling activity of anthocyanins of *M. lucida* leaf, further lending credence to the claims of the traditional medical practitioners (Mpiana et al., 2010, 2012). It was proposed that anthocyanins might have exerted their chemoprotective potentials in sickle cells through an antioxidative mechanism because they are potent antioxidants (Mpiana et al., 2010, 2012). The *in vitro* anti-sickling activities of two plants, *M. lucida* and *Newbouldia laevis* (Bignoniaceae) roots, widely used for the treatment of sickle cell disease in Togo, was evaluated by Joppa et al. (2008). A concentration-dependent decrease in the rate of sickling of red blood

**Table 5**  
Pharmacological activities of *Morinda lucida* Benth (Rubiaceae)

| Diseases for which pharmacological activities of plant have been established | Part used                       | Extract/solvent used                                        | Dosage/duration                                 | Duration   | Model used      | Effect elicited                                                                                                                                                                                                                  | References                                        |
|------------------------------------------------------------------------------|---------------------------------|-------------------------------------------------------------|-------------------------------------------------|------------|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Malaria                                                                      | Leaves, root                    | Methanol                                                    | 100–400 mg/kg/5 days                            | 5 days     | Mice            | Antimalarial                                                                                                                                                                                                                     | Umar et al. (2013)                                |
| Malaria                                                                      | Leaves                          | Crude peptide extract<br>Partially purified peptide extract | 62.5–500 mg/kg/4 days<br>15.62–125 mg/kg/4 days | 4 days     | Mice            | Antimalarial                                                                                                                                                                                                                     | Adebayo et al. (2017)                             |
| Malaria                                                                      | Stem bark, root bark and Leaves | Not specified                                               | Not available                                   | 4 days     | Mice            | Antimalarial                                                                                                                                                                                                                     | Obih et al. (1985)                                |
| Malaria                                                                      | Leaves                          | Not specified                                               | Not available                                   | 4 days     | Mice            | Antimalarial                                                                                                                                                                                                                     | Makinde and Obih (1985)                           |
| Malaria                                                                      | Leaves                          | Petroleum ether fractions                                   | Not available                                   |            | <i>In vitro</i> | Antiplasmodial                                                                                                                                                                                                                   | Awe and Makinde (1998a)                           |
| Malaria                                                                      | Leaves                          | Petroleum ether fractions                                   | 25–50 mg/kg/4 days                              | 4 days     | Mice            | Antimalarial                                                                                                                                                                                                                     | Awe and Makinde (1998b)                           |
| Malaria                                                                      | Leaves                          | Ethanol (N-Hexane, chloroform fractions)                    | 0.6 mg/mL                                       |            | <i>In vitro</i> | Antiplasmodial                                                                                                                                                                                                                   | Bello et al. (2009)                               |
| Malaria                                                                      | Leaves                          | Methanol                                                    | 200 mg/kg/5 days                                | 5 days     | Mice            | Antimalarial                                                                                                                                                                                                                     | Arise et al. (2013)                               |
| Malaria                                                                      | Leaves                          | Petroleum ether                                             | 25–50 mg/kg/4 days                              | 4 days     | Mice            | Antimalarial                                                                                                                                                                                                                     | Awe and Makinde (1998b)                           |
| Malaria                                                                      | Leaves                          | Ethanol, dichloromethane                                    | 20 mg/mL                                        |            | <i>In vitro</i> | Antiplasmodial                                                                                                                                                                                                                   | Tona et al. (1999)                                |
| Malaria                                                                      | Leaves                          | Ethanol, dichloromethane                                    | 100–400 mg/kg/4 days                            | 4 days     | Mice            | Antimalarial                                                                                                                                                                                                                     | Tona et al. (1999)                                |
| Malaria                                                                      | Leaves                          | Aqueous                                                     | 100–800 mg/kg/4 days                            | 4 days     | Mice            | Antimalarial                                                                                                                                                                                                                     | Unekwujo et al. (2011)                            |
| Diabetes                                                                     | Leaves                          | Aqueous                                                     | 400 mg/kg/21 days                               | 21 days    | Rats            | anti-hyperglycaemic, anti-hyperlipidaemic, antioxidant                                                                                                                                                                           | Ojewunmi et al. (2013)                            |
| Diabetes                                                                     | Leaves                          | Aqueous                                                     | 1.25–10 mg/mL                                   |            | <i>In vitro</i> | Inhibition of $\alpha$ -Amylase and $\alpha$ -Glucosidase                                                                                                                                                                        | Kazeem et al. (2013)                              |
| Diabetes                                                                     | Leaves                          | Aqueous                                                     | 120–240 mg/kg                                   |            | Rat             | Hypoglycaemic                                                                                                                                                                                                                    | Bamisaye et al. (2013)                            |
| Diabetes                                                                     | Leaves                          | Ethanol                                                     | 50–400 mg/kg/7 days                             | 7 days     | Rat             | Hypoglycaemic                                                                                                                                                                                                                    | Adeneye and Agbaje (2008)                         |
| Diabetes                                                                     | Leaves                          | Methanol                                                    | 50–400 mg/kg/4–12 h/3 days                      |            | Rat             | Hypoglycaemic/antidiabetic                                                                                                                                                                                                       | Olajide et al. (1999a)                            |
| Diabetes                                                                     | Stem bark                       | Aqueous/methanol                                            | 0.240/240 mg/kg/7 day                           |            | Rat             | Hypoglycaemic                                                                                                                                                                                                                    | Odutuga et al. (2010)                             |
| Diabetes                                                                     | Stem bark                       | Aqueous                                                     | 500 mg/kg/14 h, 2 h and 28 h                    |            | Rat             | Hypoglycaemic                                                                                                                                                                                                                    | Domekouo et al. (2016)                            |
| Diabetes                                                                     | Stem bark                       | Water infusion                                              | 125–500 mg/kg/eight days                        | eight days | Rat             | Antihyperglycemic, Antihyperlipidemic                                                                                                                                                                                            | Adeneye et al. (2017)                             |
| Diabetes                                                                     | Root                            | Aqueous                                                     | 140–280 mg/kg/24 h                              |            | Mice            | Hypoglycaemic                                                                                                                                                                                                                    | Kamanyi et al. (1994)                             |
| Sickle cell Disease                                                          | Leaves/stem bark                | Ethanol                                                     | 30 $\mu$ g/mL                                   |            | <i>In vitro</i> | Antidrepanocytary                                                                                                                                                                                                                | Mpiana et al. (2007)                              |
| Sickle cell Disease                                                          | Stem bark                       | Aqueous                                                     | $\geq 0.195$ $\mu$ g/mL                         |            | <i>In vitro</i> | Antidrepanocytary                                                                                                                                                                                                                | Mpiana et al. (2007)                              |
| Sickle cell Disease                                                          | Leaves                          | Ethanol                                                     | 1–30 mg/mL                                      |            | <i>In vitro</i> | Antisickling                                                                                                                                                                                                                     | Joppa et al. (2008)                               |
| Sickle cell Disease                                                          | Root                            | Aqueous                                                     | 5 mg/mL                                         |            | <i>In vitro</i> | Inhibition of haemolysis                                                                                                                                                                                                         | Avaligbe et al. (2012b)                           |
| Sickle cell Disease                                                          | Root                            | Aqueous                                                     | 15 mg/mL                                        |            | <i>In vitro</i> | Antisickling                                                                                                                                                                                                                     | Avaligbe et al. (2012a)                           |
| ROS-mediated diseases                                                        | Stem bark                       | Methanol                                                    | 0.005–0.035 mg/mL                               |            | <i>In vitro</i> | Inhibition of $\beta$ -carotene oxidation, ferric reducing antioxidant power                                                                                                                                                     | Ogunlana et al. (2008)                            |
| ROS-mediated diseases                                                        | Leaves                          | Aqueous (cysteine-stabilised peptide extract)               | 50–500 mg/mL                                    |            | <i>In vitro</i> | DPPH radical scavenging activity, ferric reducing antioxidant activity                                                                                                                                                           | Adewole et al. (2018)                             |
| ROS-mediated diseases                                                        | Leaves                          | Aqueous (cysteine-stabilised peptide extract)               | 15.63–1000 mg/mL                                |            | <i>In vitro</i> | Hydroxyl radical scavenging                                                                                                                                                                                                      | Adewole et al. (2018)                             |
| ROS-mediated diseases                                                        | Leaves                          | Aqueous (cysteine-stabilised peptide extract)               | 15.63–125 mg/kg/4 days                          |            | Mice            | Reduction of malondialdehyde concentration, increased the activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and glutathione-S-transferase and the concentration of reduced glutathione | Adebayo et al. (2017); Adewole and Adebayo (2017) |
| ROS-mediated diseases                                                        | Root                            | Aqueous (yellow dye extract)                                | 6.25–100.00 mg/mL                               |            | <i>In vitro</i> |                                                                                                                                                                                                                                  | Oboh et al. (2012)                                |

(continued on next page)

Table 5 (continued)

| Diseases for which pharmacological activities of plant have been established | Part used          | Extract/solvent used                                               | Dosage/duration                           | Duration        | Model used                        | Effect elicited                                                                                                                              | References                                 |
|------------------------------------------------------------------------------|--------------------|--------------------------------------------------------------------|-------------------------------------------|-----------------|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| ROS-mediated diseases                                                        | Root               | Aqueous (yellow dye extract)                                       | 0.5, 1.0% dietary inclusion/14 days       |                 | Rat                               | DPPH radical scavenging activity, reduced ferric reducing antioxidant activity, chelation of Fe(II) Inhibition of malondialdehyde production | Oboh et al. (2012)                         |
| ROS-mediated diseases                                                        | Leaves             | Raw liquid (no solvent used)                                       | 70 mL/day/7 days                          |                 | Human                             | Increase in superoxide dismutase activity                                                                                                    | Olaniyan and Babatunde (2016),             |
| ROS-mediated diseases                                                        | Stem bark          | Aqueous                                                            | 500 mg/kg/14 h, 2 h and twenty eight days |                 | Rat                               | Prevented reduction in activities of superoxide dismutase, catalase and prevented increase in lipid peroxidation                             | Domekouo et al. (2016)                     |
| ROS-mediated diseases                                                        | Leaves             | Aqueous                                                            | 400 mg/kg/21 days                         |                 | Rat                               | Increased the level of reduced glutathione and the activities of catalase and superoxide dismutase. Reduced the level of malondialdehyde     | Ojewunmi et al. (2013)                     |
| ROS-mediated diseases                                                        | Leaves, stem       | Aqueous                                                            | 0.1–0.35 mg/mL                            |                 | <i>In vitro</i>                   | DPPH radical scavenging activity                                                                                                             | Appiah-opong et al. (2016)                 |
| ROS-mediated diseases                                                        | Stem bark          | Aqueous                                                            | 10 mg/mL<br>2 mg/mL                       |                 | <i>In vitro</i>                   | DPPH radical scavenging activity, ferric reducing antioxidant activity                                                                       | Christophe et al. (2017)                   |
| ROS-mediated diseases                                                        | Leaves, root       | Extracted volatile oil                                             | 25–500 µg/mL                              |                 | <i>In vitro</i>                   | DPPH and ABTS radical scavenging activities, inhibition of lipid peroxidation, ferric reducing antioxidant activity                          | Okoh et al. (2011)                         |
| Trypanosomiasis                                                              | Leaves             | Methanol                                                           | 800, 1000 mg/kg/3 days                    |                 | Mice                              | Trypanocidal activity                                                                                                                        | Asuzu and Chineme (1990)                   |
| Trypanosomiasis                                                              | Leaves             | Methanol (3 fractions obtained)                                    | 1, 10 mg/kg                               |                 | <i>In vitro</i>                   | Anti-trypanosomal activity                                                                                                                   | Nweze (2012)                               |
| Trypanosomiasis                                                              | Leaves             | Aqueous                                                            | 100–400 mg/kg                             |                 | Rat                               | Anti-trypanosomal activity                                                                                                                   | Alli et al. (2011)                         |
| Trypanosomiasis                                                              | Leaves             | Ethanol, trichloromethane (molucidin and other compounds isolated) | 0.78 µg/mL to 200 µg/mL/48 h              | 48 h            | <i>In vitro</i>                   | Anti-trypanosomal activity                                                                                                                   | Kwofie et al. (2016); Suzuki et al. (2015) |
| Trypanosomiasis                                                              | Leaves             | Ethanol, trichloromethane (molucidin and other compounds isolated) | 30 mg/kg/5 days                           | 5 days          | Mice                              | Anti-trypanosomal activity                                                                                                                   | Kwofie et al. (2016)                       |
| Trypanosomiasis                                                              | Stem bark          | Methanol                                                           | 100–400 mg/kg/14 days                     | 14 days         | Mice                              | Anti-trypanosomal activity                                                                                                                   | Abubakar et al. (2016)                     |
| Leishmaniasis                                                                | Leaves             | Ethanol, trichloromethane (molucidin and other compounds isolated) | 0.78 µg/mL to 50 µg/mL/48 h               | 48 h            | <i>In vitro</i>                   | Anti-leishmanial activity                                                                                                                    | Amoa-bosompem et al. (2016)                |
| Onchocerciasis                                                               | Leaves             | Methanol                                                           | 3.91 µg/mL – 500 µg/mL/5 days             | 5 days          | <i>In vitro</i>                   | Anti-Onchocerca activity                                                                                                                     | Moses Samje et al. (2014)                  |
| Typhoid fever                                                                | Leaves             | Chloroform                                                         | 12.50–100 mg/mL                           |                 | <i>In vitro</i>                   | Anti-typhoid                                                                                                                                 | Musa et al. (2014)                         |
| Bacterial infection                                                          | Leaves, stem, root | Aqueous, methanol                                                  | 5–20 mg/mL/72 h                           | 72 h            | <i>In vitro</i>                   | Antibacterial                                                                                                                                | Fakoya et al. (2014)                       |
| Microbial infection                                                          | Leaves             | Ethanol, dichloromethane                                           | 10 mg/mL/24 h                             | 24 h            | <i>In vitro</i>                   | Antimicrobial                                                                                                                                | Addy et al. (2013)                         |
| Bacterial infection                                                          | Root               | Ethanol                                                            | 100 mg/mL/18 h                            | 18 h            | <i>In vitro</i>                   | Antibacterial                                                                                                                                | Chukwujekwu et al. (2005)                  |
| Bacterial infection                                                          | Stem bark          | Aqueous, ethanol                                                   | 250–1000 mg/mL/24 h                       | 24 h            | <i>In vitro</i>                   | Antibacterial                                                                                                                                | Adomi (2006)                               |
| Bacterial infection                                                          | Root bark          | Aqueous, ethanol                                                   | 250–1000 mg/mL/24 h                       | 24 h            | <i>In vitro</i>                   | Antibacterial                                                                                                                                | Adomi and Umukoro (2010)                   |
| Bacterial infection                                                          | Leaves             | Methanol                                                           | 25 mg/mL/24 h                             | 24 h            | <i>In vitro</i>                   | Antibacterial                                                                                                                                | Ogundare and Onifade (2009)                |
| Fungal infection                                                             | Root               | Dichloromethane, methanol (anthraquinones isolated)                | ≤20 µg/mL                                 |                 | <i>In vivo</i><br><i>In vitro</i> | Antifungal activity                                                                                                                          | Rath et al. (1995)                         |
| Fungal, bacterial infection                                                  | Leaves             | Methanol                                                           | 1.56–200 mg/mL/72, 24 h                   | 72, 24 h        | <i>In vitro</i>                   | Antifungal, antibacterial                                                                                                                    | Anowi et al. (2013)                        |
| Rheumatic disorders                                                          | Leaves             | Ethanol                                                            | 300 mg/kg                                 | 3 h             | Rat                               | Anti-inflammatory effect                                                                                                                     | Akah and Nwambie (1994)                    |
| Inflammation                                                                 | Leaves             | Petroleum ether, dichloromethane                                   | 250 µg/mL<br>8–10 min                     | 8–10 min        | <i>In vitro</i>                   | Inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2)                                                                          | Chukwujekwu et al. (2005)                  |
| Immunological anomalies                                                      | Leaves             | Aqueous                                                            | 100–250 mg/kg/21 days                     | 12, 14, 21 days | Rat                               | Immunorestitution effect: Increased sera antibody (IgG1 (and IgG2a)                                                                          | Nworu et al. (2012)                        |

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Table 5 (continued)

| Diseases for which pharmacological activities of plant have been established | Part used | Extract/solvent used | Dosage/duration       | Duration | Model used            | Effect elicited                                                                                                                                                           | References                  |
|------------------------------------------------------------------------------|-----------|----------------------|-----------------------|----------|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Immunological anomalies                                                      | Leaves    | Aqueous              | 12.5 and 50 µg/mL     |          | <i>In vitro</i>       | production, weight gain and recovery after treatment with cyclophosphamide, amelioration of cyclophosphamide-induced leucopenia, increased rate of excision wound healing |                             |
| Immunological anomalies                                                      | Leaves    | Ethanol              | 100–300 mg/kg/14 days | 14 days  | Mice                  | Immunostimulatory effect: Activation of CD69 and CD25, increased secretion of cytokines (interferon-gamma (IFN-γ) and interleukine- 4 (IL-4)).                            | Nworu et al. (2012)         |
| Atherosclerosis                                                              | Leaves    | Methanol             | 50–200 mg/kg/14 days  | 14 days  | Rat                   | Increased immune responses: increased white blood cell count                                                                                                              | Ala et al. (2017)           |
| Atherosclerosis                                                              | Root      | Ethanol              | 50–300 mg/kg/21 days  | 21 days  | Rats                  | Increased plasma concentration of HDL cholesterol                                                                                                                         | Balogun and Akinloye (2012) |
|                                                                              |           |                      |                       |          |                       | Reduction in the serum levels of cholesterol, high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C)                                | Ashafa and Olunu (2011)     |
| Cancer                                                                       | Stem bark | Ether, acetone       | 50 mg/kg/7 days       | 7 days   | Mice                  | Carcinostatic activity                                                                                                                                                    | Durodola (1974)             |
| Cancer                                                                       | Leaves    | Aqueous              | 0.25–1.25 mg/mL/24 h  | 24 h     | <i>In vitro</i>       | Antiproliferative effect                                                                                                                                                  | Appiah-opong et al. (2016)  |
| Cognitive defects                                                            | Leaves    | Ethyl acetate        | 42.5 µg/mL            | Ns       | <i>In vitro</i>       | Inhibition of acetyl and butyrylcholinesterases                                                                                                                           | Elufioye et al. (2013)      |
| Cognitive defects                                                            | Leaves    | Ethyl acetate        | 4–8 mg/kg/3 days      | 3 days   | Mice                  | Enhancement of cognition: amelioration of scopolamine- induced memory deficit                                                                                             | Elufioye and Hameed (2017)  |
| Anomalies of Muscle contractility                                            | Leaves    | Aqueous              | 0.015–1.5 mg/mL       |          | <i>Ex vivo</i> (mice) | Reduction of muscle contractility                                                                                                                                         | Elias et al. (2007)         |
| Anomalies of Muscle contractility                                            | Leaves    | Aqueous              | 0.25–8 mg/mL          |          | <i>Ex vivo</i> (rat)  | Relaxation of aortic Rings                                                                                                                                                | Ettarh and Emeka (2004)     |
| Constipation                                                                 | Leaves    | Methanol             | 400–1600 mg/kg/4 h    | 3–4 h    | Mice                  | Purgative effect                                                                                                                                                          | Asuzu and Chineme (1990)    |
| Constipation                                                                 | Leaves    | Methanol             | 12.5–100 mg/kg/12 h   | 12 h     | Rat                   | Induction of early appearance of faeces and increased production of wet faeces.                                                                                           | Olajide et al. (1999b)      |

ROS – Reactive oxygen species.

cells induced by 2% sodium metabisulphite was observed after incubation with the extracts compared to 0.9% NaCl solution. For instance, the SS blood genotype inhibition rate produced by *M. lucida* was 17.3% at a concentration of 1 mg/mL and 92.3% at a concentration of 30 mg/mL. The AS blood genotype inhibition rate of *M. lucida* was 48.1% at a concentration of 1 mg/mL and 99.3% at a concentration of 30 mg/mL (Joppa et al., 2008). These findings showed that *M. lucida* had clear-cut *in vitro* anti-sickling activity, still lending credence to its use in traditional medicine. In another *in vitro* study on the haemolysis inhibitory activity of aqueous extracts of six plants used in the traditional treatment of sickle cell disease in Benin Republic, *M. lucida* exhibited erythrocyte osmotic resistance and an *in vitro* anti-sickling effect (Avaligbe et al., 2012b). A decrease in the rate of sickling has also been reported after incubation of erythrocytes with decoction of *M. lucida* root (Avaligbe et al., 2012a). However, these findings have not been supported by more robust *in vivo* and clinical studies. A possible reason could be the unavailability of the *in vivo* model of sickle cell disease in many parts of the world, especially underdeveloped and developing countries. However, such studies are necessary to fully validate the traditional claims.

#### 5.4. Antioxidant property

The methanolic extract of *M. lucida* stem bark, containing up to 80% phenolics, exhibited antioxidant activity in a concentration-dependent manner (Ogunlana et al., 2008, Table 5). Antioxidant activity of partially purified cysteine-stabilised peptide fraction (CSPF) of aqueous extract of *M. lucida* leaf was evaluated *in vitro*. The results showed that CSPF exhibited 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) scavenging activity, ferric reducing antioxidant power and hydroxyl radical

scavenging activity (Adewole et al., 2018). Further studies on CSPF revealed that it was able to revert, in a dose-dependent manner, the observed increase in malondialdehyde (MDA) concentration and reduction in glutathione concentration and superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and glutathione-S-transferase activities in selected tissues and erythrocyte of *P. berghei* NK65-infected mice (Adebayo et al., 2017; Adewole and Adebayo, 2017), suggesting the ability of CSPF to induce antioxidant defense system in subjects with *Plasmodium* species infection. Oboh et al. (2012) assessed the antioxidant and protective effects of dietary inclusion of 0.5 and 1.0% of yellow dye from the root of *M. lucida* on cyclophosphamide-induced oxidative stress (COS) in the brain of Wistar albino rats. The results showed that the administration of the extract inhibited oxidative stress in the brain of the animals by causing a significant decrease in the MDA concentration in the brain and activities of aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase in the serum in a dose-dependent manner compared to the untreated COS rats. The activity of the extract was attributed to its high phenolic content and ferric reducing power, free-radical scavenging ability, Fe(II) chelating ability and inhibition of lipid peroxidation (Oboh et al., 2012). The preventive and scavenging properties of the crude liquid extract of *M. lucida* leaf was also reported in another study (Olaniyan and Babatunde, 2016). In the study, forty-eight *Plasmodium*-infected patients who had not been treated with any antimalarial drug, but had decided to be treated traditionally using *M. lucida* leaf extract, were recruited from fifteen traditional homes in ATISBO, Saki-East, and Saki-West local government areas of Oke-Ogun, Oyo State, Nigeria. Crude liquid extract of *M. lucida* leaf increased the activity of plasma SOD in the *Plasmodium*-infected patients compared to

normal subjects after treatment with the extract (Olaniyan and Baba-tunde, 2016).

The antioxidant activity of *M. lucida* stem bark aqueous extract has also been confirmed in streptozotocin-induced diabetic animal model. The stem bark aqueous extract significantly prevented reduction in weight gain and alteration in erythrocyte SOD and CAT activities but reduced erythrocyte MDA concentration, plasma cholesterol, triglyceride and glucose concentrations and aspartate aminotransferase activity compared to diabetic rats, thus indicating an ameliorative effect of the extract on diabetes and its complications (Domekouo et al., 2016). Furthermore, the antioxidant activity of *M. lucida* leaf extract has been confirmed in alloxan-induced diabetic animal model (Ojewunmi et al., 2013). The *in vitro* antioxidant activities of the ethanolic stem bark, leaf and root extracts (Osuntokun et al., 2016a, 2016b), the aqueous leaf extract (Appiah-opong et al., 2016) and the aqueous stem bark extract (Christophe et al., 2017) of *M. lucida* have also been reported. Moreover, the volatile oils from the leaves and roots of *M. lucida* have been reported to exhibit *in vitro* DPPH and ABTS radical scavenging activities, lipid peroxidation inhibitory activity and ferric ion reducing activity, which favourably compared with those of standard antioxidants (Okoh et al., 2011). Phenolic compounds and polyphenols have been well reported to possess antioxidant activities (Tungmunthum et al., 2018). *M. lucida* is rich in polyphenols and phenolic compounds which are also chemotaxonomic markers for the genus *Morinda*. More robust *in vivo* tests and clinical studies are required to attest to the function of *M. lucida* extracts as antioxidants.

#### 5.5. Anti-trypanosomal, anti-leishmanial and anti-onchocercal activities

*Trypanosoma brucei* parasites are protozoans that cause human African trypanosomiasis (HAT). Human African trypanosomiasis, commonly known as sleeping sickness, has remained a serious health problem in many African countries with thousands of new infected cases annually (Kwofie et al., 2016). Resistance and severe side effects limit the use of current drugs. Methanolic extract of *M. lucida* leaf has been shown to suppress the level of parasitaemia following *Trypanosoma brucei* infection in mice, with a higher trypanocidal activity obtained when treatment with the extract was started simultaneously with trypanosome inoculation (Table 5; Asuzu and Chineme, 1990). Nweze (2012) reported that three fractions obtained from bioassay-guided fractionation of the crude methanolic extract of *M. lucida* leaf exhibited anti-trypanosomal activity in cultures of *Trypanosoma brucei brucei* S427. The spectroscopic analysis of one of the fractions revealed the presence of  $\beta$ -sitosterol/stigmasterol (Nweze, 2012). The possibility of the identified compounds being responsible for the activity of the traditionally prepared extract may not be outrightly discarded because ethanol (a solvent used traditionally) has a very close solvent polarity to that of methanol and will certainly extract the same compounds. The aqueous extract of *M. lucida* leaf has been investigated and shown to have anti-trypanosomal activity in albino rats infected with *Trypanosoma brucei brucei* (Alli et al., 2011). A study by Kwofie et al. (2016) identified three tetracyclic iridoids, molucidin, ML-2-3 and ML-F52, from the ethanolic fraction of *M. lucida* leaves as the active anti-trypanosomal compounds (Table 6). ML-2-3 and ML-F52 suppressed the expression of paraflagellum rod protein subunit 2 and caused cell cycle alteration, which preceded induction of apoptosis in the bloodstream form of *Trypanosoma* parasites. The study showed that these tetracyclic iridoids from *M. lucida* leaf may be promising lead compounds for the development of new chemotherapies for African trypanosomiasis. It was revealed by a structure–activity relationship study that molucidin and oregonin have similar aromatic rings (Suzuki et al., 2015). These metabolites are identical to the anti-trypanosomal active components of *Alnus japonica*. The methanolic extract of *M. lucida* stem bark and leaves have also been reported to exhibit anti-trypanosomal activity in mice (Abubakar et al., 2016).

Leishmaniasis is an infectious disease transmitted by the sand fly.

**Table 6**

Pharmacological activities of some phytochemicals isolated from *Morinda lucida* Benth (Rubiaceae)

| SN | Phytochemicals                                                        | Biological Activities                                                   | References                                                              |
|----|-----------------------------------------------------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------|
| 1  | Damnacanthol (3)                                                      | Anti-inflammatory, Antiplasmodial, Antifungal and Anticancer activities | Nualsanit et al. (2011); Koumaglo et al. (1992); Ali et al. (2000).     |
| 2  | Soranjidiol (5)                                                       | Anticancer activity                                                     | Ali et al. (2000)                                                       |
| 3  | Alizarin-1-methyl ether (6)                                           | Antifungal and Anticancer activities                                    | Rath et al. (1995); Ali et al. (2000)                                   |
| 4  | Rubiadin (7)                                                          | Anticancer activity                                                     | Ali et al. (2000)                                                       |
| 5  | Rubiadin-1-methyl ether (8)                                           | Antiplasmodial and Anticancer activities                                | Koumaglo et al. (1992); Rath et al. (1995); Ali et al. (2000);          |
| 6  | 2-Methyl-antraquinone (9)                                             | Antifungal activity                                                     | Rath et al. (1995)                                                      |
| 7  | 1-Hydroxy-2-methyl anthraquinone (11)                                 | Anticancer activity                                                     | Ali et al. (2000)                                                       |
| 8  | 1-Methoxy-2-methyl-antraquinone (12)                                  | Antifungal activity                                                     | Rath et al. (1995)                                                      |
| 9  | 3-Hydroxyanthraquinone-2-carbaldehyde (13)                            | Antifungal activity                                                     | Rath et al. (1995)                                                      |
| 10 | Morindone-5-methyl ether (14)                                         | Anticancer activity                                                     | Ali et al. (2000)                                                       |
| 11 | Morindin (20)                                                         | Antifungal and                                                          | Rath et al. (1995)                                                      |
| 12 | 5,15-O dimethylmorindol (23)                                          | Antimalarial activities                                                 | Chithambo et al. (2017)                                                 |
| 13 | 3-Hydroxy-2-hydroxymethyl anthraquinone (24)                          | Antimalarial and Antifungal activities                                  | Rath et al. (1995); Sittie et al. (1999)                                |
| 14 | Damnacanthol (25)                                                     | Antimalarial and Antifungal activities                                  | Rath et al. (1995); Sittie et al. (1999)                                |
| 15 | 1,5,6-Trihydroxy-2-methyl anthraquinone (morindon) (26)               | Antifungal activity                                                     | Rath et al. (1995)                                                      |
| 16 | 1,5,6-Trimethoxy-2-methyl anthraquinone (morindontrimethylether) (27) | Antifungal activity                                                     | Rath et al. (1995)                                                      |
| 17 | Digitolitein (28)                                                     | Antiplasmodial activity                                                 | Koumaglo et al. (1992)                                                  |
| 18 | $\beta$ -sitosterol (29)                                              | Anticancer and Antitrypanosomal activities                              | Nweze (2012)                                                            |
| 19 | Stigmasterol (30)                                                     | Antitrypanosomal activity                                               | Nweze (2012)                                                            |
| 20 | Campesterol (31)                                                      | Antimalarial activity                                                   | Chithambo et al. (2017)                                                 |
| 21 | (+)-catechin (32)                                                     | Antioxidant and Anti-inflammatory activities                            | Akinmoladun et al. (2020); Abd El-Aziz et al. (2012)                    |
| 22 | (+)-catechin hydrate (33)                                             | Anticancer activity                                                     | Al-Hazzani and Alshatwi (2011)                                          |
| 23 | (-)-epicatechin (34)                                                  | Antioxidant activity                                                    | Osuntokun et al. (2017)                                                 |
| 24 | Phytol (35)                                                           | Cognition enhancement                                                   | Eluffoye et al. (2015).                                                 |
| 25 | Cycloartenol (36)                                                     | Antimalarial activity                                                   | Chithambo et al. (2017)                                                 |
| 26 | Ursolic acid (37)                                                     | Antitrypanosomal activity                                               | Kwofie et al. (2016)                                                    |
| 27 | Oleanolic acid (38)                                                   | Antitrypanosomal activity                                               | Kwofie et al. (2016)                                                    |
| 28 | Molucidin (40)                                                        | Antiplasmodial, Antitrypanosomal and Antileishmanial activities         | Amoa-bosompem et al. (2016); Suzuki et al. (2015); Kwofie et al. (2016) |
| 29 | Asperuloside (41)                                                     | Antimalarial activity                                                   | Chithambo et al. (2017)                                                 |
| 30 | Asperulosidic acid (42)                                               | Antimalarial activity                                                   | Chithambo et al. (2017)                                                 |
| 31 | Cis-Sabinene hydrate (43)                                             | Antioxidant activity                                                    | Mezza et al. (2018)                                                     |
| 32 | Borneol (46)                                                          | Antiviral activity                                                      | Armaka et al. (1999)                                                    |
| 33 | Neryl acetate (47)                                                    | Antiviral activity                                                      | Senthil Kumar et al. (2020)                                             |
| 34 | Carvacrol (49)                                                        | Anticancer activity                                                     | Chen et al. (2015)                                                      |
| 35 | $\beta$ -bisabolene (52)                                              | Anticancer activity                                                     | Yeo et al. (2016)                                                       |

(continued on next page)

Table 6 (continued)

| SN | Phytochemicals   | Biological Activities                       | References                             |
|----|------------------|---------------------------------------------|----------------------------------------|
| 36 | 1,8-cineole (55) | Anti-inflammatory and Anticancer activities | Juergens (2014); Sampath et al. (2018) |
| 37 | p-Cymene (63)    | Anti-inflammatory activity                  | Zhong et al. (2013).                   |
| 38 | Limonene (64)    | Antiviral activities                        | Senthil Kumar et al. (2020)            |

Leishmaniasis chemotherapy is limited by the high cost and/or toxicity of available drugs. Molucidin and ML-F52 have also been shown to exhibit anti-leishmanial activities against field strain, O10, and the laboratory strain *Leishmania hertigi* (Amoa-bosompem et al., 2016). Molucidin and ML-F52 from *M. lucida* might be good lead compounds for the development of new anti-leishmanial drugs (Table 6; Amoa-bosompem et al., 2016). Molucidin and ML-F52 induced formation of abnormal parasites with two sets of nucleus and kinetoplast in a cell, suggesting that compounds might inhibit cytokinesis in leishmanial parasites (Amoa-bosompem et al., 2016). This brings to the fore the issue of repurposing some of the active isolated compounds for an infectious disease for other infectious diseases.

Onchocerciasis, caused by *Onchocerca volvulus*, is the second leading infectious disease causing blindness globally. Suboptimal response is increasingly being reported for ivermectin, the current drug of choice for treating the disease (Awadzi et al., 2004). The methanolic extract of *M. lucida* leaf has been reported to exhibit high activity against both the microfilariae and adult worms of bovine and the most popular model of the parasite, *Onchocerca ochengi* (Samje et al., 2014). The genus *Morinda* is known to accumulate high amounts of terpenes and anthraquinones as its chemical markers, which have been documented to possess varied bioactivities, including antimicrobial and anti-parasitic activities (Mbatchou et al., 2017; Huang et al., 2019).

##### 5.6. Antibacterial and antifungal activities

The crude chloroform extract of *M. lucida* leaf has been reported to exhibit bacteriostatic activity at the concentration range of 12.5–100 mg/mL and bactericidal activity at 100 mg/mL, lending credence to the traditional use of the plant for the treatment of typhoid fever (Musa et al., 2014, Table 5). Fakoya et al. (2014) reported the inhibitory activities of both aqueous and methanolic extracts of the root, stem bark and leaf of *M. lucida* against *Escherichia coli*, *Salmonella paratyphi*, *Salmonella typhi* and *Salmonella typhorum* *in vitro*. *M. lucida* extracts were more active against all the tested bacteria compared to the standard antibiotics, chloramphenicol and ciprofloxacin, at the same concentrations of 5, 10 and 20 mg/mL (Fakoya et al., 2014). This reveals the possibility of the phytochemicals of the extracts having conserved target (s) in the genus *Salmonella* and the presence of the same compound(s) in the extracts of the different parts, though these are subject to further studies. The crude leaf extract of *M. lucida* exhibited inhibitory activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus* at a concentration of 10 mg/mL (Addy et al., 2013). Ethanolic extract of *M. lucida* root has been shown to exhibit antibacterial activity against Gram-positive bacteria, especially *S. aureus* and *Micrococcus luteus* (Chukwujekwu et al., 2005). The aqueous and ethanolic extracts of the stem bark of *M. lucida* have been reported to be active against *Bacillus subtilis*, *S. aureus*, *E. coli*, *Klebsiella pneumoniae*, *S. typhi*, *P. aeruginosa* and *Flavobacterium sp.*, comparing favourably well with standard antibiotics (Adomi, 2006; Adomi and Umukoro, 2010). This indicates a broad spectrum of the antibacterial activity of the stem bark extracts which were prepared using the traditional methods. This lends credence to the use of the extract in African traditional medicine for the treatment of different bacterial infections. The inhibitory activities of the methanolic extract of *M. lucida* leaf against *E. coli* both *in vitro* and *in vivo* have also been reported by Ogunbare and Onifade (2009). Despite the fact that the

plant appears to be a promising source of novel antibacterial compounds, there is paucity of information on the antibacterial compounds isolated from the plant and the mechanisms of action of such compounds.

The activity of dichloromethane/methanol extract of *M. lucida* root against *Candida albicans* has been reported (Rath et al., 1995, Table 5). Further investigation showed that alizarin-1-methyl displayed the highest fungicidal activity of all the anthraquinones isolated from this extract (Rath et al., 1995). The antifungal activity of methanolic extract of the leaves of *M. lucida* against *Candida albicans* has also been reported (Anowi et al., 2013).

##### 5.7. Anti-inflammatory and immunostimulatory activities

The methanolic extract of *M. lucida* leaf was active against acute inflammation (Akan and Nwambie, 1994, Table 5). The petroleum ether and dichloromethane extracts of *M. lucida* leaf exhibited anti-inflammatory activity by inhibiting COX-2 activity while the petroleum ether extract also exhibited anti-inflammatory activity by inhibiting COX-1 activity (Chukwujekwu et al., 2005). The aqueous leaf extract of *M. lucida* produced anti-inflammatory activity in rat and antipyretic activity in rabbit (Nwobodo et al., 2011), while it exhibited immunostimulatory activity *in vitro* and immunorestorative activity *in vivo* (Nwobodo et al., 2011). Administration of aqueous extract of *M. lucida* leaf increased specific total IgG, IgG1, and IgG2a responses to ovalbumin by as much as two to ten fold compared to untreated controls (Nworu et al., 2012). In cyclophosphamide-treated mice, the rate of wound healing, leukopoiesis and body weight recovery were all enhanced by oral supplementation with the extract in a dose-dependent manner. *In vitro* cultures of BALB/C splenocytes treated with the extract for 24 h resulted in 5–10 fold increase in IFN $\gamma$  and IL-4 concentrations (Nworu et al., 2012). Surface expression of immunostimulatory markers, CD69 and CD25, were also upregulated on splenic T and B cells by as much as eight to twenty fold (Nworu et al., 2012). Ethanolic leaf extract of *M. lucida* improved the function of the immune system of Balb/c mice induced with rhabdomyosarcoma cells, suggesting its beneficial effects in normalizing compromised immune systems associated with cancer (Ala et al., 2017). These findings validate the traditional uses of *M. lucida* leaf extracts for the treatment of infections and immuno-inflammatory disorders. Damnacanthol has been isolated from *M. lucida* stem bark and roots by various research groups (Koumaglo et al., 1992). Damnacanthol has been reported to exhibit anti-inflammatory activity by the suppression of paw and ear edema in rats and mice, and the down-regulation of lipopolysaccharide-induced nuclear factor- $\kappa$ B (NF- $\kappa$ B), thereby suppressing the expression of pro-cytokines, COX-2 and inducible nitric oxide synthase (iNOS) (Nualsanit et al., 2011). All the studies carried out thus far on the anti-inflammatory and immunostimulatory activities focused on the leaf. Future research should focus on evaluating other parts of the plant for their anti-inflammatory and immunomodulatory potentials.

##### 5.8. Effects on blood lipids

Methanolic extract of *M. lucida* leaf has been reported to increase plasma concentration of high density lipoprotein cholesterol (HDL-C) in male albino rats (Balogun and Akinloye, 2012, Table 5). The ethanolic root extract has been reported to cause significant reduction in serum levels of cholesterol, HDL-C and low density lipoprotein cholesterol (LDL-C) (Ashafa and Olunu, 2011). Some compounds isolated from *M. lucida*, including asperulosidic acid (37) and  $\beta$ -sitosterol (39), exhibited plasma cholesterol-reducing activity (Careri et al., 2001; Hirata et al., 2011, Table 6). The results suggest that *M. lucida* extracts may protect against atherosclerosis. However, the mechanism underlying this effect needs to be delineated.

### 5.9. Anticancer activity

Cancer is a major global public health issue (Siegel et al., 2014). It is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. It is believed that if metastasis is controlled, then cancer can be managed (ACS, 2015). *M. lucida* was frequently mentioned in recipes for the management of cancers and cancer-related problems in ethnobotanical surveys conducted amongst traditional medical practitioners in South West Nigeria (Sowemimo et al., 2007; Segun et al., 2018). It was claimed that infusion and decoction of *M. lucida* leaf and stem bark are used in South West Nigeria for the treatment of cancer (Ashidi et al., 2010). It was reported that a crystalline compound isolated from the stem bark of *M. lucida* exhibited carcinostatic effect on sarcoma 180 ascites in mice (Durodola, 1974, Table 5). *M. lucida* ethanolic root bark extract has been shown to cause inhibition of telomerase activity, indicating a possible anticancer activity and selectivity for human chromosomes, thereby justifying its use in the management of cancer in South West Nigeria, although it was also mutagenic and cytotoxic (Sowemimo et al., 2007). Aqueous extract of *M. lucida* leaf exhibited antiproliferative activity *in vitro* against HL-60 cells by causing apoptotic cell death (Appiah-opong et al., 2016). Furthermore,  $\beta$ -sitosterol isolated from *M. lucida* leaf was cytotoxic to normal prostate cells (PNT2A) and prostatic carcinoma cell lines, DU-145, PC-3 and LNCAP AS (Nweze, 2012). This lack of cytotoxic selectivity for cancer cells by  $\beta$ -sitosterol (probably because of the high concentration used in the study) may be a setback for its use as an anticancer agent (Nweze, 2012). The methanolic extract of *M. lucida* leaf was cytotoxic to monkey kidney epithelial cells (LLCMK2), with the Median lethal dose (MLD<sub>50</sub>) ranging from 15.625  $\mu$ g/mL to 31.25  $\mu$ g/mL for the most active fractions of the extract (Samje et al., 2014). Furthermore, molucidin from *M. lucida* leaf has been reported to be cytotoxic, having a MLD<sub>50</sub> that was less than 10  $\mu$ M for some cancer cell lines. For example, the MLD<sub>50</sub> values for LoVo (colon cancer cell line) and KATO III (stomach cancer cell line) were as low as 0.11 and 0.21  $\mu$ M respectively, with high selectivity indices (SI) for some cancer cell lines (Suzuki et al., 2015). Findings have also shown that aqueous extract of *M. lucida* stem bark significantly inhibited P-glycoprotein, a protein responsible for multidrug resistance of cancer cells, *in vitro* and, thus, could potentiate the activities of anticancer agents (e.g. etoposide, tamoxifen, topotecan, everolimus, imatinib, lapatinib, nilotinib) when co-administered with them (Oga et al., 2012). An *in silico* study has also reported the possibility of *M. lucida*-derived phytochemicals and triterpenes inhibiting anti-apoptotic BCL-XL, BCL-2 and MCL-1 (Adewole and Ishola, 2019). However, *in vitro* and *in vivo* studies are required to validate the anticancer activities of these compounds and their proposed mechanisms of action.

### 5.10. Cognition enhancement

Cognitive disorders associated with aging have successfully been managed by African traditional medical practitioners using various plant species. The ethyl acetate fraction of *M. lucida* leaf extract inhibited both acetylcholinesterase and butyrylcholinesterase activities (Elufioye et al., 2013, Table 5). This indicates the potential of *M. lucida* leaf to enhance cholinergic neuron function and possible role in ameliorating cholinergic memory impairment. Activity-directed phytochemical and spectroscopic analyses have been used to isolate and characterize phytol (3, 7, 11, 15-tetra methyl- 2-hexadecan-1-ol) as the compound with acetyl cholinesterase and butyryl cholinesterase inhibitory activities in *M. lucida* leaf (Table 6; Elufioye et al., 2015). Elufioye and Hameed (2017) also reported the cognitive enhancing potential of the ethyl acetate extract of *M. lucida* leaf in scopolamine-induced amnesic animals.

### 5.11. Effect on muscle contractility

The aqueous extract of *M. lucida* leaf has been reported to have a

relaxant effect on uterine smooth muscle of both pregnant and non-pregnant mice; it inhibited both the degree and frequency of contractile responses and blocked contractile responses to oxytocin and acetylcholine in the muscle (Elias et al., 2007, Table 5). The aqueous extract of *M. lucida* leaf has a vasorelaxant effect on vascular smooth muscle of rat aorta by both endothelium-dependent and -independent mechanisms (Ettarh and Emeka, 2004). Also, *M. lucida* has been listed among tropical plant species with cardio-active properties (Oliver-Bever, 1982). However, there has been no documented report on the use of *M. lucida* extracts as muscle relaxants in African traditional medicine.

### 5.12. Purgative/anti-diarrhoeal activity

The methanolic leaf extract of *M. lucida* induced purging in mice following oral administration (Asuzu and Chineme, 1990). This was said to be in agreement with the traditional claim of some indigenous people who use *M. lucida* aqueous leaf extract as a remedy for frequent constipation associated with malaria infection in patients (Asuzu and Chineme, 1990, Table 5). In another study, the methanolic extract of the leaves of *M. lucida* (12.5–100 mg/kg) induced a pronounced increase in the number of wet faeces in rats and potentiated castor oil-induced diarrhoea in mice after oral treatment (Olajide et al., 1999b). However, the aqueous leaf and fruit extracts of *M. lucida* have also been reported to attenuate castor oil-induced diarrhoea in experimental rat model (Adejo et al., 2015). These discrepancies in experimental findings, however, need further clarification.

### 5.13. Hepatoprotective activity

Various studies have also evaluated the hepatoprotective potentials of the extracts of different parts of *M. lucida*. The aqueous extract of *M. lucida* leaf has been reported to be hepatoprotective at 300 mg/kg body weight against chronic ethanol-induced hepatotoxicity in rabbits (Olubunmi et al., 2011) and rhabdomyosarcoma cell-induced hepatotoxicity in rats (Ala et al., 2017). The aqueous extract of *M. lucida* stem bark (100 and 500 mg/kg p. o.) protected against acetaminophen-induced liver damage in Wistar albino rats (Fogha et al., 2015). However, the doses reported in this study are too high to be used clinically.

### 5.14. Genoprotective activity

Adejo and Atawodi (2014) reported the genoprotective properties of methanolic stem bark, leaf and root extracts of *M. lucida* against Fenton's reagent-induced damage in pUC18 plasmid DNA at 10  $\mu$ g/ $\mu$ l. However, further *in vivo* studies are required.

### 5.15. Limitations of experimental pharmacological activities

Most of the studies conducted to evaluate the pharmacological activities of *M. lucida* extracts supported the acclaimed medicinal properties of this plant as used traditionally. However, some of the studies used organic solvents for the extraction of the plant materials as against the two conventionally used solvents (water and ethanol) in the traditional medical system. This limits the usefulness of such reports in validating the indigenous uses of the plant extracts in African traditional medical system. It has been recommended that solvents used traditionally for the preparation of the extracts should be used while evaluating them for pharmacological activities (Willcox et al., 2011). Meanwhile, some of the reported doses used for the evaluation of the pharmacological activities of the plant extracts were too high (e.g. 1000 mg/kg body weight, Table 5), the feasibility of which is not realistic in African traditional medical practice. Also, some of the studies appear to be preliminary with the use of one concentration because the use of a concentration range is the norm for any standard *in vitro* assay. Moreover, some studies that were carried out on human subjects did not

administer the extracts on the basis of doses but rather administered the same volume to all subjects irrespective of their body weights, which made the standardization of the extracts for clinical use difficult. The routes of administration used in some of the studies, e.g. subcutaneous, are not the normal route of administration used in African traditional medical system, thereby making the results of such studies not applicable to the traditional medical system.

## 6. Toxicity studies

Several toxicity studies on the various parts of *M. lucida* have been carried out using different models.

### 6.1. Toxicities of the leaves and fruits

The ethanolic leaf extract of *M. lucida* exerted an inhibitory effect (>30%) on CYP3A7 *in vitro* (Agbonon et al., 2010). CYP3A7 is mainly found in the fetal liver where it plays an important role during pregnancy (Leeder et al., 2005). Agbonon et al. (2010) inferred that the inhibition of CYP3A7 by ethanolic extract of *M. lucida* leaf may be of great concern when used during pregnancy. Though the methanolic leaf extract of *M. lucida* has been reported to be genoprotective at a lower concentration, as earlier stated, it exerted genotoxic effect at a higher concentration (specifically at 50 µg/µl) on pUC18 plasmid DNA (Adejo and Atawodi, 2014). A recent study has shown that compounds from *M. lucida* leaf (molucidin and ML-F52) were cytotoxic (with IC<sub>50</sub>s ranging between 4.74 µM and 14.24 µM) to four human normal cell lines, including NB1RGB (skin fibroblast), HF-19 (lung fibroblast), Chang Liver and Hs888Lu (lung) (Kwofie et al., 2016).

The LD<sub>50</sub> of the aqueous extract of *M. lucida* leaf from an acute oral toxicity test using rat was >16,265 mg/kg body weight (Saganuwan et al., 2014). This result was corroborated by the finding of Oduola et al. (2010) who reported that the oral administration of aqueous leaf extract of *M. lucida* was non-lethal at concentrations less than or equal to 6400 mg/kg body weight in Wistar albino rats. The aqueous leaf and fruit extracts of *M. lucida* have also been reported to exhibit no toxicity at 5000 mg/kg body weight in rats (Adejo et al., 2015). Adejo and Atawodi (2014) reported an oral LD<sub>50</sub> of >5000 mg/kg body weight for methanolic extracts of the fruit and leaf of *M. lucida* in adult male albino. It has been established that extracts with LD<sub>50</sub> of more than 5000 mg/kg body weight are not toxic (Lorke, 1983). Asuzu and Chineme (1990) performed acute toxicity test in mice and found that the intraperitoneal LD<sub>50</sub> of the methanolic leaf extract of *M. lucida* was 2000 mg/kg body weight, though the route of administration of the extract in this study is not used traditionally. Nwobodo et al. (2011) reported an oral LD<sub>50</sub> of 986.6 mg/kg body weight for the aqueous leaf extract in mice. Sub-chronic toxicity study of the aqueous extract of *M. lucida* leaf administered for forty-two days at 3200 mg/kg body weight showed that it had no toxic effect on liver and kidney functions (Oduola et al., 2010). Another study showed that no biochemical toxicity was observed after fourteen days of administration of the methanolic leaf extract of *M. lucida* to male albino rats at doses less than or equal to 200 mg/kg body weight (Balogun and Akinloye, 2012). Meanwhile, Samje et al. (2014) reported that the methanolic leaf extract of *M. lucida* (at about 39 µg/mL) had no overt toxicity following fourteen days of intraperitoneal administration to Balb/c mice. The aqueous leaf extract of *M. lucida* orally administered for twenty-eight days at 1626.5 mg/kg body weight significantly increased packed cell volume, erythrocyte count, haemoglobin concentration, mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration in Wistar albino rats (Saganuwan et al., 2014). The extract was safe at the doses of 16.3 and 162.7 mg/kg body weight but caused kidney degeneration and exhibited mild to moderate deleterious effects on the lung, liver, heart and spleen when administered for eight days at the dose of 1626.5 mg/kg body weight (Saganuwan et al., 2014). However, the use of logarithmic doses is not the norm for standard subchronic toxicity studies because a lot of

vital dose response data will be lost. The ethyl acetate extract of *M. lucida* leaf had no effect on the histology of the hippocampus of mice at doses less than or equal to 8 mg/kg body weight, but caused increased density of cells in the hippocampus (Elufioye and Hameed, 2017). Results of histopathological studies after administration of aqueous extract of leaves of *M. lucida* to normal rabbits for twenty-eight days indicated that it was not hepatotoxic at 300 mg/kg body weight (Olubunmi et al., 2011). The results indicate a preliminary study; a dose response is normally required for such a study, which is evidently lacking in this report.

### 6.2. Toxicity of the stem bark

Adejo and Atawodi (2014) reported an oral LD<sub>50</sub> of >5000 mg/kg body weight for methanolic extracts of the stem bark of *M. lucida* in adult male albino rats. However, there is paucity of information on the oral LD<sub>50</sub>s for the aqueous and ethanolic extracts which are used traditionally; these should still be evaluated. The aqueous extract of the stem bark was well tolerated at doses less than 5000 mg/kg body weight but was toxic at doses higher than or equal to 5000 mg/kg body weight after sub-chronic administration to Wistar albino rats (Agbor et al., 2012). Methanolic extract of *M. lucida* stem bark administered orally for ten days at 750 mg/kg body weight had no cytotoxic effect but exhibited genotoxic effect in albino mice (Awodiran et al., 2018).

### 6.3. Toxicity of the roots

Ashafa and Olunu (2011) reported that the ethanolic root extract of *M. lucida* was not haematotoxic, hepatotoxic or nephrotoxic in Wistar albino rats at doses below 300 mg/kg body weight, following twenty-four days of administration. Mutagenic and genotoxic properties of aqueous extract of *M. lucida* root have been reported (Akintonwa et al., 2009). The methanolic extract of the leaves of *M. lucida* has been reported to cause reversible antispermato-genic activity in male albino rats after ninety-one days of intragastric administration at 400 mg/kg body weight (Raji et al., 2005). There is paucity of information on the LD<sub>50</sub>s of the aqueous and ethanolic extracts of the root. Thus, studies bothering on these are still required.

## 7. Limitations to effective use of the plant in African traditional medical system

While the RITAM Scoring system for the evaluation of antimalarial herbal remedies (Willcox et al., 2011) has accelerated drug discovery efforts via prioritization of medicinal plants for further studies, it is not so for other disease conditions lacking scoring systems. This could lead to the exclusion of the most effective and safe herbal remedies from further scientific investigation, and by extension, exclusion of a safe and effective drug/template from the drug discovery pipeline. In addition, this deficiency could limit the selection of plant species for research and the effective use of medicinal plants in African traditional medicine. Thus, the lack of Efficacy Scoring Systems for evaluating the efficacies of botanical extracts for other disease conditions may limit the effective use of *M. lucida* in African traditional medical system as well as drug discovery efforts on the plant. These scoring systems, as earlier stated, take into consideration the results of ethnobotanical, laboratory and clinical studies on the pharmacological activities and toxicities of medicinal plants. For many of the pharmacological activities of *M. lucida* extracts presented in this review, no clinical studies have been reported. This limits the possible ranking of the extracts of different parts of the plant in order of efficacies for each disease condition and for the various disease conditions in the African traditional medical system. Such information will enhance the effective use of medicinal plant materials, which are marketed as listed/registered products in some African countries. Thus, further empirical studies in this regard should be embarked on. These evidence-based traditional medicines could effectively complement

orthodox medicines in meeting the primary healthcare needs of the rural populations. Moreover, owing to the limited number of standardized plant extracts with well documented phytochemistry and pharmacological activities available for comparison with the activities of *M. lucida* extracts reported in this review, there is the limitation of prioritizing the plant extracts used in the Nigerian Traditional Medicine for each disease.

## 8. Summary and future perspectives

Findings from this review have revealed that the use of *M. lucida* for the treatment of malaria traditionally is the most mentioned indication, which has received the widest application of the plant in African traditional medical systems. This is consistent with the importance of the Rubiaceae family in the historical treatment of malaria in traditional medical systems in various parts of the World and in the discovery of the antimalarial quinine, an indole alkaloid from *Cinchona* bark about 400 years ago. Though the presence of anthraquinones in different parts of the plant has been well reported (some of which have been isolated), these parts have not been extensively investigated for alkaloids. Therefore, further studies tailored towards the isolation of alkaloids, which could yield some leads for the treatment of various diseases (especially malaria), are required. The potent antimalarial terpenes, represent another important chemical fingerprint isolated from the leaves of *M. lucida* and do lend credence to the traditional use of the leaves for malaria treatment in tropical Africa. These bioactive terpenoids have recently attracted scientific attention as they offer a ray of hope in overcoming antimalarial drug resistance when combined with other active compounds (Cox-Georgian et al., 2019). Thus, further studies on the combination of these phytochemicals with existing cheap, but now, ineffective antimalarials, with the aim of potentiating the activities of those antimalarials against resistant strains of the parasite, are still needed. Also, many of the traditional applications of *M. lucida* for the treatment of various diseases across sub-Saharan African region have been scientifically authenticated. However, further studies on the isolation of the bioactive principles responsible for these pharmacological activities, their mechanisms of action, toxicities, efficacies and effectiveness in clinical evaluation are required.

The leaves of *M. lucida* are the most traditionally used and scientifically investigated part of the plant, followed by the stem bark and then, the root. The flowers and seeds, which are produced abundantly by the plant, have not been scientifically investigated because the bulk of documented reports on the plant were informed by its traditional uses. The phytochemical screening of the seed and flower extracts and the evaluation of such for various pharmacological activities are required. Also, further studies on the stem bark and roots are required for possible isolation of novel bioactive compounds of chemotaxonomic importance and pharmacological relevance.

Some of the traditional uses of the plant have not received any scientific attention such as the treatment of dysmenorrhea, ulcer, pain and hypertension. Thus, *in vitro*, *in vivo* and clinical studies are required to validate these claims. Also, the bioactive principles for the acclaimed medicinal uses which are confirmed empirically will have to be isolated and their mechanisms of action delineated.

Efficacy scoring systems for herbal remedies traditionally used for the treatment of various diseases, such as the RITAM scoring system for antimalarial herbal remedies (Willcox et al., 2011), are urgently required. This will facilitate the prioritization of herbal remedies for the treatment of various diseases and standardization of the herbal remedies sold in the market, thereby promoting quality assurance by regulatory bodies. Some of these herbal remedies are sold in form of the plant parts which the end users eventually extract with water or ethanol without being able to give accurate account of the doses being consumed. Also, the parts of many plants are mixed together at times for a disease which a single plant extract can effectively treat, leading to enhanced toxicities of such herbal mixtures. This can be prevented by using the efficacy

scoring systems. In some countries, some efforts are already being made to present these herbal remedies in form of powder or formulate them into tablets (Majekodunmi et al., 2008) to standardize the doses used. The efficacy scoring systems will also help the regulatory bodies to approve these herbal remedies (based on scientific evidence), which are presented in form of powder or tablets for the treatment of appropriate diseases.

## 9. Conclusion

In this review, we have attempted to provide a critical analysis of the ethnomedicinal applications, phytochemistry and pharmacology of a highly valued plant species, *M. lucida*, which is widely used in African traditional medical system. Empirical studies on the medicinal properties of *M. lucida* have validated the traditional claims and, thus, lend credence to the indigenous use of this plant species as a remedy for various disease conditions. The extensive literature search revealed that 100 metabolites have been isolated from various parts of the plant. However, most of the documented studies on this plant have concentrated more on the crude solvent extract, a few on fractions and even far less studies on isolated pure compounds. Only very limited report is available on the public domain regarding the mechanisms of action of bioactive compounds isolated from *M. lucida* while there is no report on an elaborate clinical evaluation.

Generally, different solvent extracts of *M. lucida* were considered to be non-toxic following scientific evaluation using toxicity tests in animal models, though a few cytotoxic effects have been reported *in vitro*. These reported toxic effects call for some caution in the application of the extracts in the traditional medical system. The discrepancies in some of the reported pharmacological activities call for a more holistic and extensive investigation. Moreover, there is the need for an in-depth study to decipher the molecular targets of the isolated compounds. Furthermore, clinical studies on some experimentally validated pharmacological activities of this plant species should be ambitiously initiated in order to limit its use in the traditional medical system to the treatment of diseases for which they are clinically relevant and potent. Moreover, concerted research efforts on *M. lucida* may lead to the discovery of affordable, more potent and less toxic hits or leads which have the potential to combat the diverse diseases plaguing the African continent and the world at large.

## Declaration of competing interest

The authors declare that there is no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jep.2021.114055>.

## Contribution of authors

AKE and AAF were involved in the conception of the idea while AKE, AAF and AJO were involved in writing the manuscript and critically analyzing the data.

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