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A review on antimicrobial efficacy, toxicity and phytochemicals of selected medicinal plants used in Africa against pathogenic microorganisms

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Abstract

Medicinal plants have been widely used as antimicrobial agents to treat a variety of infectious diseases such as pneumonia, stomach, urinary tract infection, gonorrhoea and dysentery. According to an estimate, 80% of the antimicrobial agents which are widely used worldwide for the management of infectious diseases are derived from native plants. A variety of native plants in Africa have shown promise to treat different infectious diseases and some of them possess broad spectrum antimicrobial activities. This article therefore describes potential antimicrobial efficacy and safety of medicinal plants namely *Mystroxydon aethiopicum*, *Lonchocarpus capassa*, *Albizia anthelmentica* and *Myrica salicifolia* which are used by ethnic groups in Africa for the management of infectious diseases. Since these plants possess broad spectrum antimicrobial properties, the article suggests future *in vivo* studies which will ultimately lead to the development plant based pharmaceutical formulations.

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Introduction

In recent years, there has been a growing interest in researching and developing new antimicrobial agents from various sources to combat infectious diseases from various sources to combat infectious diseases (Balouiri *et al.*, 2016). Infectious diseases, also known as transmissible diseases or communicable diseases are caused by pathogenic microorganisms that can be found almost everywhere such as in the air or in water and can be transmitted through touching, eating, drinking or breathing (Blomberg, 2007). Infectious diseases are a great human concern as they have been severely affects large number of people worldwide, especially in developing countries where the economic resources are scarce (Elkadry, 2013). Comparatively to the developed countries where majority of incidents of cardiovascular and neoplastic diseases affects the older populations, in developing countries, infectious diseases have an important impact on children especially less than 5 years (Blomberg, 2007).

It is estimated that more than 300,000 children from developing countries die each year for infectious diseases mostly caused by bacterial species such as *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Klebsiella oxytoca*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Salmonella kisarawe*, *Salmonella typhi* and *Escherichia coli* (Akomo *et al.*, 2009). The infectious diseases caused by these bacteria are therefore a global hazard and put every developing country at greater risk due to the worse situation of poor sanitation and ignorance of good hygienic practices (Rubaka, 2014). In addition, a big burden of infectious diseases in developing countries is attributed by the tropical conditions which favor survival and multiplications of many diseases causing pathogens (WHO, 1999). Fungal diseases represent a critical problem to health and they are one of the main causes of morbidity and mortality worldwide (Thevasundari and Rajendran, 2012). Human infections particularly those involving the skin and mucosal surfaces, constitute a serious problem especially in tropical and subtropical developing countries (Portillo *et al.*, 2011).

In humans, fungal infections range from superficial to deeply invasive or disseminated, and have increased dramatically in recent years (Duraipandiyan and Ignacimuthu, 2011). According to Hamza *et al.*, 2006, fungal infections particularly those caused by *Candida albicans* and *Cryptococcus neoformans* are the most challenging infections facing immune compromised patients such as HIV/AIDS patients. The *C. albicans* mostly affect skin, nails, oral cavity & and esophagus and vagina (Verónica *et al.*, 2011) while *C. neoformans* is mostly responsible for central nervous system infections, and occasionally the skin, lungs, urinary tract, eyes and bones (Klepser, 2006).

Medicinal plants have been used as antimicrobial agents to treat the above listed infections. The effectiveness of medicinal plants in human body is mostly attributed by a wide range of substances present in plants which have been used to treat chronic as well as infectious diseases (Elnour *et al.*, 2013). In this regard, a large proportion of the population especially in developing countries rely heavily on traditional practitioners and medicinal plants to meet their primary health care needs (Politi *et al.*, 2013). Although conventional medicines may be available in these countries, but herbal medicines have often maintained popularity for historical and cultural reasons (Elnour *et al.*, 2013). Medicinal plants therefore are now being given serious attention, as evidenced by the World Health Organization's recommendation that, proven traditional remedies with known efficacy should be incorporated in national drug policies and increased commercialization of pharmaceutical products (WHO, 2002).

Taking into consideration the prominence of medicinal plants, it is paramount importance to assess their efficacy in order to promote the use of such herbal plants to combat microbes responsible for infectious diseases in humans (Bohlin and Bruhn, 1999). However, in recent years, there has been a growing interest in researching and developing new antimicrobial agents from different medicinal plants such as *Myroxylon aethiopicum*, *Lonchocarpus capassa*, *Albizia anthelmentica* and *Myrica salicifolia* (Kilonzo *et al.*, 2016a).

These plant species were earlier reportedly to be used by many ethnic groups in Africa for the management of infectious diseases (Boer *et al.*, 2005). Despite the wide use of such plants in the management of infectious diseases, little work has been done regarding their therapeutic effects and safety. In addition, phytochemicals responsible for the therapeutic effects are yet to be validated. This review therefore aimed at validating efficacy, safety and photochemical compounds of *M. aethiopicum*, *L. capassa*, *A. anthelmentica* and *M. salicifolia* growing in Tanzania. These plants were selected on the basis of verbal information collected from local traditional healers in Monduli and Arumeru district, northern Tanzania.

Pathogenic microbes responsible for human infectious diseases

Bacteria are often dismissed as germs, and are one of the main groups of pathogenic microbes that are commonly responsible for human infectious diseases (WHO, 2016a). Bacterial infections are a leading cause of severe morbidity and mortality in developing countries, especially among high risk groups such as the elderly and young children (Joseph *et al.*, 2013). Antibiotic therapies have been readily available to the health centers for control and prevention of bacterial infections (Joseph *et al.*, 2013). These antibiotics have saved lives of millions of people from previously deadly bacterial infectious diseases and contributed to improving quality and expectancy of human life since their introduction in 1940's (Bhalodia and Shukla, 2011). However, the long term use of these drugs has facilitated some microorganisms to develop resistance to many antibiotics and create immense clinical problems in the treatment of bacterial infections (Rachana *et al.*, 2012). Resistance cases on the use of antibiotics have been reported in many places of the world especially in developing countries where the burdens of bacterial infectious diseases are more evident (Arora and Kumar, 2013). According to Okeke *et al.* (2005), antibiotic resistance is high in several African countries including Tanzania, and it is more likely to be increasing. Likewise, human fungal infections are likely to be increased significantly, associated with high morbidity and mortality rates (Matthaiou *et al.*, 2015).

It is estimated that over 1 billion people are being affected by fungal infectious diseases globally each year (Rodriguez *et al.*, 2015). The lack of adequate diagnostic methods, together with the fact that many emerging fungal species are resistant to the currently available antifungal agents, contributes to the profound impact of these infections in the health care systems (Carvalho, 2008). Although most antifungal medications have saved lives of many people by curing dangerous fungal diseases, some fungi species just like bacterial strains have developed resistance to certain types of antifungal medications that are designed to cure them (Blomberg, 2007). This highlights the need for greater attention for developing more accurate, rapid and affordable new antifungal agents in fighting against drug resistance fungal species. According to Rubaka *et al.* (2014), medicinal plants can be a good approach for providing valuable source of secondary metabolites which can be further developed into antimicrobial agents. In this regard, plant extracts or plant derived compounds are likely to provide valuable source of medicinal agent that can be active against drug resistance fungal species.

Antimicrobial resistance against human infectious disease pathogens

Antimicrobial resistance is a common phenomenon in which microorganisms resist the presence of antimicrobial agents and pathogens that are resistant to multiple antimicrobial agents are considered as multidrug resistant or super bugs (Sharma *et al.*, 2015). Today, antimicrobial resistance is a serious and growing phenomenon in conventional drugs and has emerged as one of the pre-eminent public health concerns (Vadhana *et al.*, 2015). World health organization's 2014 report on global surveillance of antimicrobial resistance states that "antimicrobial resistance is a serious threat and no longer a prediction for the future as it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country". In this regard, microbial infections due to antimicrobial resistance are more often fatal and may lead to prolonged illness (WHO, 2000).

Due to prolonged illness, there is a risk of spreading infection to other people. Not only that, but also costs increased, not only because of the use of more expensive antimicrobial agents, but also because of longer duration of care and hospitalization (Blomberg, 2007). According to WHO, (2016b) emergence of antimicrobial resistance is accelerated by the misuse of antimicrobial drugs. Additionally, poor infection control practices, inadequate sanitary conditions and inappropriate food handling encourage spread of the antimicrobial resistance (Tanwar *et al.*, 2014). Moreover, the scenario of antimicrobial resistance is not only restricted to human pathogens, but also commonly in veterinary pathogens (Vadhana *et al.*, 2015). Antimicrobial resistance therefore has been a public health concern throughout the world which causes health sectors, policy makers and academic communities preoccupied to control (Taulo *et al.*, 2008). The evolutionary ability of microorganisms presents serious challenges to successfully stop the development of antimicrobial resistance (Stephan and Mathew, 2005). Predisposing factors such as self-medication, over the counter sales of antimicrobial agents and flooding the markets with fake and substandard drugs further aggravates the situation (Doughari *et al.*, 2009). In an attempt to combat multiple antimicrobial resistance challenge that has emerged from time immemorial up to date, different types of antimicrobial agents have been developed from microorganisms or synthesized derivatives (Cowan, 1999). However, there is still a need to search for prompt treatment with novel antimicrobial agents from medicinal plants which appear to be the focus of mainstream medicine today, that will not only active against drug resistant pathogens, but also kill persistent microorganisms and shorten the length of treatment.

Mechanisms of antimicrobial resistance

Microorganisms have a remarkable ability to adapt to adverse environmental conditions which is an example of one of the ancient laws of nature of survival of the fittest (Bockstael and Aerschot, 2009). It appears that the emergence of antimicrobial resistant is inevitable to most every new drug and it is

recognized as a major problem in the treatment of microbial infections in hospitals and in the communities (Yoneyama and Katsumata, 2006).

Based on the fact that microorganisms have been developed antimicrobial resistance and are the causative agents of infectious diseases, antimicrobial agents are indicated for the treatment of these microbial infections (Kumar and Varela, 2013). However, use of antimicrobial agents for the treatment of infectious diseases, selects for pathogenic microbes within a population that are less resistant to the antimicrobial agent used, hence leading to a situation where resistant microorganisms will continue to dominates under such selective phenomenon (Summers, 2002). In this phenomenon, the resistant microorganisms have ability to counteract lethal effects of the antimicrobial agents by either intrinsic or acquired mechanism (Sosa, 2010). Generally, intrinsic resistance is considered to be natural or inherited property whereby microorganisms naturally do not possess target sites for drugs and therefore the drug does not affect them because of the differences in the chemical nature of the drug and the microbial membrane structures (Fluit *et al.*, 2001). Similarly, acquired resistance mechanism occurs in such a way that susceptible microorganism acquire ways of not being affected by the drug (Tenover, 2006).

In this regard, microorganisms produce enzyme that destroy or inactivate the antimicrobial agent. The typical example of enzymes which inactivate antimicrobial agent is beta lactamases (Blomberg, 2007). These enzymes are produced by bacteria that provide multi-resistance to mostly β -lactam antibiotics such as penicillins, cephamycins and carbapenems by breaking the antibiotic's structure (Bush and Fisher, 2011). These antibiotics have a common element in their molecular structure which is a four atom ring known as a β -lactam (Ahmad *et al.*, 2013). Through hydrolysis, the lactamase enzyme breaks the β -lactam ring and deactivates the molecule's antibacterial properties. The beta-lactamases produced by mostly Gram negative

bacteria are usually secreted, especially when antibiotics are present in the environment. In view of the above, there is an urgent need to find out effective antimicrobial agents with high ability of prohibiting microorganisms to develop resistance.

Medicinal plants as antimicrobials agents to combat resistance

Bioactive natural compounds exhibiting antimicrobial activities have been isolated mainly from cultivable microbial strains (Pandey and Shashank, 2013). There is a need to exploit the untapped natural resources of different origins including plants to help responding the current health care situation of antimicrobial resistant (Emma *et al.*, 2001). The primary benefits of using derived products from medicinal plants are that they are natural, offering profound therapeutic benefits and more affordable treatment than conventional drugs (Ghosh *et al.*, 2008; Pandey and Kumar, 2012). Medicinal plants with antimicrobial activities are therefore considered a potent source of novel antimicrobial function (Mahunnah and Mshigeni, 1996). For example, in Tanzania, among 1,000 plant species that are widely used as traditional medicine, *M. aethiopicum*, *L. capassa*, *A. anthelmentica* and *M. salicifolia* have been scientifically proven to possess bioactive compounds that are likely to combat antimicrobial resistance (Kilonzo *et al.*, 2016a).

Mystroxydon aethiopicum which is also known as the spike thorn is widely distributed in highlands of Arusha and Kilimanjaro regions where it is locally known as “*Oldonyanangu*” in Maasai language. On the basis of earlier reports, the stem barks of *M. aethiopicum* is considered to be used by ethnic groups in Tanzania for treatment of different infectious diseases including diarrhea (Boer *et al.*, 2005). In Kenya, stem barks of the plant is boiled separately and used singly and taken with meat soup for various ailments or just for good health (Onyango *et al.*, 2014). The stem barks of this plant is the most commonly medicinal plants used in Madagascar and its being valued especially for its beneficial effect upon the stomach and is sold in local markets

(Burkill, 2004). Furthermore, leaves of the plant are traditionally used in Uganda to manage helminthosis (Ndukupi *et al.*, 2014). The plant is therefore serving a potential alternative medication for patients suffering from different infectious diseases caused by microbes.

The *Lonchocarpus capassa* is usually found in deciduous woodlands and wooded grasslands especially along water courses, is locally known as “Mvale” in Swahili language. Some other vernacular names of this plant according to different localities in Tanzania include Mpaapala (Gogo), Mkunguaga (Luguru), Muvale (Rangi) and Muvare (Sambaa) (Mbuya *et al.*, 1994). In Tanzania, the plant is commonly found in Arusha, Tabora, Dodoma, Kondoa, Morogoro and Iringa (Mbuya *et al.*, 1994). Fine powder prepared from stem bark of this plant is reportedly used by the Nyamwezi people in Tanzania for management of wounds by mixing and taking the same with porridge (Moshi *et al.*, 2006). Root bark extracts are reportedly used to treat stomach ache and hookworm in Kenya (Kokwaro, 1993).

Likewise, *Albizia anthelmentica* which is a thorny/spiny, deciduous, multi-stemmed tree is commonly found in deciduous or evergreen bush lands and scrubland, especially along seasonal rivers and on termite-mound clump thickets. It is medium canopy and grows to an average height of 8 meters (Orwa *et al.*, 2015). The plant is native in Botswana, Kenya, Namibia, Somalia, South Africa, Swaziland, Tanzania and Uganda. A decoction of the stem and root bark of this plant is reportedly used by many ethnic groups throughout East Africa for treatment of helminthic infections mainly tapeworm in both humans and livestock (Grade *et al.*, 2008). The leaf is also used for the treatment of worms specifically *Caenorhabditis elegans* in Sudan (Desta, 1995).

Regarding *Myrica salicifolia*, is a shrub with average height of about one meter and may occasionally grow to a tree of up to 20 m and is usually aromatic and resinous (Grade *et al.*, 2008). The plant is mostly found in temperate, subtropical and tropical montane regions of the world (Kariuki *et al.*, 2014).

The *M. salicifolia* has several names according to different localities in Tanzania. Some commonly vernacular names of this plant include Muangwi (Pare), Olgetalasua (Maasai), Mghosa (Luguru), Mfuruwe (Chagga), Mwehi (Hehe), Nkuguti (Makonde) and Mshegheshe (Sambaa) (Mbuya *et al.*, 1994). Root barks of this plant are used by many ethnic groups in Africa for the management of different ailments such as chest congestion, pneumonia, diarrhea, hypertension, respiratory diseases and nervous disorders (Maara *et al.*, 2014). In Kenya, root bark extracts of *M. salicifolia* is traditionally consumed by Maasai warriors to prime themselves for battle. They believed that consumption of these extracts would produce feelings of detachment from the environment, invincibility, irritability, aggressiveness, overreaction to extraneous sounds and tendency to keep a posture for a long time (Njung'e *et al.*, 2002). Based on previous reports, leaves of *M. salicifolia* reportedly to be crushed and squeezed with water to form a juice which is drunk in small amount for three days to treat cancer in Ethiopia (Yineger, 2007). In view of the foregoing information on the contribution of *M. aethiopicum*, *L. capassa*, *A. anthelmintica* and *M. salicifolia* for management of infectious disease, a huge potential exist for validating these plants as antimicrobials agents to combat resistance against human infectious disease causing pathogens.

Toxicity of medicinal plants used as antimicrobial agents

The increase in number of users and scarcity of scientific evidences on the safety of the plant products has raised concern regarding toxicity and detrimental effects of these remedies (Mengistu, 2015). Plant products are assumed to be safe and less damaging to the human body than conventional drugs because they are of natural origin (Nasri and Shirzad, 2013). However, it must be noted that not all products are safe for consumption in the crude form (Ojo *et al.*, 2013). Some plant products which are being used for treatment of infectious diseases are reported to be having toxic compounds which may cause allergic reaction in people exposing to them and damages to

the internal organs such as liver, heart, lungs, spleen and kidneys (Moreira *et al.*, 2014). The severity of toxic effect may depend on several factors, such as plant species, growth stage or part of the plant, route of administration, amount consumed and susceptibility of the victim (Botha and Penrith, 2008). Other factors that may influence the severity of toxins include solubility of the toxin in body fluids, frequency of intoxication as well as the age of the victim (Mounira, 2015).

These toxic effects are being attributed with several factors including over dosage, misidentification of plants, lack of standardization, contamination and incorrect preparations (Goldman, 2001; Wojcikowski *et al.*, 2004). In this regard, it is always wise idea to consult a qualified practitioner having clinical herbal experience about the compatibility of herb intend to use (WHO, 2002).

Since plant products from medicinal plants have been used for many years without scientific proven to treat various ailments all over the world, efficacy, toxicological and phytochemical profiles of these plants have to be scientifically evaluated like conventional drugs (Botha and Penrith, 2008; Bussmann *et al.*, 2011). To meet these criteria, the toxicity testing using brine shrimp larvae and animal models is required (Kaigongi, 2014). Brine shrimp lethality bioassay is an efficient, rapid and inexpensive assay for testing the toxicity of plant extracts (Naidu *et al.*, 2014).

It is an excellent choice for preliminary toxicity investigations based on the ability to kill laboratory cultured *Artemia naupli* (Carballo *et al.*, 2002). According to Meyer *et al.* (1982), brine shrimp lethality bioassay, is the primary screening of the plants crude extracts as well as the isolated compounds to evaluate the toxicity towards brine shrimps larvae, which could also provide an indication of toxic profile of the test materials. Several studies have been conducted on brine shrimp toxicity tests against plants derived products so as to draw inferences on the safety of such plants.

For example Kilonzo *et al.* (2016b), performed a study on crude extracts from leaves, stem barks and root barks of *M. aethiopicum*, *L. capassa*, *A. anthelmentica* and *M. salicifolia* in brine shrimp larvae. From this study, it was revealed that among the plants extracts tested, *M. aethiopicum* root bark extracts was the most toxic as compared to the rest of the plants extracts.

Regarding the animal models, depending on the duration of exposure of animals to drug, toxicological studies may be of three types namely acute, sub-acute and chronic studies (Baki *et al.*, 2007). Acute toxicity represents the adverse effects occurring within a short period after the administration of a single dose of the tested substance (Duffus *et al.*, 2009). In this method, animals should be individually observed daily for a total of 14 days, except where they need to be removed from the study and humanely killed for animal welfare reasons or are found dead (OECD, 425). Acute toxicity tests are performed on either rats or mice because of the low costs and availability of these animals (Loomis and Hayes, 1996).

In addition, these animals may have a similar metabolism manner and metabolites pharmacodynamics as well as human (Kaigongi, 2014). In sub-acute toxicity studies, the animals are introduced repeated doses of drug and observation to each individual animal is done daily for a period of 14 to 21 days (Baki *et al.*, 2007). Likewise, the chronic toxicity is the adverse effects occurring as a result of the repeated daily exposure of experimental animals to a drug in different doses for a period of 90 days (Belgu *et al.*, 2010).

In view of the toxicological profiles of the medicinal plants commonly used as antimicrobial agents, toxicity evaluation helps in assessing the right dosage to be administered without causing health risks to the users (Ashafa *et al.*, 2012). Furthermore, toxicity evaluation in medicinal plants provides important preliminary information to help selecting natural remedies with potential health beneficial properties (Rosenthal and Brown, 2007).

Therefore, evaluating the toxicological effects of any product from medicinal plant intended to be used in humans as alternative treatment is essential.

Plant secondary metabolites as source of antimicrobial agents

All plants produce primary and secondary metabolites which encompass a wide array of functions (Croteau *et al.*, 2000). In plants, primary metabolites are often concentrated in seeds and vegetative organs and play an important role in the physiological development and basic cell metabolism (Zwenger and Basu, 2008).

Secondary metabolites are organic compounds produced by specific or all parts of the plant to interact with its environment and other organisms (Oksman-caldentey and Barz, 2002). Unlike primary metabolites, absence of secondary metabolites does not result an immediate death, but rather in long term impairment of the plant's survivability, fecundity or perhaps in no significant change at all (Salim *et al.*, 2008). Secondary metabolites play an important role in plant defense against herbivores and other interspecies defenses (Devika and Koilpillai, 2012).

Furthermore, secondary metabolites are suggested to have medicinal properties due to their ability to inhibit growth of various microorganisms (Harborne, 2003). Humans use secondary metabolites as sources of antimicrobial agents as they have reclaimed attention to the mostly pharmaceutical industries (Lahlou, 2013). According to Harborne (2003), large proportions of secondary metabolites are formed from medicinal plants.

In the past few years, several secondary metabolites such as anethole (1), eugenol (2), gallic acid (3), kaempferol (4), isoquercitrin (5) and quercetin (6) (Fig. 1) have been isolated from *M. salicifolia* and *A. anthelmentica* (Kishore *et al.*, 2011; Mohamed *et al.*, 2013). These secondary metabolites can be broadly classified on the basis of chemical structure or pathway by which they are synthesized

(Tiwari and Rana, 2015). Based on their biosynthetic pathway, three classes namely terpenes,

alkaloid and phenolic are normally considered (Harborne, 1996).

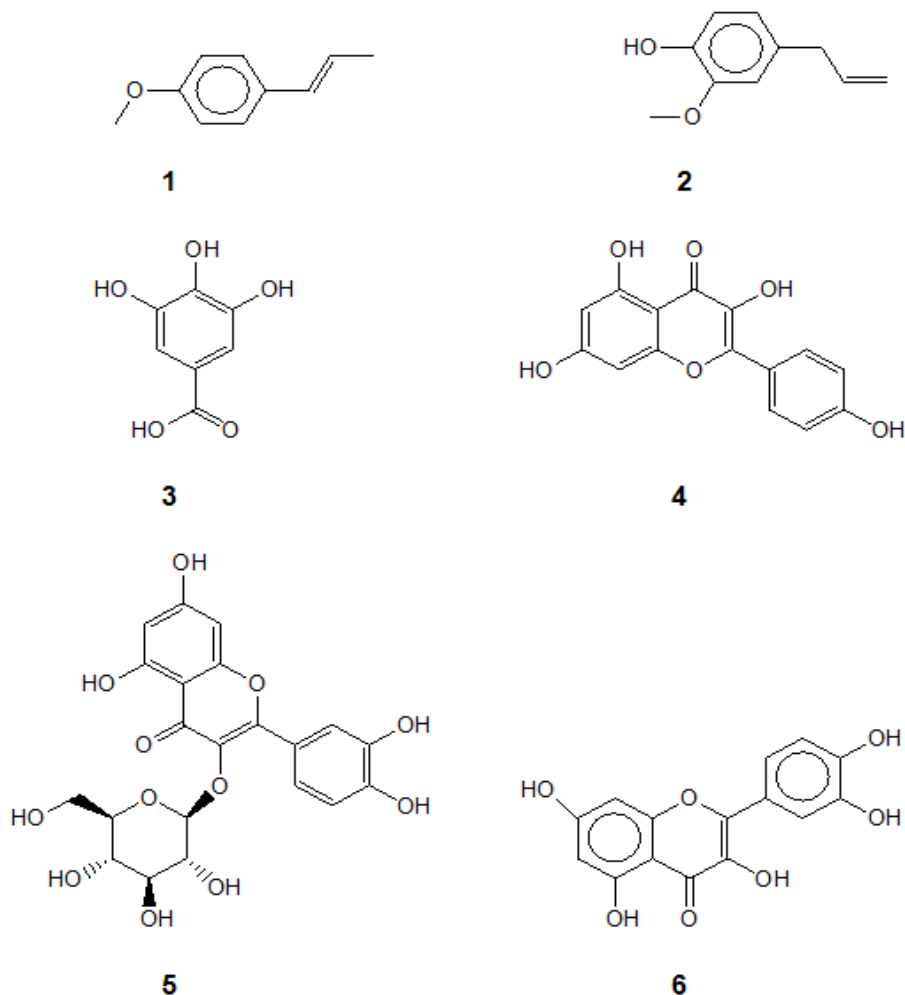


Fig. 1. Structures of secondary metabolites from *M. salicifolia* (1-2) and *A. anthelmintica* (3-6).

Terpenes are the largest and most prevalent class of secondary metabolites in plants with currently more than 30,000 known structures (Singh and Sharma, 2015). Terpenes can also be found in some insects and marine organisms (Zhang *et al.*, 2002). The name terpene is derived from the word turpentine, a product of coniferous oleoresins (Zhang *et al.*, 2002). Biosynthesis of terpenes occurs through two different biological pathways, the mevalonic-acid pathway which mostly produces sesquiterpenes, sterols and ubiquinones and methyl-erythritol phosphate pathway, which the majority of the compounds synthesized are hemiterpenes, monoterpenes and diterpenes (Carson and Hammer, 2010; Savoia, 2012; Ramawat, 2007). Terpenes may be classified according to the number of isoprene units they possess.

For instance, 1 isoprene unit is called hemiterpene, 2 isoprene units are called monoterpenes, 3 isoprene units are called sesquiterpenes, 4 isoprene units are diterpenes and so forth (Compean and Ynalvez, 2014). Of these different major classes of terpenes, the diterpenes are structurally most diversified, possessing at least 6 large structural groups, within which are more than 20 sub structural types (Saikia *et al.*, 2008). The biological active compounds are found in each class of the terpenes particularly among the monoterpenes, diterpenes and sesquiterpenes (Zhang *et al.*, 2002). These biological activities include antimicrobial properties against a wide variety of pathogens, anticancer, antimalarial, anti-inflammatory and insecticidal (Alves *et al.*, 2013; Rubió *et al.*, 2013; Saleem *et al.*, 2010).

For several years, there has been an increased interest in the study of terpenes from medicinal plants as potential sources of new antimicrobial agents (Compean and Ynalvez, 2014). For example, in the phytochemical analysis of *M. aethiopicum*, terpenoids which is derivative of terpenes were found at high concentrations in the root bark and leaves extract of this plant (Cowan, 1999). These compounds, along with other phytochemicals found in *M. aethiopicum*, exhibited antimicrobial activities (Ndokui *et al.*, 2014). Another study conducted by Mutembei *et al.* (2014), on phytochemical analysis of *A. athelmentica* observed a high concentration of terpenoids present in the leaf extract. In addition, this extract was found to possess antimicrobial activities. Similarly, crude extracts from *M. salicifolia* were examined for antimicrobial activities and it was observed that root bark extracts showed highest antimicrobial activities in all extracts tested. Furthermore, the terpenoids were found to be present in the root bark extracts tested (Dharmananda, 2003).

The presence of terpenoids in the *M. aethiopicum*, *A. athelmentica* and *M. salicifolia* can therefore be associated with their various antimicrobial properties since this phytochemical has been known to possess antimicrobial as well as anthelmintic properties (Athanasiadou *et al.*, 2001).

Alkaloids constitute an important class of structurally diversified compounds that are having the nitrogen atom in the heterocyclic ring and are derived from the amino acids (Kaur and Arora, 2015). The term alkaloids was coined by the German chemist Carl Meissner in 1819 and the word is derived from the Arabic name *al-qali* that is related to the plant from which soda was first isolated (Croteau *et al.*, 2000). These compounds are low molecular weight structures and form about 20% of plant based secondary metabolites (Baikar and Malpathak, 2010). Despite alkaloids being traditionally isolated from plants, an increasing number are to be found in animals, insects, marine invertebrates and microorganisms (Dembitsky, 2005). Alkaloids have influenced the human history profoundly due to their wide range of

pharmacological properties as they have been used for hundreds of years in medicine and are still prominent drugs (Margaret and Michael, 1998). Hence this group of compounds had great prominence in many fields of scientific endeavor and continues to be of great interest (Borde *et al.*, 2014). Alkaloids are therefore used as basic medicinal agents all over the world for their analgesic, antispasmodic, anticancer and antimicrobial effects (Xie *et al.*, 2012).

A study conducted by Kilonzo *et al.* (2016a), on antimicrobial activity of *M. aethiopicum* growing in Tanzania revealed that all plant materials tested found to possess antibacterial activities against Gram negative bacteria namely *P. aeruginosa*, *K. oxytoca*, *P. mirabilis*, *K. pneumoniae*, *S. kisarawe*, *S. typhi* and *E. coli*. After performing phytochemical screening, it was revealed that the main constituents in the tested plant materials were alkaloids. In another experimental study conducted by Mu Tembei *et al.* (2014), *A. athelmentica* leaves extracts prepared from two different solvents namely aqueous and ethyl acetate. These extracts were tested against *P. aeruginosa*, *E. coli*, *B. subtilis* and *S. aureus* to determine their potential antibacterial activity. Furthermore, from the phytochemical analysis it was revealed that the aqueous plant extract was abundant with alkaloids. The discovery of alkaloids being active in inhibiting various bacteria is evident that these medicinal plants produce a variety of compounds, mainly secondary metabolites for defense mechanisms against pathogenic microbes.

In view of the foregoing information, such medicinal plants can help to treat infectious diseases that have increased resistance to current antimicrobials. Therefore, the selected medicinal plants in this article can widely provide an alternative medical treatment especially in developing countries where people may not have access to healthcare.

Phenolic compounds are plant secondary metabolites that constitute one of the most common and widespread groups of substances in plants (Dai and Mumper, 2010).

Phenolic compounds are characterized by an aromatic ring having one or more hydroxyl substituent and functional derivatives such as esters, methyl ethers and glycosides (Beecher, 2003). Phenolic compounds are broadly divided into three categories namely flavonoid, tannin and saponin (Morales, 2013; Robbins, 2003). Flavonoids are the largest group of phenolic compounds that is widely distributed throughout the plant kingdom (Adelowo and Oladeji, 2016). They are mostly found in many common edible plant parts such as fruits, nuts and seeds (Compean and Ynalvez, 2014).

Flavonoid compounds have been known to possess various pharmacological activities such as antioxidant, anti-inflammatory, antitumor, antibacterial and antifungal (Cekic *et al.*, 2013). For instance, the antibacterial activities of aqueous leaves extracts of *M. salicifolia* was evaluated against *E. coli*, *S. typhi*, *K. pneumoniae*, *P. aeruginosa* and *S. aureus*. In this study, it was revealed that the tested plant extracts exhibited the growth of all bacteria strains (Kariuki *et al.*, 2014). Furthermore, in the phytochemical screening it was revealed that flavonoids were the main constituents present at higher concentration in the extract. It was therefore concluded that phenolic compounds were responsible for the antibacterial activity of *M. salicifolia* leaves extracts (Njung'e, 1986).

Tannins is a general descriptive name for a group of polymeric phenolic substances capable of tanning leather or precipitating gelatin from solution, a property known as astringency (Pandey and Kumar, 2013). Tannins are found in nearly every part of the plant and divided into two groups, condensed and hydrolysable tannins (Adelowo and Oladeji, 2016). Condensed tannins are compounds formed by the linkage of flavonoid units and they are frequent constituents of woody plants (Bennett and Walls grove, 1994). Condensed tannins can often be hydrolyzed to anthocyanidins by treatment with strong acids and so are called proanthocyanidins (Pinto, 1999). Hydrolyzable tannins are heterogeneous polymers containing phenolic acids, especially gallic acid and simple sugars.

This type of tannins may be hydrolyzed more easily with dilute acid (Hemingway and Laks, 2012). In previous studies, tannins have been known to display different biological activities including antifungal and antibacterial (Carson and Hammer, 2010). For example, a study on phytochemical analysis of *M. aethiopicum*, *L. capassa*, *A. anthelmentica* and *M. salicifolia* which are used for the management of infectious diseases caused by pathogenic bacteria and fungi, revealed presence of tannins in their root bark extracts (Ndukupi *et al.*, 2014; Mutembei *et al.*, 2014; Njung'e 1986). According to Dharmananda (2003), plants with tannins as their main component are astringent in nature and are used for treating intestinal disorders and skin diseases, thus inhibiting antimicrobial activity.

However, many human physiological activities such as stimulation of phagocytic cells, host mediated tumor activity and a wide range of anti-infective actions have been assigned to tannins (Prakash and Shelke, 2014). Hence their mode of antimicrobial action may be related to their activity to inactivate microbial adhesins (Pandey and Kumar, 2013).

Saponin compounds are a diverse family of secondary metabolites produced by many plants species used as traditional medicine (Sparg *et al.*, 2004). Saponins are believed to form the main constituents in various plants which are widely used as traditional medicine worldwide (Estrada *et al.*, 2000). For example, saponins reported to form the main compounds in the leaf extracts of *M. aethiopicum*, and such compound has been found *in vitro* to have antimicrobial properties (Cowan, 1999).

Saponins are also believed to be toxic to cold blooded animals as reported by Dini *et al.*, 2001. However, their oral toxicity to mammals is very low and therefore the toxicity to various cold blooded animals can be utilized for pharmacological activities such as antibacterial, antifungal, antiviral and antitumor activities (Dini *et al.*, 2001). Saponins compounds can be classified into two groups based on the nature of their aglycone skeleton.

The first group consists of the steroidal saponins, which are almost absolutely present in the monocotyledonous angiosperms. The second group consists of triterpenoid saponins, which are the most common and occur mainly in the dicotyledonous angiosperms (Bruneton, 1995). The wide chemical diversity of both steroidal and triterpenoid saponins has resulted in the renewed interest and investigations of these compounds, particularly as potential chemotherapeutic agents. As a result, the chances of discovering new plant constituents, including novel saponins, which may be biologically active are therefore promising.

Future perspective of medicinal plants as antimicrobial agents

The importance of plants is becoming clear from the fact that more than 80% of the world population fulfills its medical needs from medicinal plants (Murtaza *et al.*, 2015). In some African countries such as Tanzania, about 60% of the people especially in rural areas rely on traditional medicine for their healthcare needs (Görge, 2001). The demand for these herbal medicines for therapeutic purposes is increasing and will continue in the future mainly because of less toxicity and side effects of these medicines (Ramanan *et al.*, 2007). Since the demand of such plants as antimicrobial agents is highly increasing in both developed and developing countries, public sectors including policy makers and health care professionals has also demanded evidences on the efficacy, safety, quality, availability and preservation of these plants (Ghani, 2013). In order to allay these concerns and to meet public demands, extensive researches on herbal plants are needed to be undertaken not only for their great healthcare value but also for the commercial benefits (Ramanan *et al.*, 2007). Furthermore, conservation status of all herbal plant species should also be studied in order to open up challenges for the conservationists, policy makers and researchers. Similarly, herbal medicines should be brought under legal control in all countries where they are used for therapeutic purposes and more efforts should be made to raise public awareness about the risks and benefits of using these herbal medicines (Ramanan *et al.*, 2007).

With this cautionary note, it is evident that herbal medicines hold good future prospects and they may one day emerge as good substitutes or better alternatives for conventional drugs or even replace them.

Conclusion

Based on extensive literatures, the four plant species namely *M. aethiopicum*, *L. capassa*, *A. anthelmintica* and *M. salicifolia* had numerous potential to consider as useful medicinal plants for treatment of various diseases. More information relating to their phytochemicals and biological activities has been discussed in this review which gives scientific approach towards future *in vivo* studies which will ultimately lead to the development plant based pharmaceutical formulations. It is also important to note that the phytochemicals and biological effectiveness of these plants provide the most useful information for researchers to carry out further studies on the isolation and identification of all compounds from these herbal plants and hence to determine exactly which compound is contributing to the antimicrobial activity. This is attributed by the fact that plant materials in many studies confirmed to possess antimicrobial activities tested for various secondary metabolites. However, it is not certain which components are exhibiting this activity or if it is a synergy among different compounds. This review therefore encourages a detailed research on the identification, purification and antimicrobial activities for these secondary metabolites.

Competing interests

Authors have declared that no competing interests exist.

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