



Traditional uses, ethnopharmacology, antibacterial and antiparasitic activities of *Symphonia* spp

Ben Lukubye^{a,*}, Rapheal Wangalwa^{a,b}, Grace Kagoro-Rugunda^a

^a Department of Biology, Mbarara University of Science and Technology, P. O. Box 1410, Mbarara, Uganda

^b Pharm-Biotechnology and Traditional Medicine Centre, Mbarara University of Science and Technology, P. O. Box 1410, Mbarara, Uganda

ARTICLE INFO

Keywords:

Antibacterial activity
Antiparasitic activity
Ethnomedicine
Symphonia globulifera
Clusiaceae

ABSTRACT

Introduction: Genus *Symphonia* has evident medicinal importance reported in different literature but with no contextualized review of the ethnopharmacology, antibacterial and antiparasitic activity. This study reviewed and contextualized the ethnomedical uses, antibacterial and antiparasitic activities of medicinal *Symphonia* species.

Methods: A literature search was performed using search terms; *Symphonia* and ethnobotanical surveys, *Symphonia* and ethnomedicine, *Symphonia* and antimicrobial activity, *Symphonia* and antiparasitic activity. Studies (36) on the ethnomedical value, antimicrobial and antiparasitic activities of either isolated compounds or solvent extracts of the genus *Symphonia* were obtained and relevant data extracted and summarized in tables.

Results: The genus *Symphonia* has five medicinally useful species; *S. globulifera*, *S. clusioides*, *S. pauciflora*, *S. fasciculata* and *S. tanalensis* with *S. globulifera* as the most utilized in ethnomedicine. These species treat over 30 ailments including diseases of the digestive system, skin and subcutaneous tissue infections, musculoskeletal system and connective tissue. *Symphonia* spp are largely prepared as a decoction from the stem bark. *Symphonia globulifera* stem bark, root bark, seeds and leaf extracts, isolated compounds showed good antibacterial activity against *Staphylococcus aureus*. They also had good in-vitro anti-leishmanial, antiparasitic and anti-trypanosomal activities.

Conclusion: *Symphonia globulifera* was the most commonly used *Symphonia* spp in herbal medicine because of its ability to grow in different soil types, climates and environments unlike other *Symphonia* species. The bioactivity of the genus *Symphonia* is mainly linked to the abundance of xanthenes and benzophenones, within this genus. The genus *Symphonia* has novel compounds for example manniflavanone, biflavonoid GB2, symphonins with potential antiparasitic and antibacterial activity.

1. Introduction

The genus *Symphonia* belongs to a large family of woody plants called Clusiaceae with over 37 genera and 1610 species worldwide (Gustafsson et al., 2002). The genus is characterized by medium to large trees, with a crown of short horizontal branches, inflorescence with 8–9 flowers, smooth filaments, anthers approximately 1.7–5 mm long. The leaves have an opposite arrangement, petiolate and an entire margin (Stevens, 2007). The genus consists of over 24 species, including *Symphonia globulifera*, *Symphonia tanalensis* and *Symphonia clusioides* mainly distributed in lowland tropical forests in sub-Saharan Africa and Madagascar. Majority of the *Symphonia* species (16) except *Symphonia globulifera* are highly endemic to Madagascar (Abdul-Salim, 2002).

Symphonia species offer a wide range of ethnomedicinal importance. For example, the stem bark, seeds and root bark of *S. globulifera* are used in the management of malaria, leishmaniasis, poliomyelitis, stomach ache, diarrhea and skin diseases in Cameroon, Uganda, Nicaragua, and Madagascar (Nkengfack et al., 2002; Ngouela et al., 2006; Zofou et al., 2013). Similarly, other species such as *S. tanalensis*, *S. clusioides*, *S. pauciflora* are used in the treatment of digestive diseases like diarrhea (Pan et al., 2010; Riondato et al., 2019). This ethnomedicinal value has resulted in a series of studies to determine the phytochemical composition, antimicrobial activity, efficacy, and distribution of the bioactive agents in the genus *Symphonia* (Lígia and Castilho, 2013; Mkoungaa et al., 2009; Oliveira et al., 2013; Rakotoniriana et al., 2010; Ruddock et al., 2011). However, to date all these studies (ethnomedical uses,

* Corresponding author.

E-mail address: lukubyeben@gmail.com (B. Lukubye).

<https://doi.org/10.1016/j.hermed.2023.100666>

Received 1 March 2021; Received in revised form 28 November 2022; Accepted 2 December 2022

Available online 11 May 2023

2210-8033/© 2023 Elsevier GmbH. All rights reserved.

ethnopharmacology, antibacterial and antiparasitic activities) remain independently isolated with no or limited contextualization and summary.

The above reported ethnomedical importance is not surprising as the genus *Symphonia* is characterized by key bioactive classes of compounds, such as xanthenes (globuliferin, symphonins, globulixanthenes C and D, globuxanthone and gaboxanthone) and bioflavonoids (manniflavanone, biflavonoid GB2 and morelloflavone). These compounds have variable activity against gram positive and gram negative bacteria, *Plasmodium* spp, *Leishmania donovani* strains and trypanosomes as determined in different studies (Lenta et al., 2004; Mkoungaa et al., 2009; Ngouela et al., 2006). This creates the need for a comparative analysis to determine the most efficacious isolate or extract for each parasite and bacteria.

The present study, therefore, focused on reviewing the available literature on *Symphonia* plants in order to summarize the ethnomedical uses of the species in different countries. The review also assessed the antibacterial and antiparasitic activities of isolated compounds and extracts from medicinal *Symphonia* species.

2. Materials and methods

2.1. Search strategy

A summary of the literature search strategy is summarized in Fig. 1. A systematic literature search was carried out from databases using Google scholar, Web of Science and Scopus with no specified start date and July, 2019 as the end date. The search considered studies which focused on ethnomedical importance and bioactivity of the extracts and isolated compounds of *Symphonia* species. The search was based on the combination of search terms; *Symphonia* and ethnobotanical surveys, *Symphonia* and ethnomedicine, *Symphonia* and antimicrobial activity, *Symphonia* and antiparasitic activity.

2.2. Inclusion and exclusion criteria

Inclusion criteria was, any study that indicated in the results section any species of *Symphonia* with its ethnomedical value, antimicrobial and antiparasitic activities of either isolated compounds or solvent extracts, and also available in full text under open access.

Exclusion criteria was, all studies that did not conform to the inclusion criteria above. In addition, literature from reports, a review and books were excluded from the review.

2.3. Data extraction and statistical analysis

Relevant information was extracted from the identified articles. This included, the *Symphonia* species, local name, plant part used in treatment, ailments treated, any other traditional uses of the *Symphonia*

species, method of preparation, mode of administration. We also extracted information about the antimicrobial activity (minimum inhibitory concentration) and antiparasitic activity (half maximal inhibitory concentration (IC₅₀), cytotoxicity and selective index) of extracts and isolated metabolites of *Symphonia* species. The extracted data were summarized in tables as either qualitative or quantitative reports. These were then computed into percentages of the studies reviewed using microsoft excel package. A summary of the literature search strategy and selection of articles for review is presented in Fig. 1 below.

3. Results and discussion

3.1. Species of *Symphonia* genus that have ethnomedical importance

The genus *Symphonia* has 5 species of reported ethnomedical value (*S. globulifera*, *S. clusioides*, *S. pauciflora*, *S. fasciculata* and *S. tanalensis*) (Table 2 and Table 1) making about 20.83 % of the total *Symphonia* species. The most frequently cited of these was *S. globulifera* (87.5 %), which was used for ethnomedical purposes such as brushing teeth and gums, treating skin rashes and sores, treatment of pancreatic cancer, poliomyelitis, and cutaneous leishmaniasis, among others (Table 2). *S. globulifera*'s dominance could be attributed to its ability to grow in different soil types, climates and environments, hence being widely distributed in the tropical rain forests of the world (Abdul-Salim, 2002; Ngouela et al., 2005). *Symphonia tanalensis* and *Symphonia fasciculata*, endemic to Madagascar have only been reported to treat digestive diseases like stomach ache and diarrhea (Rakotoarivelo et al., 2015; Riondato et al., 2019) as shown in Table 1. Endemicity of any medicinal plant species limits its ethnomedical exploitation to only the cultures and communities within that given geographical area.

3.2. Traditional preparations of *Symphonia globulifera* herbal medicines

Herbal medicine preparation methods have different potentials in the extraction of bioactive compounds from the plants hence affecting the efficacy of the medicine. Herbal remedies of *Symphonia globulifera* are traditionally prepared as decoctions, poultice, and by peeling/splitting, burning, boiling, and pounding/crushing (Table 1). The stem bark of *Symphonia globulifera* was the most commonly used part for herbal medicine, and largely prepared as a decoction with a percentage preference at 33.33 %. Similarly, poultice (6.06 %), peeling and splitting of roots, burning, boiling and pounding/ crushing had the lowest preference (3.03 %) as methods of preparation as shown in Table 1. Other common methods of herbal medicine preparation such as infusion, tincture, and maceration were not frequently reported in the ethnomedical surveys included in this review. Decoctions of *Symphonia globulifera* stem bark are used to treat hemorrhoids in Democratic Republic of Congo (DRC), cough and intestinal worms in Uganda, malaria in Cameroon, aches and pains in Nicaragua (Table 1).

Decoction was the only method of preparation of herbal remedies from the leaves and stem bark of *Symphonia tanalensis* and *Symphonia fasciculata* respectively (Rakotoarivelo et al., 2015; Riondato et al., 2019). This high preference for decoction is due to its numerous advantages including; effectiveness in extraction of bioactive compounds from hard plant parts such as roots, bark and seeds, and possible administration of decoctions by both oral and topical routes (Nagalingam, 2017; Yang and Ross, 2010). Other studies (Boadu and Asase, 2017; van't Klooster et al., 2016) have too reported a high preference for decoction. Furthermore, decoctions have a high rate of absorption into the body (Yang and Ross, 2010). The duration of boiling and storage of the decoction were not specified in the reviewed articles, despite the fact that these factors have a significant impact on the bioactivity of the prepared herbal remedy.

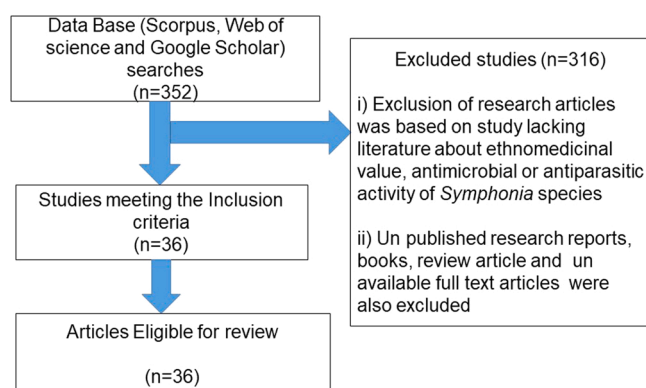


Fig. 1. Summary of the literature search strategy for the review.

Table 1
Ethnomedicinal values of medicinal *Symphonia* species.

	Local name	Parts used	Study area	Disease treated	Way of traditional medicinal use (Preparation, route, dosage)	Mode of administration	Other ethnomedicinal use	Refs.
<i>Symphonia globulifera</i>	Samu/ Sambhogam	Bark	Eastern Nicaragua	Aches and pains	Decoction Poultice	**	Poles for construction of traditional dwelling	(Coe and Anderson, 1996) (Coe, 2008) (Coe et al., 2012) (Coe and Anderson, 1996) (Coe, 2008) (Coe et al., 2012)
<i>Symphonia globulifera</i>	Samu	Sap	Eastern Nicaragua	Skin rashes and sores	Poultice	Topical		
<i>Symphonia globulifera</i>	Samu	Bark Whole plant Sap	Eastern Nicaragua	Aches and pains Malaria Skin rashes and sores Malaria	**	**	**	(Roy et al., 2018) (Kuete et al., 2011) (Simoben et al., 2018) (Zofou et al., 2013) (Simoben et al., 2018) (Zofou et al., 2013) (Nkengfack et al., 2002) (Ntie-Kang et al., 2013) (Ngouela et al., 2005) (Simoben et al., 2018) (Zofou et al., 2013) (Zofou et al., 2013) (Ntie-Kang et al., 2013) (Ngouela et al., 2006) (Lenta et al., 2007)
<i>Symphonia globulifera</i>	**	Leaves	Cameroon	Pancreatic Cancer	**	**	**	
<i>Symphonia globulifera</i>	**	Leaves	Bangangté, Cameroon	Malaria	**	**	**	
<i>Symphonia globulifera</i>	**	Leaves	Bangangté, Cameroon	Laxative for pregnant women	**	**	**	
<i>Symphonia globulifera</i>	**	Leaves	Bangangté, Cameroon	Skin rashes	**	Topical	**	
<i>Symphonia globulifera</i>	**	Seed shells	Cameroon	Malaria	**	**	**	
<i>Symphonia globulifera</i>	**	Leaves	Cameroon	Leishmaniasis	**	**	**	
<i>Symphonia globulifera</i>	Ohoru		Western Province Orinoco River Delta, Venezuela	Wound healing	**	**	**	(Gomez-Beloz., 2002)
<i>Symphonia globulifera</i>	**	Leaves	Cameroon	Stomach ache	**	Oral	**	(Simoben et al., 2018) (Zofou et al., 2013) (Ntie-Kang et al., 2013) (Kadiri, 2008)
<i>Symphonia globulifera</i>	**	Bark	Cameroon	Malaria	Decoction	Oral	**	
<i>Symphonia globulifera</i>	**	Fruits, Leaves, Exudates	Lagos State, Nigeria	Diuretic, Wound dressing, Venereal diseases, stomachic, tonic, surgical splint or dressing. Toothache,	**	**	**	
<i>Symphonia globulifera</i>	Aba	Roots	Oyo State, Nigeria	Poliomyelitis	**	**	**	(Fingesi et al., 2018)
<i>Symphonia globulifera</i>	Efiatndua	Leaves	Akwa Ibom State, Nigeria	Skin disease	Decoction Internal use; 3 × 1 times for 7 days	**	**	(Ajibesin et al., 2007)
<i>Symphonia globulifera</i>	Efiatndua	Root bark	Akwa Ibom State, Nigeria	Cancer	Decoction Internal use; 3 × 1 times for 7 days	**	**	(Ajibesin et al., 2007)

(continued on next page)

Table 1 (continued)

	Local name	Parts used	Study area	Disease treated	Way of traditional medicinal use (Preparation, route, dosage)	Mode of administration	Other ethnomedicinal use	Refs.
<i>Symphonia globulifera</i>	Aba	Roots	Oyo State, Nigeria	Poliomyelitis			**	(Buochuama and Amiofori, 2018)
<i>Symphonia globulifera</i>	**	Leaves	Oyo State, Nigeria	Stroke & paralysis	Pounding/Crushing leaves of <i>S. Globulifera</i> are pounded with <i>Hyptis suaveolens</i> , <i>Allium ascalonicum</i> , <i>Vitellaria paradoxa</i> and black local soap	Topical by washing or massaging affected body part	**	(Borokini et al., 2013)
<i>Symphonia globulifera</i>		Bark	Gabon	Scabies	Decoction	Topical	**	(López Sarria, 2003)
<i>Symphonia globulifera</i>	Machare	Bark	Bajo Calima Colombia	Cutaneous Leishmaniasis	Decoction	Topical	**	(López Sarria, 2003)
<i>Symphonia globulifera</i>	Machare	Bark	Colombia	Cutaneous Leishmaniasis	Decoction	Topical	**	(Simoben et al., 2018)
<i>Symphonia globulifera</i>	Kijibonaka	Leaves	Maromizaha forest, Madagascar	Digestive diseases, Diarrhea, Stomach Ache	Decoction	Oral	**	(Lopez et al., 2001)
<i>Symphonia fasciculata</i>	Kijy	Bark	Ambalabe, Eastern Madagascar	Diarrhea	Decoction	Oral	**	(Riionato et al., 2019)
<i>Symphonia pauciflora</i>	**	Leaves, Flowers and fruits	Madagascar rainforest	Ovarian Cancer	**	**	**	(Rakotoarivelo et al., 2015)
<i>Symphonia clusioides</i>	**	**	Madagascar	**	**	Topical	Hair ointment	(Pan et al., 2010)
<i>Symphonia globulifera</i>	**	**	Tanzania	HIV	**	**	**	(Rakotoniriana et al., 2010)
<i>Symphonia globulifera</i>	Omusaali	Bark	Southern Uganda	Cough, Intestinal worms, Pre-hepatic jaundice, Fever	Decoction	Oral	**	(Vermani and Garg, 2002)
<i>Symphonia globulifera</i>	Omusaali	Sap	Southern Uganda	**	Burning and smoking sap within and around the homestead		Chasing and deterring away of evil spirits	(Thapa et al., 2019)
<i>Symphonia globulifera</i>	Omusaali	Stem bark	Central Uganda	Common cold	Boiling about 9 leaves to cool 1 × 3 spoons daily for Children 2 × 3 spoons daily for adults	Oral	**	(Ssegawa and Kasenene, 2007)
<i>Symphonia globulifera</i>	Ossolo	Bark	Kisangani, DR Congo	Hemorrhoids	Decoction	**	**	(Ssegawa and Kasenene, 2007)
<i>Symphonia globulifera</i>	**	**	Maroon village, Suriname	Wound navel baby(birth)	**	**	**	(Walugembe et al., 2016)
<i>Symphonia globulifera</i>	Matakki	Resin	Paramaribo Suriname		**	**	Traditional winti rituals (sorcery)	(Mbula et al., 2015)
<i>Symphonia globulifera</i>	**	Tender Roots	Creoles and Maroons in Suriname	Oral odor and diseases	Peeling and splitting of roots	Oral	Cleaning of teeth and gums	(van't Klooster et al., 2016)
<i>Symphonia globulifera</i>	Mawinae	Latex	Sikuani, Colombia	Analgesic for external application		Topical	**	(Van Andel et al., 2007)

Key: **: - Indicates No literature available.

Table 2
Ethnopharmacology percentage citation for medicinal *Symphonia* species.

Category	Sub category	Percentage of ethnomedicinal value citation (%)
<i>Symphonia species</i>	<i>S. globulifera</i>	87.5
	<i>S. clusioides</i>	3.125
	<i>S. pauciflora</i>	3.125
	<i>S. fasciculata</i>	3.125
	<i>S. tanalensis</i>	3.125
Method of preparation*	Decoction	33.33
	Poultice	6.06
	Peeling and splitting	3.03
	Burning	3.03
	Boiling	3.03
	Pounding/	3.03
	Crushing	
	Uncertain	48.48
	Topical	24.24
Method of administration	Oral	21.21
	Uncertain	54.55
Part/organ used for medicine*	Bark	28.95
	Sap/Latex	13.16
	Leaves	28.95
	Roots	7.89
	Seed	2.63
	Fruit	5.26
	Flowers	2.63
	Resin	2.63
	Whole plant	2.63
	Uncertain	5.26

*:- Percentage citations were computed from only articles containing *Symphonia globulifera*.

Table 3
Classification of ailments managed by *Symphonia* species.

International classification of diseases	Health use	Number of records per health use	Percentage of record per health use	<i>Symphonia</i> species	Number of records per disease category (%)
Diseases of Digestive system	Stomach ache	3	6.38	<i>Symphonia tanalensis</i> <i>Symphonia globulifera</i>	23.40
	Intestinal worms,	1	2.13	<i>Symphonia globulifera</i>	
	Digestive diseases/ complications/digestive /tonic	2	4.26	<i>Symphonia tanalensis</i> <i>Symphonia globulifera</i>	4.26
	Diarrhea	2	4.26	<i>Symphonia fasciculata</i> , <i>Symphonia tanalensis</i>	
	Pre-hepatic jaundice	1	2.13	<i>Symphonia globulifera</i>	
	Toothaches	1	2.13	<i>Symphonia globulifera</i>	
	Oral disease and odor	1	2.13	<i>Symphonia globulifera</i>	6.38
	Common cold	1	2.13	<i>Symphonia globulifera</i>	
Diseases of respiratory system	Cough,	1	2.13	<i>Symphonia globulifera</i>	17.02
Injuries of External Causes	Wound healing/dressing	3	6.38	<i>Symphonia globulifera</i>	
Diseases of the skin and Subcutaneous tissue	Skin rashes	3	6.38	<i>Symphonia globulifera</i>	23.40
	Skin sores	2	4.26	<i>Symphonia globulifera</i>	
	Scabies	1	2.13	<i>Symphonia globulifera</i>	
	External allergies	1	2.13	<i>Symphonia globulifera</i>	
Infectious and Parasitic diseases	Skin disease (uncertain cause)	1	2.13	<i>Symphonia globulifera</i>	6.38
	Cutaneous Leishmaniasis	3	6.38	<i>Symphonia globulifera</i>	
	Malaria	5	10.64	<i>Symphonia globulifera</i>	
	HIV	1	2.13	<i>Symphonia globulifera</i>	
	Poliomyelitis	2	4.26	<i>Symphonia globulifera</i>	
Diseases of the musculoskeletal system and connective tissue	Aches and pains	2	4.26	<i>Symphonia globulifera</i>	4.26
	Stroke and Paralysis	1	2.13	<i>Symphonia globulifera</i>	
Diseases of Circulatory system	Hemorrhoids	1	2.13	<i>Symphonia globulifera</i>	6.38
	Venereal diseases	1	2.13	<i>Symphonia globulifera</i>	
Cancers	Ovarian cancers	1	2.13	<i>Symphonia pauciflora</i>	
	Pancreatic Cancer	1	2.13	<i>Symphonia globulifera</i>	
	Cancer (unspecific)	1	2.13	<i>Symphonia globulifera</i>	4.26
General Health Symptoms	Fever	1	2.13	<i>Symphonia globulifera</i>	
	Diuretic	1	2.13	<i>Symphonia globulifera</i>	4.26
Pregnancy, Child birth and perinatal period	Laxative for pregnant women	1	2.13	<i>Symphonia globulifera</i>	
	Wound navel baby(birth)	1	2.13	<i>Symphonia globulifera</i>	
Total		47	100.00		100.00

3.3. Mode of administration

Herbal remedies from the *Symphonia* species are mainly administered through topical (24.24 %) and oral routes (21.21 %) (See Table 2). The method of administration was not specified in 54.55 % of the reviewed literature. Focusing on *Symphonia globulifera*, the most common route of administration was topical (24.14 %). Decoctions were mainly administered through the oral (57.14 %) route. This is consistent with previous studies indicating that the oral route is the most commonly used method of administering decoctions and infusions (Boadu and Asase, 2017). There is a relationship between the method of administration, disease, and the bioactive compounds in the extracts (Coe and Anderson, 1996; Lopez et al., 2001). In this review, the topical method of administration was primarily used to treat skin conditions such as cutaneous leishmaniasis, skin rashes, ulcers, scabies, and wounds (Table 1). However, oral administration is used to treat internal conditions like malaria, tumors, digestive disorders, diarrhea, and cough, among others. The disease and the affected body part determine the modes of drug administration. This ensures the administration of bioactive compounds directly to the affected or diseased body part to facilitate easy absorption and faster antimicrobial and antiparasitic activity. Interestingly, modern drugs follow the same mode of administration with most skin infections being treated with topical drugs, while invasive systemic infections are treated orally.

3.4. Composition of herbal remedies in terms of plant parts

The review found that the bark, sap/latex, leaves, roots, seeds, fruits, flowers and resins of *Symphonia* species are used in herbal medicine (Table 1 and Table 2). The stem bark and leaves were the most used plant parts in herbal medicine followed by sap/ latex/ exudates.

Table 4Antibacterial and antiviral activity of extracts of *Symphonia* species.

Plant	Extraction technique	Solvent	Plant part	Microorganism	Antimicrobial activity (µg/mL or mm)		Source
					Extract	Standard	
<i>Symphonia clusioides</i>	Cold maceration	Methanol	Leaves	<i>Bacillus subtilis</i> (clinical)	MIC > 8000 µg/mL	MIC = 3.9 µg/mL (Streptomycin)	(Rakotoniriana et al., 2010)
	Cold maceration	Methanol	Leaves	<i>Staphylococcus aureus</i> (Clinical)	MIC > 8000 µg/mL	MIC = 3.9 µg/mL (Streptomycin)	(Rakotoniriana et al., 2010)
	Cold maceration	Methanol	Leaves	<i>Escherichia coli</i> (Clinical)	MIC > 8000 µg/mL	MIC = 31.3 µg/mL (Streptomycin)	(Rakotoniriana et al., 2010)
	Cold maceration	Methanol	Leaves	<i>Salmonella typhi</i> (Clinical)	MIC > 8000 µg/mL	MIC = 31.3 µg/mL (Streptomycin)	(Rakotoniriana et al., 2010)
	Cold maceration	Methanol	Leaves	<i>Pseudomonas aeruginosa</i> (clinical)	MIC > 8000 µg/mL	MIC > 64 µg/mL (Streptomycin)	(Rakotoniriana et al., 2010)
	Cold maceration	Methanol	Leaves	<i>Candida albicans</i> (MUCL 31360)	MIC > 8000 µg/mL	**	(Rakotoniriana et al., 2010)
	Infusion	Water	Leaves	<i>Staphylococcus aureus</i> ATCC 25923	ZI = 3.66 mm± 0.76 (40.6 % inhibition)	ZI = 9 mm± 0 (Ciprofloxacin)	(Oliveira et al., 2013)
<i>Symphonia globulifera</i>	Maceration	Dichloromethane: methanol (1:1)	Stem bark	<i>Staphylococcus aureus</i>	MIC = 100 µg/mL	MIC = 6.25 µg/mL (Streptomycin)	(Mkougaa et al., 2009)
	Maceration	Dichloromethane: methanol (1:1)	Stem bark	<i>Bacillus subtilis</i>	MIC = 100 µg/mL	MIC = 0.85 µg/mL (Streptomycin)	(Mkougaa et al., 2009)
	Maceration	Dichloromethane: methanol (1:1)	Stem bark	<i>Vibrio anguillarum</i>	MIC = 100 µg/mL	MIC = 4.12 µg/mL (Streptomycin)	(Mkougaa et al., 2009)
	Maceration	Dichloromethane: methanol (1:1)	Stem bark	<i>Escherichia coli</i>	MIC = 150 µg/mL	MIC = 2.44 µg/mL (Gentamicin)	(Mkougaa et al., 2009)
	Maceration	Dichloromethane: methanol (1:1)	Leaves	<i>Enterococcus faecalis</i>	MBC = 0.31 mg/mL	**	(Ligia and Castilho, 2013)
	**	Methanol	Seeds	<i>Staphylococcus aureus</i>	MIC = 300 µg/mL	MIC = 0.60 µg/mL (Gentamicin)	(Ngouela et al., 2005)
	**	Methanol	Seeds	<i>Streptococcus faecalis</i>	MIC = 300 µg/mL	MIC = 4.52 µg/mL (Gentamicin)	(Ngouela et al., 2005)
	**	Methanol	Seeds	<i>Klebsiella pneumonia</i>	MIC = 300 µg/mL	MIC = 8.00 µg/mL (Gentamicin)	(Ngouela et al., 2005)
	**	Methanol	Seeds	<i>Escherichia coli</i>	MIC = 300 µg/mL	MIC = 8.00 µg/mL (Gentamicin)	(Ngouela et al., 2005)
	**	Dichloromethane-methanol (1:1)	Root bark	<i>S. aureus</i> (ATCC 6538)	MIC = 100 µg/mL	MIC = 6.25 µg/mL (Streptomycin sulfate)	(Nkengfack et al., 2002)
	**	Dichloromethane-methanol (1:1)	Root bark	<i>B. subtilis</i> (ATCC 6633)	MIC = 100 µg/mL	MIC = 0.85 µg/mL (Streptomycin sulfate)	(Nkengfack et al., 2002)
	**	Dichloromethane-methanol (1:1)	Root bark	<i>Vibrio anguillarum</i> (ATCC 19264)	MIC = 100 µg/mL	MIC = 4.12 µg/mL (Streptomycin sulfate)	(Nkengfack et al., 2002)
	**	Methanol	Root bark	<i>S. aureus</i> (ATCC 6538)	MIC = 500 µg/mL	MIC = 6.25 µg/mL (Streptomycin sulfate)	(Nkengfack et al., 2002)
	**	Methanol	Root bark	<i>B. subtilis</i> (ATCC 6633)	MIC = 500 µg/mL	MIC = 0.85 µg/mL (Streptomycin sulfate)	(Nkengfack et al., 2002)
	**	Methanol	Root bark	<i>Vibrio anguillarum</i> (ATCC 19264)	MIC = 500 µg/mL	MIC = 4.12 µg/mL (Streptomycin sulfate)	(Nkengfack et al., 2002)
	**	Methanol	Seed	<i>Staphylococcus aureus</i>	MIC = 300 µg/mL	MIC = 4.52 µg/mL (Gentamicin)	(Lenta et al., 2004)
	**	Methanol	Seed	<i>Streptococcus faecalis</i>	MIC = 300 µg/mL	MIC = 4.12 µg/mL (Gentamicin)	(Lenta et al., 2004)
	**	Methanol	Seed	<i>Klebsiella pneumonia</i>	MIC = 300 µg/mL	MIC = 8.00 µg/mL (Gentamicin)	(Lenta et al., 2004)
	**	Methanol	Seed	<i>Escherichia coli</i>	MIC = 300 µg/mL	MIC = 0.90 µg/mL (Gentamicin)	(Lenta et al., 2004)
	**	Methanol	Root bark	<i>Escherichia coli</i> (ATCC 8739)	MIC > 100 µg/mL	MIC > 100 µg/mL (Streptomycin sulfate)	(Nkengfack et al., 2002)
	**	Acetone	Leaves	<i>N. gonorrhoeae</i> (WHO V)	ZI = 20 mm	**	(Ruddock et al., 2011)
	**	Methanol (99.8%)	Stem bark	HSV	MIC = 25 µg/mL	**	(Lopez et al., 2001)

Key: MIC:- Minimum inhibitory concentration, ZI:- Zone of inhibition, **:- No literature available, ATCC:- American Type Culture Collection.

In ethnomedicine, the use of specific plant parts in preparing herbal remedies ensures extraction of high concentrations of targeted bioactive compounds against a particular disease or ailment due to variations in the distribution of phytochemicals in plant organs (Figueiredo et al., 2008). Leaves are usually the most commonly used plant part in *Symphonia* species herbal medicines possibly due to a high concentration and diversity of bioactive compounds as a result of their primary role in photosynthesis (Fanta Yadang et al., 2019; Ghasemzadeh et al., 2014). On the other hand, seeds and fruits are less used for herbal medicine because of their seasonal occurrence on the plant. The use of leaves for

herbal medicine poses a much lower threat to the survival and conservation of medicinal *Symphonia* species compared to the roots and bark. Because of the observed dominance of the use of *Symphonia* stem bark in herbal medicine, sustainable bark harvesting methods, such as alternate stripe method should be employed.

Symphonia globulifera plant parts have also been mixed with other non-*Symphonia* spp to obtain a synergistic combination effect for treating an ailment. For instance, leaves of *Symphonia globulifera*, *Allium ascalonicum*, *Vitellaria paradoxa* when crushed with black local soap are used to make an infusion for treating stroke and paralysis. The infusion is

Table 5
Antibacterial activity of isolated metabolites of *Symphonia globulifera*.

Isolated metabolite	Plant part	Microorganism	Minimum inhibitory concentration (µg/mL)		Source
			Isolated metabolite	Standard drug	
Symphonin	Seed	<i>S. aureus</i> *	3.12	4.52 (Gentamicin)	(Lenta et al., 2004)
Symphonin	Seed	<i>S. faecalis</i> *	4.2	4.12 (Gentamicin)	(Lenta et al., 2004)
Symphonin	Seed	<i>K. pneumonia</i> *	25.90	8.00 (Gentamicin)	(Lenta et al., 2004)
Symphonin	Seed	<i>E. coli</i> *	No activity	0.90 (Gentamicin)	(Lenta et al., 2004)
Globuliferin	Seed	<i>K. pneumonia</i> *	15.24	8.00 (Gentamicin)	(Ngouela et al., 2005)
Globulixanthone C	Root bark	<i>S. aureus</i> (ATCC 6538)	14.05	6.25 (Streptomycin sulfate)	(Nkengfack et al., 2002)
Globulixanthone C	Root bark	<i>B. subtilis</i> (ATCC 6633)	8.24	0.85 (Streptomycin sulfate)	(Nkengfack et al., 2002)
Globulixanthone C	Root bark	<i>E. coli</i> (ATCC 8739)	> 100	> 100 (Streptomycin sulfate)	(Nkengfack et al., 2002)
Globulixanthone D	Root bark	<i>S. aureus</i> (ATCC 6538)	8.00	6.25 (Streptomycin sulfate)	(Nkengfack et al., 2002)
Globulixanthone D	Root bark	<i>B. subtilis</i> (ATCC 6633)	12.5	0.85 (Streptomycin sulfate)	(Nkengfack et al., 2002)
Globulixanthone D	Root bark	<i>E. coli</i> (ATCC 8739)	> 100	> 100 (Streptomycin sulfate)	(Nkengfack et al., 2002)
Globulixanthone E	Root bark	<i>S. aureus</i> (ATCC 653)	4.51	6.25 (Streptomycin sulfate)	(Nkengfack et al., 2002)
Globulixanthone E	Root bark	<i>B. subtilis</i> (ATCC 6633)	3.12	0.85 (Streptomycin sulfate)	(Nkengfack et al., 2002)
Globulixanthone E	Root bark	<i>Vibrio anguillarum</i> (ATCC 19264)	5.56	4.12 (Streptomycin sulfate)	(Nkengfack et al., 2002)
Globulixanthone E	Root bark	<i>E. coli</i> (ATCC 8739)	> 100	> 100 (Streptomycin sulfate)	(Nkengfack et al., 2002)
Globulixanthone F	Stem bark	<i>S. aureus</i> (ATCC 6538)	4.50	6.25 (Streptomycin sulfate)	(Mkougaa et al., 2009)
Globulixanthone F	Stem bark	<i>B. subtilis</i> (ATCC 6633)	1.25	0.85 (Streptomycin sulfate)	(Mkougaa et al., 2009)
Globulixanthone F	Stem bark	<i>Vibrio anguillarum</i> (ATCC 19264)	5.05	4.12 (Streptomycin sulfate)	(Mkougaa et al., 2009)
Manniflavanone GB3	Stem bark	<i>S. aureus</i> (ATCC 6538)	8.50	6.25 (Streptomycin sulfate)	(Mkougaa et al., 2009)
Manniflavanone GB3	Stem bark	<i>E. coli</i> (ATCC 8739)	4.50	2.44 (Gentamicin)	(Mkougaa et al., 2009)
Biflavonoid GB2	Stem bark	<i>S. aureus</i> (ATCC 6538)	8.50	6.25 (Streptomycin sulfate)	(Mkougaa et al., 2009)
Biflavonoid GB2	Stem bark	<i>E. coli</i> (ATCC 8739)	7.50	2.44 (Gentamicin)	(Mkougaa et al., 2009)

Key: *- Clinical microorganism isolate, ATCC:- American Type Culture Collection.

gently rubbed on the paralyzed body parts in the evening before bed time in Oyo State, Nigeria (Borokini et al., 2013).

3.5. Health conditions treated or managed using *Symphonia* species

Symphonia species are used in the management of about 30 different health conditions of varying complexity (Tables 1 and 3). This shows the great potential of *Symphonia* species in disease management and directly confirms earlier reports indicating use of the family Clusiaceae and genus *Symphonia* in the treatment of several parasitic diseases (Lenta et al., 2007; Pan et al., 2010). The diseases managed by *Symphonia* species are grouped into 9 categories according to the international classification of diseases and related health problems (van't Klooster et al., 2016). These categories included infectious and parasitic diseases, injuries of external causes, diseases of the digestive system, skin and subcutaneous tissue, musculoskeletal system, connective tissue, circulatory system, cancers, pregnancy, child birth and perinatal disorders (Table 3). Diseases of the digestive system, infectious and parasitic diseases are the most treated ailments (23.40 %) using *Symphonia* spp followed by diseases of the skin and subcutaneous tissue with 17.02 % citation record. The least reported categories were pregnancy, child birth and perinatal period, general health symptoms, diseases of circulatory and respiratory systems with each at 4.26 % record per disease category (Table 3). With regard to the particular disease, malaria had the highest percentage of record per health use/disease (10.64 %) followed by cutaneous leishmaniasis, skin rashes, wounds and stomach ache at 6.38 % with all five diseases being treated with *Symphonia*

globulifera.

Plants like *Symphonia globulifera* with high citations of ethnobotanical surveys for treating malaria have played an essential role in reducing the mortality and morbidity of malaria within the tropics especially in the rural communities of African countries with poor health care systems like Cameroon and Uganda. This calls for the need to regulate and incorporate herbal medicine into the countries' healthcare systems based on empirical evidence. On the other hand, some reported medicinal uses of *Symphonia* species had only a single record for treatment of diseases such as pre-hepatic jaundice, scabies, HIV, stroke and paralysis among others, and need to be investigated further to ascertain this ethnomedical importance.

In comparison to other *Symphonia* species, *Symphonia globulifera* treats a higher number of diseases or health issues, which poses a challenge to the species' viability, abundance, and distribution as an ethnomedicine resource. Plants with a high medicinal value, such as *Prunus africana* and *Symphonia globulifera* are being threatened or in danger of extinction due to pressures arising from poor harvesting methods, especially in the developing world where over 80 % of the population use traditional medicine for their health care needs (Ingram et al., 2015; Ekor, 2014).

3.6. Antibacterial activity of *S. globulifera* and *S. clusioides*

The antibacterial activity of crude extracts and isolated compounds from *S. globulifera* and *S. clusioides* has been empirically established (Fromentin et al., 2015; Lígia and Castilho, 2013; Mkougaa et al., 2009;

Table 6Antiparasitic activity of extracts and isolated compounds of *Symphonia globulifera*.

Plant part (solvent)/ compound	Parasite species	Antiparasitic activity		Standard IC ₅₀ (µg/mL)	Cytotoxicity IC ₅₀ (µg/ mL)	Selectivity Index (SI)	Cell line	Source
		IC ₅₀	%parasite inhibition (concentration)					
Leaves (Methanol)	<i>Plasmodium falciparum</i> K1	4.1 ± 0.50 µg/mL	**	0.002 µg/mL (Artemisinin)	52.3 ± 5.6 µg/ mL	14.0	L-6 cells	(Lenta et al., 2007)
Leaves (Methanol)	<i>Trypanosoma cruzi</i>	> 30 µg/mL	**	0.400 µg/mL (Benznidazole)	**	**	**	(Lenta et al., 2007)
Leaves (Methanol)	<i>Trypanosoma brucei</i> <i>rhodesiense</i>	11.5 ± 0.50 µg/mL	**	0.002 µg/mL (Melarsoprol)	**	**	**	(Lenta et al., 2007)
Leaves (Methanol)	<i>Leishmania donovani</i>	2.1 ± 0.80 µg/mL	**	0.080 µg/mL (Miltefosine)	**	**	**	(Lenta et al., 2007)
Guttiferone A	<i>L. donovani</i> amastigotes (MHOM/ET/67/L82)	0.16 µM	82.1 (0.8 µg/mL)	57.6 % (Miltefosine)	7.3 µM	46	L-6 cells	(Lenta et al., 2007)
Globulixanthone C	<i>L. donovani</i> amastigotes (MHOM/ET/67/L82)	0.16 µM	98.7 (4.8 µg/mL)	57.60 µg/mL (Miltefosine)	**	**	**	(Lenta et al., 2007)
Guttiferone A	<i>L. donovani</i> (MHOM/ET/ 67/HU3)-promastigotes	5.83 ± 0.35 µM	**	16.24 ± 2.34 µM (Miltefosine)	7.05 ± 0.36 µM	1.2	Vero cell lines	(Fromentin et al., 2013)
Gaboxanthone	<i>P. falciparum</i> strain W2	3.53 µM	**	0.130 µM (chloroquine phosphate)	**	**	**	(Ngouela et al., 2006)
Symphonin	<i>P. falciparum</i> strain W2	1.29 µM	**	0.13 µM (chloroquine phosphate)	**	**	**	(Ngouela et al., 2006)
Globuliferin	<i>P. falciparum</i> strain W2	3.86 µM	**	0.13 µM (chloroquine phosphate)	**	**	**	(Ngouela et al., 2006)
Guttiferone A	<i>P. falciparum</i> strain W2	3.17 µM	**	0.13 µM (chloroquine phosphate)	**	**	**	(Ngouela et al., 2006)
Guttiferone A	<i>P. falciparum</i> FcB1/ Colombia	3.32 ± 0.45	98.10 (10 µg/mL)	**	**	**	**	(Fromentin et al., 2013)
Guttiferone A	<i>T. brucei brucei</i> strain 93	2.95 ± 0.94	96.45 (10 µg/mL)	0.0005 µM (Pentamidine)	7.05 ± 0.36 µg/ mL	2.4	Vero Cells	(Fromentin et al., 2013)

Key: IC₅₀:- Half-maximal inhibitory concentration, **:- No available literature.

Nkengfack et al., 2002; Rakotoniriana et al., 2010). Crude extract of the dry leaves of *Symphonia clusioides* extracted using methanol by cold maceration overnight at room temperature was tested against clinical bacteria strains *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi* and standard fungi *Candida albicans* (MUCL 31360). These generally had MIC > 8 mg/mL (Table 4) an indication of no antimicrobial activity against both gram negative and gram positive bacteria (Rakotoniriana et al., 2010). However only methanol, was used in the extraction, which creates room for investigation of antimicrobial activity of other solvent extracts. *Symphonia globulifera* root bark, stem bark and leaves crude extracts had antibacterial activity against *S. aureus* with MIC ranging between 100 µg/mL and 500 µg/mL (Table 4). Dichloromethane-methanol (1:1) stem bark extract of *Symphonia globulifera* showed the strongest antimicrobial activity (MIC = 100 µg/mL) against *S. aureus* (Mkougaa et al., 2009) while the methanol root bark had the least antimicrobial activity against *S. aureus* (MIC = 500 µg/mL) (Nkengfack et al., 2002). Dichloromethane-methanol (1:1) mixture had a high extraction efficiency that enables the extraction of a wide range of bioactive compounds soluble in either of these solvents, hence a stronger antimicrobial activity against *S. aureus*. Similarly, a 40.6 % inhibition of *S. aureus* (ATCC 25923) was reported by Oliveira et al. (2013).

Secondary metabolites responsible for bioactivity of seed, stem bark and root bark extracts of *Symphonia globulifera* against *S. aureus* include symphonin, globulixanthone C, globulixanthone D, globulixanthone E, globulixanthone F, manniflavanone GB3 and biflavonoid GB2 illustrated in Table 7. Their MIC's ranged between 3.12 µg/mL and 14.05 µg/mL (Table 5). *Symphonia globulifera* isolated compounds such as symphonin, globulixanthone E and globulixanthone F had stronger antimicrobial activity (MIC's 3.12 µg/mL, 4.51 µg/mL and 4.50 µg/mL respectively) than gentamicin and streptomycin sulfate (Table 5). This illustrated the

potential of the three isolated compounds for use in drug discovery and development.

Dichloromethane-methanol (1:1) and methanol stem bark extracts of *S. globulifera* showed antimicrobial activity against spore forming *B. subtilis* with MIC ranging between 100 and 500 µg/mL (Table 4). *Bacillus subtilis* was less susceptible to globulixanthones like globulixanthone C, globulixanthone D, globulixanthone E and globulixanthone F with MIC values 8.24 µg/mL, 12.5 µg/mL, 3.12 µg/mL and 1.25 µg/mL respectively (Mkougaa et al., 2009; Nkengfack et al., 2002). The mode of action of the above compounds has not been investigated however xanthones cause bacterial cytoplasmic membrane disintegration (Sivaranjani et al., 2019).

Seed methanolic extracts of *S. globulifera* also have activity against *Klebsiella pneumoniae* the causative agent for bronchopneumonia and bronchitis. According to Ngouela et al. (2005), methanol extracts of *S. globulifera* seeds have bioactivity against *K. pneumoniae* (MIC = 300 µg/mL). This activity is mainly attributed to globuliferin and symphonin with MIC values 15.25 µg/mL and 25.90 µg/mL respectively close to that of gentamicin (MIC = 8.00 µg/mL) (Lenta et al., 2004; Ngouela et al., 2005). In addition, growth of other gram-negative rods such as *E. coli* was inhibited by the extracts and isolated compounds of *S. globulifera*. For example dichloromethane: methanol (1:1) stem bark extract and methanol seed extract inhibited the growth of *E. coli* in vitro (MIC = 150 µg/mL and 300 µg/mL respectively) as shown in Table 4. The antimicrobial activity against *E. coli* could be due to the presence of manniflavanone GB3, and biflavonoid GB2 in the stem bark, which individually inhibited the growth of *E. coli* at very low concentrations (4.50 and 7.50 µg/mL) (Table 5). Symphonin, globulixanthone C, globulixanthone E and globulixanthone D showed inactivity against *E. coli* (Lenta et al., 2004; Nkengfack et al., 2002). The leaves, seed and

root bark extracts of *S. globulifera* were also active against other microorganisms like *Neisseria gonorrhoeae*, *S. feacalis*, *Vibrio anguillarum* as summarized in Table 4. Largely the reported antibacterial activity in this review was generally observed *in vitro* assays. This calls for an assessment of this antibacterial potential *in vivo*, but also other studies to investigate the antifungal activity and cytotoxicity.

Besides the bacteria, *S. globulifera* extracts have also been investigated for their anti-viral activity. For instance, the methanol stem bark extract showed antiviral activity against Herpes simplex virus-type 1 by inhibiting the development of cytopathic effects in the Vero cell lines (MIC = 25 µg/mL). However, the extract had no antiviral activity against the poliovirus (Lopez et al., 2001). The results of the same study indicated no visible cytotoxicity of the methanol stem bark extract on Vero cell lines (Lopez et al., 2001).

3.7. Antiparasitic activity of *Symphonia globulifera*

Symphonia globulifera has potential antiplasmodial and leishmanicidal activity (Table 6). Generally, the antiplasmodial activity of the *S. globulifera* extracts is mainly rooted on the high concentrations of xanthenes in the plant which have been reported to have antimalarial activity against *Plasmodium falciparum* (Mazimba et al., 2013). Crude methanol extracts from the leaves of *S. globulifera* demonstrated antiplasmodial activity ($IC_{50} = 4.1 \pm 0.5$ µg/mL) when tested against the K1 multidrug pyrimethamine/chloroquine-resistant strain of *Plasmodium falciparum* (Lenta et al., 2007). Furthermore, Ngouela et al. (2006) also indicated significant antiplasmodial activity of symphonin against chloroquine resistant strain *Plasmodium* W2, ($IC_{50} = 1.29$ µM). This strong antiplasmodial activity against chloroquine resistant strains is

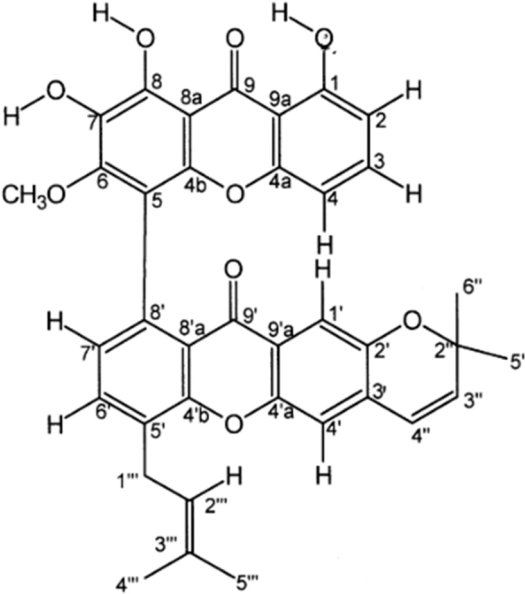
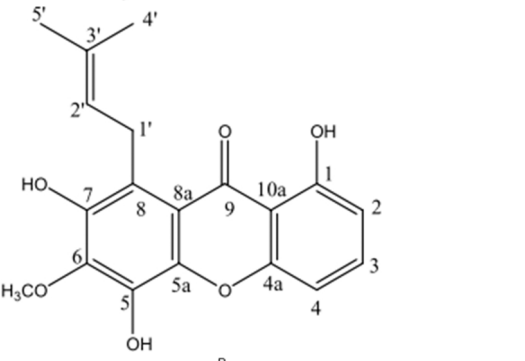
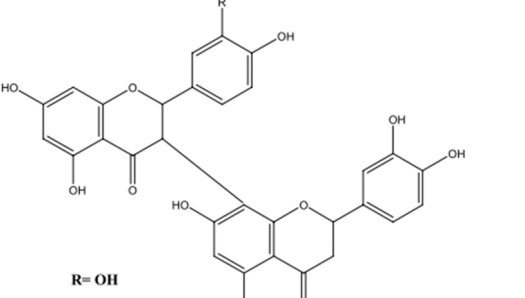
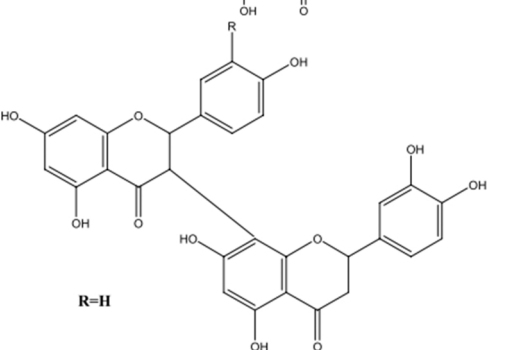
Table 7

Structure of compounds isolated from *Symphonia globulifera*.

Isolated compound	Plant part	Structure	Source
Symphonin	Seed		(Lenta et al., 2004)
Globuliferin	Seed		(Ngouela et al., 2005)
Globulixanthone C	Root bark		(Nkengfack et al., 2002)
Globulixanthone D	Root bark		(Nkengfack et al., 2002)

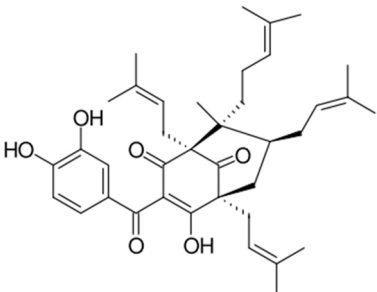
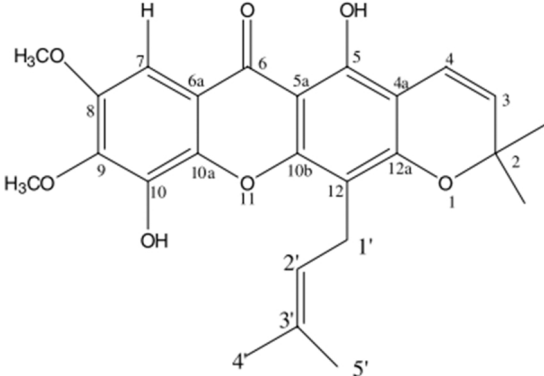
(continued on next page)

Table 7 (continued)

Isolated compound	Plant part	Structure	Source
Globulixanthone E	Root bark		(Nkengfack et al., 2002)
Globulixanthone F	Stem bark		(Mkougaa et al., 2009)
Manniflavanone GB3	Stem bark		(Mkougaa et al., 2009)
Biflavonoid GB2	Stem bark		(Mkougaa et al., 2009)

(continued on next page)

Table 7 (continued)

Isolated compound	Plant part	Structure	Source
Guttiferone A	Seeds		(Ngouela et al., 2006)
Gaboxanthone	Seeds		(Ngouela et al., 2006)

very important and can be used to develop new antimalarials especially for tropical countries, where chloroquine resistant *Plasmodium* strains are endemic. Other reported compounds with antiplasmodial activity include gaboxanthone, globuliferin and guttiferone A isolated from the dry seed of *S. globulifera* (Table 6). The mode of action of these compounds against *Plasmodium spp* parasites has not been investigated and remains a key research question. One possible mode of action may be through competitive inhibition of the degradation of toxic heme into less toxic haemozoin, a mechanism observed in other antiplasmodial xanthone compounds (Mamede et al., 2020). This leads to the heme accumulating in membranes, hence free heme toxicity to the *Plasmodium* parasites (Slater and Cerami, 1992).

This mode of action is similar to that of quinolones which act through inhibiting the detoxification or digestion of heme. In addition to the above, seed extracts of *S. globulifera* have antioxidative potential with compounds such as guttiferone A exhibiting over 89 ± 0.5 % inhibition of 1,1-Diphenyl-2-picrylhydrazyl (DPPH) free radicals (Ngouela et al., 2006). For a single compound or extract to show both strong antiplasmodial and antioxidative properties is highly unique and very important in the development of antimalarials. This is because plasmodium infections induce the immune system to produce high concentrations of oxidant and reactive nitrogen species which collectively imparts oxidative stress on the erythrocyte (Fromentin et al., 2015). Therefore, this suggests that the *S. globulifera* extracts act against *Plasmodium* parasites through counteracting the oxidative stress of the infected erythrocyte and inhibition of heme digestion in the erythrocyte. There is need to assess the activity of guttiferone A and other xanthenes against other *Plasmodium* species and strains.

S. globulifera leaves are also used in treatment of cutaneous leishmaniasis in Colombia (Lopez et al., 2001; López Sarria, 2003). This is not surprising as methanol extracts of the leaves showed leishmanicidal activity with low IC_{50} values ($IC_{50} = 2.1 \pm 0.8$ µg/mL) (Lenta et al., 2007). Furthermore, guttiferone A and globulixanthone C had higher growth inhibition (82.1 % and 98.7 %) of *Leishmania donovani* compared to the standard drug, miltefosine (57.6 %) at 0.8 µg/mL (Lenta et al., 2007). However at a high concentration (4.8 µg/mL), only

guttiferone A inhibited the *Leishmania donovani* parasites' growth by 98.3% slightly above 95.0% inhibition by miltefosine (Lenta et al., 2007). Guttiferone A showed leishmanicidal activity against both amastigotes and promastigotes of *Leishmania donovani* (Fromentin et al., 2013; Lenta et al., 2007). Development of multiple phenotypes within same host offers parasites an adaptive advantage to survive chemotherapeutics. However, guttiferone A is likely to overcome such a challenge due to its activity against both promastigotes and amastigotes. Just like other benzophenones, guttiferone A has a mode of action that involves the inhibition of cysteine proteases of the *Leishmania* parasite hence interfering with its life cycle (Almeida et al., 2015). The inhibition of cysteine proteases of trypanosomatids also reduces the parasites virulence which slows the progression of the disease, resulting in low cell deaths (Bryson et al., 2009).

The uptake of guttiferone A into drug development due to its good antiplasmodial and leishmanicidal activity is limited by the cytotoxic levels of the extract against different cell lines. For example guttiferone A at a concentration of 7.05 µM inhibits the growth of half (50 %) of the Vero cells with a low selective index of 1.2 against the *Leishmania donovani* promastigotes (Fromentin et al., 2013). Guttiferone A can be optimized and used in the synthesis of new derivatives with high selective index for *Leishmania donovani*, *Plasmodium* species and low cytotoxicity to the host cells.

Leaves of *S. globulifera* are also used in the treatment of trypanosomiasis in humans. Methanol extracts of *S. globulifera* leaves show a good antitrypanosomal activity against *Trypanosoma brucei rhodesiense* ($IC_{50} = 11.5 \pm 0.5$ µg/mL) (Lenta et al., 2007). Guttiferone A (10 µg/mL) showed a 96.45% inhibition of the growth of *T. brucei brucei* strain 93 (Fromentin et al., 2013). However, low guttiferone A concentration (1 µg/mL), showed a much lower inhibition (38.51 %) of *T. brucei brucei* strain 93 (Fromentin et al., 2013). Despite the good antitrypanosomal activity of guttiferone A against *T. brucei brucei* strain 93, the selective index of the isolate is low (SI = 2.4) indicating risk to host cells before killing the parasite (Fromentin et al., 2013). Lenta et al. (2007) reported no significant bioactivity of *S. globulifera* extracts against *Trypanosoma cruzi* the causative pathogen of chagas disease.

4. Conclusion

The genus *Symphonia* through its medicinal species (*S. globulifera*, *S. clusioides*, *S. pauciflora*, *S. fasciculata* and *S. tanalensis*) demonstrates high ethnomedical potential for treatment or management of over 30 different health conditions. However, the current review showed that *Symphonia globulifera* was the most commonly used among all other *Symphonia* spp. These indigenous ethnomedical uses have been empirically confirmed by biological assays. Extracts of the stem bark, leaves, root bark and seeds of *Symphonia* species and *Symphonia globulifera* possess moderate and good antibacterial activity against both gram positive and gram-negative bacteria. The antibacterial activity of *Symphonia* species is mainly attributed to different isolates of xanthenes and benzophenones. Furthermore, *Symphonia globulifera* possesses antiplasmodial, leishmanicidal and antitrypanosomal activity.

Declaration of Competing Interest

On behalf of myself and the other two co-authors Mr. Rapheal Wangalwa and Associate Prof. Grace Kagoro-Rugunda of Mbarara University of Science and Technology, the authors of research article: "Traditional uses, ethnopharmacology, antibacterial and antiparasitic activities of *Symphonia* spp" hereby declare that there is no conflict of interest and together approve of the submission and publication of the article in the Journal of herbal medicine.

Acknowledgements

The authors wish to acknowledge the members of the Department of Biology, Mbarara University of Science and Technology, for all the support and encouragement they offered during the writing of the article and also proof reading.

References

- Abdul-Salim, K., 2002. Systematics and biology of *Symphonia* L. f.(Clusiaceae) (Ph.D. diss). Harvard University, Cambridge.
- Ajibesin, K.K., Ekpo, B.A., Bala, D.N., Essien, E.E., Adesanya, S.A., 2007. Ethnobotanical survey of Akwa Ibom State of Nigeria. *J. Ethnopharmacol.* 115 (3), 387–408. <https://doi.org/10.1016/j.jep.2007.10.021>.
- Almeida, L., Ferreira, K., Maciel-rezende, C.M., Oliveira, L., De, Jesus, P., Ribeiro, F., Viegas, C., Augusto, M., Alves, W., Júdice, D.S., Henrique, M., José, M., 2015. Benzophenone derivatives as cysteine protease inhibitors and biological activity against *Leishmania* (L.) amazonensis amastigotes. *Biomed. Pharmacother.* 75, 93–99. <https://doi.org/10.1016/j.biopha.2015.08.030>.
- Boadu, A.A., Asase, A., 2017. Documentation of herbal medicines used for the treatment and management of human diseases by some communities in Southern Ghana. *Evid.-Based Complement. Altern. Med.* 2017, 2–7. <https://doi.org/10.1155/2017/3043061>.
- Borokini, T., Clement, M., Dickson, N.J., Edagbo, D.E., 2013. Ethnobiological survey of traditional medicine practice for Men's reproductive health in Oyo State, Nigeria. *Topclass J. Herb. Med.* 2 (6), 111–120.
- Bryson, K., McGachy, H.A., Coombs, G.H., Mottram, J.C., Alexander, J., Mmun, I.N.I., 2009. Overexpression of the natural inhibitor of cysteine peptidases in *Leishmania mexicana* leads to reduced virulence and a Th1 response. *Infect. Immun.* 77 (7), 2971–2978. <https://doi.org/10.1128/IAI.00558-08>.
- Buochuama, A., Amiofori, F.I., 2018. The utilization of plant species in the treatment of some identifiable viral diseases in Southwestern Nigeria. *World Sci. News* 95, 111–123.
- Coe, F.G., 2008. Ethnomedicine of the Rama of Southeastern Nicaragua. *J. Ethnobiol.* 28 (1), 1–38. [https://doi.org/10.2993/0278-0771\(2008\)28](https://doi.org/10.2993/0278-0771(2008)28).
- Coe, F.G., Anderson, G.J., 1996. Ethnobotany of the Garífuna of Eastern Nicaragua. *Econ. Bot.* 50 (1), 71–107. <https://doi.org/10.1007/BF02862114>.
- Coe, F.G., Parikh, D.M., Johnson, C.A., Anderson, G.J., 2012. The good and the bad: alkaloid screening and brineshrimp bioassays of aqueous extracts of 31 medicinal plants of eastern Nicaragua. *Pharm. Biol.* 50 (3), 384–392. <https://doi.org/10.3109/13880209.2011.608077>.
- Ekor, M., 2014. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front. Pharm.* 4, 177. <https://doi.org/10.3389/fphar.2013.00177>.
- Fanta Yadang, S.A., Taiwe Sotoing, G., Ngatcha Zouakeu, K.S., Khan, M.A., Agbor, G.A., Ur-Rahman, N., Ngo Bum, E., 2019. Quantification of bioactive compounds and evaluation of the antioxidant activity of *Carissa edulis* Valh (Apocynaceae) leaves. *Sci. World J.* 2019, 7549620. <https://doi.org/10.1155/2019/7549620>.
- Figueiredo, A.C., Barroso, J.G., Pedro, L.G., Scheffer, J.J.C., 2008. Factors affecting secondary metabolite production in plants: volatile components and essential oils. *Flavour Fragr. J.* 23 (4), 213–226. <https://doi.org/10.1002/ffj.1875>.
- Fingesi, U.I., Buochuama, A., Abduirahman, Q.A., 2018. Ethnobotanical survey of medicinal plants used in treating viral infection in Saki west Local Government Area, Oyo state, Nigeria. *World News Nat. Sci.* 17.
- Fromentin, Y., Cottet, K., Kritsanida, M., Michel, S., Gaboriaud-kolar, N., Lallemand, M., 2015. *Symphonia globulifera*, a widespread source of complex metabolites with potent biological activities. *Planta Med.* 81 (2), 95–107. <https://doi.org/10.1055/s-0034-1396148>.
- Fromentin, Y., Cottet, K., Kritsanida, M., Michel, S., Gaboriaud-kolar, N., Lallemand, M. C., 2015. *Symphonia globulifera*, a widespread source of complex metabolites with potent biological activities. *Planta Med.* 81 (2), 95–107. <https://doi.org/10.1055/s-0034-1396148>.
- Fromentin, Y., Gaboriaud-kolar, N., Ndjakou, B., Duplex, J., Buisson, D., Mouray, E., Grellier, P., Loiseau, P.M., Lallemand, M., Michel, S., 2013. Synthesis of novel guttiferone A derivatives: in-vitro evaluation toward *Plasmodium falciparum*, *Trypanosoma brucei* and *Leishmania donovani*. *Eur. J. Med. Chem.* 65 (2013), 284–294. <https://doi.org/10.1016/j.ejmech.2013.04.066>.
- Ghasemzadeh, A., Jaafar, H.Z.E., Rahmat, A., Devarajan, T., 2014. Evaluation of bioactive compounds, pharmaceutical quality, and anticancer activity of curry leaf (*Murraya koenigii* L.). *Evid.-Based Complement. Altern. Med.* 2014, 5. <https://doi.org/10.1155/2014/873803>.
- Gomez-Beloz, A., 2002. Plant use knowledge of the Winikina Warao: the case for questionnaires in ethnobotany. *Economic Botany* 56 (3), 231–241. <https://doi.org/10.1663/0013-0001>.
- Gustafsson, M.H.G., Bittrich, V., Stevens, P.F., 2002. Phylogeny of Clusiaceae Based on rbcL sequences. *Int. J. Plant Sci.* 163 (6), 1045–1054 ([https://doi.org/1058-5893/2002/16306-0018\\$15.00](https://doi.org/1058-5893/2002/16306-0018$15.00)).
- Ingram, V., Loo, J., Vinceti, B., Dawson, I., Muchugi, A., Duminil, J., Awono, A., Asaah, E., Tchoundjeu, Z., 2015. Ensuring the Future of the Pygeum Tree (*Prunus africana*): Briefing on *Prunus Africana* Cultivation and Harvesting. LEI Wageningen UR.
- Kadiri, A.B., 2008. Evaluation of medicinal herbal trade (Paraga) in Lagos State of Nigeria. *Ethnobot. leafl.* 2008 (1), 90. <https://opensiuc.lib.siu.edu/ebf/vol2008/i1ss1/90>.
- Kuete, V., Wabo, H.K., Eyong, K.O., Feussi, M.T., Wiench, B., Krusche, B., Effert, T., 2011. Anticancer activities of six selected natural compounds of some Cameroonian medicinal plants. *PLoS One* 6 (8), e21762. <https://doi.org/10.1371/journal.pone.0021762>.
- Lenta, B., Ngouela, S., Nougoué, D.T., Tsamo, E., Connolly, J.D., 2004. Symphonin: A new prenylated pyranoxanthone with antimicrobial activity from the seeds of *Symphonia globulifera* (Guttiferae). *Bull. Chem. Soc. Ethiop.* 18 (2), 175–180. <https://doi.org/10.4314/bcse.v18i2.61439>.
- Lenta, B.N., Vonthron-Sénécheau, C., Weniger, B., Devkota, K.P., Ngoupayou, J., Kaiser, M., Naz, Q., Choudhary, M.I., Tsamo, E., Sewald, N., 2007. Leishmanicidal and cholinesterase inhibiting activities of phenolic compounds from *Allanblackia monticola* and *Symphonia globulifera*. *Molecules* 12 (8), 1548–1557. <https://doi.org/10.3390/12081548>.
- Lenta, N.B., Ngouela, S., Kaiser, M., Tsamo, E., Anton, R., Weniger, B., 2007. In vitro antiprotozoal activities and cytotoxicity of some selected Cameroonian medicinal plants. *J. Ethnopharmacol.* 111, 8–12. <https://doi.org/10.1016/j.jep.2006.10.036>.
- Lígia, A., Castilho, D., 2013. New trends in dentistry: plant extracts against *Enterococcus faecalis*. The efficacy compared to chlorhexidine. *Braz. Oral Res.* 27 (2), 109–115. <https://doi.org/10.1590/s1806-83242013000100017>.
- Lopez, A., Hudson, J.B., Towers, G.H.N., 2001. Antiviral and antimicrobial activities of Colombian medicinal plants. *J. Ethnopharmacol.* 77 (2), 189–196. [https://doi.org/10.1016/S0378-8741\(01\)00292-6](https://doi.org/10.1016/S0378-8741(01)00292-6).
- López Sarria, A.A., 2003. Phytochemistry and Biological Activities of Selected Colombian Medicinal Plants. The University of British Columbia. <https://doi.org/10.14288/1.0091221>.
- Mamede, L., Ledoux, A., Jansen, O., Frédéric, M., 2020. Natural phenolic compounds and derivatives as potential antimalarial agents. *Planta Med.* 86 (9), 585–618. <https://doi.org/10.1055/a-1148-9000>.
- Mazimba, O., Nana, F., Kuete, V., Singh, G.S., 2013. Xanthenes and anthranoids from the medicinal plants of Africa. In: *Medicinal Plant Research in Africa: Pharmacology and Chemistry*. Elsevier Inc, pp. 393–434. <https://doi.org/10.1016/B978-0-12-405927-6.00011-4>.
- Mbula, J.P., Kwembe, J.T.K., Tshilanda, D.D., Asimonio, J., Toegaho, A., Tshibangu, D.S. T., Mpiana, P.T., 2015. Ethnobotanical Survey of Aromatic Plants of Masako Forest Reserve (Kisangani, DR CONGO). *J. Adv. Botany Zool. V2I3* <https://doi.org/10.15297/JABZ.V2I3.04>.
- Mkougaa, P., Fomuma, Z.T., Meyer, B., Bodob, B., Nkengfack, A.E., 2009. Globulixanthone F, a new polyoxygenated xanthone with from the stem bark of *Symphonia globulifera*. *Nat. Prod. Commun.* 4 (6), 803–808. <https://doi.org/10.1177/1934578X0900400613>.
- Nagalingam, A., 2017. Drug delivery aspects of herbal medicines. In: *Japanese Kambo Medicines for the Treatment of Common Diseases: Focus on Inflammation*. Elsevier Inc, pp. 143–164. <https://doi.org/10.1016/B978-0-12-809398-6.00015-9>.
- Ngouela, S., Ndjakou, B.L., Tchamo, D.N., Zelefack, F., Tsamo, E., Connolly, J.D., 2005. A prenylated xanthone with antimicrobial activity from the seeds of *Symphonia globulifera*. *Nat. Prod. Res.* 19 (1), 23–27. <https://doi.org/10.1080/14786410310001643876>.
- Ngouela, S., Lenta, B.N., Nougoué, D.T., Ngoupayou, J., Boyom, F.F., Tsamo, E., Gut, J., Rosenthal, P.J., Connolly, J.D., 2006. Anti-plasmodial and antioxidant activities of

- constituents of the seed shells of *Symphonia globulifera* Linn f. *Phytochemistry* 67 (3), 302–306. <https://doi.org/10.1016/j.phytochem.2005.11.004>.
- Nkengfack, A.E., Mkounga, P., Meyer, M., Fomum, Z.T., Bodo, B., 2002. Globulixanthones C, D and E: three prenylated xanthones with antimicrobial properties from the root bark of *Symphonia globulifera*. *Phytochemistry* 61 (2), 181–187. [https://doi.org/10.1016/S0031-9422\(02\)00222-4](https://doi.org/10.1016/S0031-9422(02)00222-4).
- Ntie-Kang, F., Lifongo, L.L., Mbaze, L.M.A., Ekwelle, N., Owono Owono, L.C., Megnassan, E., Efange, S.M., 2013. Cameroonian medicinal plants: a bioactivity versus ethnobotanical survey and chemotaxonomic classification. *BMC Complement Altern. Med.* 13, 1–18. <https://doi.org/10.1186/1472-6882-13-147>.
- Oliveira, A.A., Segovia, J.F.O., Sousa, V.Y.K., Mata, E.C.G., Gonçalves, M.C.A., Bezerra, R.M., Paulo, O.M., Kanzaki, L.I.B., 2013. Antimicrobial activity of amazonian medicinal plants. *SpringerPlus* 2 (1), 1–6. <https://doi.org/10.1186/2193-1801-2-371>.
- Pan, E., Cao, S., Brodie, P.J., Miller, J.S., Rakotodrajaona, R., Ratovoson, F., Birkinshaw, C., Andriantsiferana, R., Rasamison, V.E., Kingston, D.G.I., 2010. An antiproliferative xanthone of *Symphonia pauciflora* from the Madagascar rainforest. *Nat. Prod. Commun.* 5 (5), 751–754. <https://doi.org/10.1177/1934578X1000500515>.
- Rakotoarivelo, N.H., Rakotoarivony, F., Ramarosandratana, A.V., Jeannoda, V.H., Kuhlman, A.R., Randrianasolo, A., Bussmann, R.W., 2015. Medicinal plants used to treat the most frequent diseases encountered in Ambalabe rural community, Eastern Madagascar. *J. Ethnobiol. Ethnomed.* 11 (1) <https://doi.org/10.1186/s13002-015-0050-2>.
- Rakotoniriana, E.F., Rajaonarison, J.F., Raelison, E.G., Rajaonarivelo, J.P., Manga, N., Solofoniaina, M., Rakotonirina, B., Randriamampionona, D., Rabemanantsoa, C., Cheuk, K., Urveg-Ratsimamanga, S., Leclercq, J.Q., 2010. Antimicrobial activity of 23 endemic plants in Madagascar. *Trop. J. Pharm. Res.* 9 (2), 165–171. <https://doi.org/10.4314/tjpr.v9i2.53704>.
- Riondato, I., Donno, D., Roman, A., Razafintsalama, V.E., Petit, T., Mellano, M.G., Torti, V., De Biaggi, M., Rakotoniriana, E.N., Giacomini, C., Beccaro, G.L., 2019. First ethnobotanical inventory and phytochemical analysis of plant species used by indigenous people living in the Maromizaha forest, Madagascar. *J. Ethnopharmacol.* 232 (January 2018), 73–89. <https://doi.org/10.1016/j.jep.2018.12.002>.
- Roy, A., Jauhari, N., Bharadvaja, N., 2018. Medicinal Plants as a Potential Source of Chemopreventive Agents. In: Akhtar, M., Swamy, M. (Eds.), *Anticancer Plants: Natural Products and Biotechnological Implements*. Springer, Singapore. https://doi.org/10.1007/978-981-10-8064-7_6.
- Ruddock, P.S., Charland, M., Ramirez, S., Liao, M., Dillon, J.R., 2011. Antimicrobial activity of flavonoids from *Piper lanceaeifolium* and other Colombian medicinal plants against antibiotic susceptible and resistant strains of *Neisseria gonorrhoeae*. vol. 38 (no. 2), pp. 82–8. (<https://doi.org/10.1097/OLQ.0b013e3181f0bdbc>).
- Simoben, C.V., Ntie-Kang, F., Akone, S.H., Sippl, W., 2018. Compounds from African medicinal plants with activities against selected parasitic diseases: Schistosomiasis, trypanosomiasis and leishmaniasis. *Nat. Prod. Bioprospecting* 8, 151–169. <https://doi.org/10.1007/s13659-018-0165>.
- Sivaranjani, M., Leskinen, K., Aravindraj, C., Saavalainen, P., Pandian, S.K., Skurnik, M., Ravi, A.V., 2019. Deciphering the antibacterial mode of action of alpha-mangostin on *Staphylococcus epidermidis* RP62A through an integrated transcriptomic and proteomic approach. *Front. Microbiol.* 10 (1), 1–16. <https://doi.org/10.3389/fmicb.2019.00150>.
- Slater, A.F.G., Cerami, A., 1992. Inhibition by chloroquine of a novel haem polymerase enzyme activity in malaria trophozoites. *Nature* 355 (6356), 167–169. <https://doi.org/10.1038/355167a0>.
- Ssegawa, P., Kasenene, J.M., 2007. Medicinal plant diversity and uses in the Sango bay area, Southern Uganda. *J. Ethnopharmacol.* 113 (3), 521–540. <https://doi.org/10.1016/j.jep.2007.07.014>.
- Stevens, P.F., 2007. Clusiaceae-guttiferae. In: *Flowering Plants-Eudicots*. Springer, pp. 48–66. https://doi.org/10.1007/978-3-540-32219-1_10.
- Thapa, S.P., Swarnkar, P., Gayoor, K.M., Umama Y., 2019. Anti- HIV herbal drugs. *World J. Pharm. Pharm. Sci.* 8 (2), 178–187.
- Van Anel, T., 2015. The reinvention of household medicine by enslaved Africans in Suriname. *Soc. Hist. Med.* 29 (4), 676–694. <https://doi.org/10.1093/shm/hkv014>.
- Van Anel, T., Behari-Ramdas, J., Havinga, R., Groenendijk, S., 2007. The medicinal plant trade in Suriname. *Ethnobot. Res. Appl.* 5, 351–372.
- van't Klooster, C., van Anel, T., Reis, R., 2016. Patterns in medicinal plant knowledge and use in a Maroon village in Suriname. *J. Ethnopharmacol.* 189 (2016), 319–330. <https://doi.org/10.1016/j.jep.2016.05.048>.
- Vermani, K., Garg, S., 2002. Herbal medicines for sexually transmitted diseases and AIDS. *J. Ethnopharmacol.* 80 (1), 49–66. [https://doi.org/10.1016/S0378-8741\(02\)00009-0](https://doi.org/10.1016/S0378-8741(02)00009-0).
- Walugembe, J., Iramiot, J.S., Katuura, E., 2016. Indigenous knowledge and antibacterial activity of selected herbs used locally to treat common cold in Central Uganda. *J. Med. Plant Res.* 10 (31), 520–528. <https://doi.org/10.5897/JMPR2016.6181>.
- Yang, Y., Ross, J., 2010. Theories and concepts in the composition of Chinese herbal formulas. *Chin. Herb. Formulas* 1–34. <https://doi.org/10.1016/b978-0-7020-3132-8.00006-2>.
- Zofou, D., Ntie-Kang, F., Sippl, W., Efange, S.M.N., 2013. Bioactive natural products derived from the Central African flora against neglected tropical diseases and HIV. *Nat. Prod. Rep.* 30 (8), 1098–1120. <https://doi.org/10.1039/c3np70030e>.