

Sub-Saharan Rubiaceae: A Review of Their Traditional Uses, Phytochemistry and Biological Activities

^{1,2}Simplice D. Karou, ¹Tchadjobo Tchacondo, ²Denise P. Ilboudo and ²Jacques Simpure

¹Centre de Formation et de Recherche sur les Plantes Médicinales (CERFOPLAM),
Université de Lomé, Togo

²Centre de Recherche Biomoléculaire Pietro Annigoni (CERBA), Ouagadougou, Burkina Faso

Abstract: Rubiaceae family is a large family of 630 genera and about 13000 species found worldwide, especially in tropical and warm regions. These plants are not only ornamental but they are also used in African folk medicine to treat several diseases. Based on online published data and library bibliographic research, we herein reported accumulated information related to their traditional usages in sub-Saharan traditional medicine, their chemical composition and the screened pharmacological activities. Indeed, more than 60 species are used for more than 70 medicinal indications including malaria, hepatitis, eczema, oedema, cough, hypertension, diabetes and sexual weakness. Through biological screening following leads supplied with traditional healers, many of these plants exhibited antimalarial, antimicrobial, antihypertension, antidiabetic, antioxidant and anti-inflammatory activities. Bioactive compounds including indole alkaloids, terpenoids and anthraquinones have been isolated from these bioguided fractionation studies. It is evidence that great attention has been paid to species such as *Nauclea latifolia*, *Morinda lucida*, *Mitragyna inermis* and *Crossopteryx febrifuga*; however, several compounds should be waiting to be discovered since none of these plants has been systematically investigated for its biochemical composition. According the current global health context with the recrudescence of HIV, much effort should be oriented towards this virus when screening Rubiaceae.

Key words: Anti-inflammatory activities, indole alkaloids, terpenoids, pharmacology, folk medicine

INTRODUCTION

The use of plant-based systems continues to play a key role in health care. Many reports estimated that approximately 80% of the population in developing countries still relies on Traditional Medicine (TM) for their primarily health care (WHO, 2011; Hostettman and Marston, 2002). In some African countries such as Ghana, Mali, Nigeria and Zambia, the first line of treatment for 60% of the children with high fevers, resulting from malaria, is the use of herbal medicines at home (WHO, 2003). In these societies, the tradition of collecting, processing and applying plants and plant-based medications have been handed down from generation to generation. Traditional medicine, with medicinal plants as their most important component are sold in marketplaces or prescribed by traditional healers in their homes (Von Maydell, 1996).

The development of resistance to most of the available antimicrobial agents and the high costs of treatment consequent upon this resistance has

necessitated a search for new, safe, efficient and effective agents for the management of infections (Okwu and Uchenna, 2009). This research for new effective agents against infectious diseases and other diseases such as, cancers, diabetes, cardio-vascular, neurological, respiratory disorders, etc has led to increased interest in existing information about the remedies of these diseases from natural sources, principally the plants (Karou *et al.*, 2007; Ouattara *et al.*, 2007). Because of this strong dependence on plants as medicines, ethnopharmacological studies have been conducted to determine their safety and their efficiency and on the other hand to find out new active principles from plants (Zongo *et al.*, 2010; Ouattara *et al.*, 2011a,b).

Rubiaceae are among plants of wide usage in traditional medicine that are continuously screened in laboratory for their pharmacological properties. According to their wide distribution, these plants are used in all parts of the world as ornamentals, foods and remedies. The most economically important members of the family are the two species of shrub *Coffea canephora* (also known

as *Coffea robusta*) and *Coffea arabica*, used in the production of coffee. *Gardenia jasminoides* is a widely grown garden plant and flower in frost-free climates worldwide. Several other species from the genus are also seen in horticulture. The genus *Ixora* also contains plants seen cultivated in warmer climate gardens.

In medicine, trees of the genus *Cinchona* are of great interest because of their alkaloids, the most familiar being quinine, the first effective agent in treating malaria. In this last topic the Rubiaceae family received great attention by scientists. The present review is focussed on the Rubiaceae growing in Sub-Saharan Africa. The online published studies enable us to summarize the uses in indigenous TM and the compounds occurring in these plants. This research finally discussed the biological activities exhibited by these plants.

Botanical data: Rubiaceae is a family of flowering plants, variously called the madder family, bedstraw family or coffee family. The family takes its name from the Madder genus *Rubia*. Other plants such as *Gardenia*, *Cinchona*, *Gambier*, *Ixora*, *Naucleaceae* and *Theligonaceae* have been included in the family. Now-a-days there are about 630 genera and more than 13000 species in the family; making the Rubiaceae one of the six largest angiosperm families including *Asteraceae*, *Orchidaceae*, *Fabaceae*, *Poaceae* and *Euphorbiaceae* in terms of number of genera and species. Rubiaceae species are concentrated in warmer and tropical climates around the world (Dalziel, 1957). A wide variety of growth forms are present in the Rubiaceae. Shrubs are most common, but members of the family can also be trees, lianas or herbs. Species are mainly woody, less than 20% of the genera are herbaceous. A large number grow in sub-Saharan Africa. The most represented are *Anthospermeae*, *Morindeae*, *Spermacoaceae*, *Cinchoneae*, *Naucleae*, *Coffeae*, *Gardenieae* and *Pavetteae*.

Traditional uses of sub-Saharan Rubiaceae

Rubiaceae members used in Sub-Saharan traditional medicine: There are more than 30 online publications on Sub-Saharan ethnobotany. The main studies are published in *Journal of Ethnopharmacology*, *Journal of Ethnobiology* and *Ethnomedicine*, *African Journal of Biotechnology* and *African Journal of Traditional, Complementary and Alternative Medicine*. A total 73 Rubiaceae species all growing in sub-tropical Africa and distributed into 34 genera are documented as having medicinal value in this part of the world. These genera are *Anthospermum*, *Borreria*, *Breonadia*, *Canthium*, *Chassalia*, *Cinchona*, *Coffea*, *Craterispermum*, *Crossopteryx*, *Diodia*, *Fadogia*, *Feretia*, *Galium*,

Gardenia, *Hallea*, *Keetia*, *Macrosphyra*, *Mitracarpus*, *Mitragyna*, *Morinda*, *Mussaenda*, *Nauclea*, *Oxyanthus*, *Oldenlandia*, *Pausinystalia*, *Pavetta*, *Pentas*, *Psychotria*, *Rothmannia*, *Rubia*, *Rytigynia*, *Sarcosaphelus*, *Spermacoce*, *Uncaria* and *Vangueria* (Fig. 1). The genus *Pentas* with the following species: *Pentas bussei* K. Krause, *Pentas decora*, *Pentas hindsoides*, *Pentas lanceolata*, (Forssk.) Deflers, *Pentas lanceolata* (Forssk.) Defl. Subsp. *quartiniana* (A. Rich.) Verdc., *Pentas longiflora* Oliver, *Pentas micrantha*, *Pentas purpurea*, *Pentas shimperana* subsp. *occidentalis* (Hook.f.) Verdc., *Pentas schimperiana* (A. Rich.)Vatke, *Pentas zanzibarica* (Klotzsch) Vatke; is the most represented followed by the genus *Gardenia* and *Canthium* with the species *Gardenia aqualla* Stapf and Hutch, *Gardenia cornuta*, *Gardenia erubescens* Stapf and Hutch, *Gardenia imperialis*, *Gardenia sokotensis* Hutch and Kew Bull, *Gardenia ternifolia* and *Gardenia triangacantha*. *Canthium glaucum* Hiern., *Canthium multiflorum* Schum and Thonn, *Canthium oligocarpum* Hiern, *Canthium setosum* Hiern., *Canthium vulgare* Bullock, *Canthium zanzibarica* Klotzsch. and *Canthium* spp; respectively. The present list of Sub-Saharan medicinal Rubiaceae could not be exhaustive since the data are based on the internet and library bibliography research. In this study there is a disparity of ethnobotanical data published online. Some countries such as Ethiopia, Nigeria, Cameroon and Kenya have more than 10 online publications on ethnobotanical studies, while these data are missing for other countries such as Togo, Niger and Benin. Of course still very little is known about the medicinal practices and plants used in the folk medicine of these countries.

Concoction and mode of administration: According to published ethnobotanical data, Rubiaceae plant parts used for medical preparations are leaves, bark, roots and fruits. In some cases the whole plant is used including the roots. The most frequently used plant parts are the leaves followed by the bark, stem and roots. Single plants may be used alone or in association with other plants or with other material of animal or mineral origin. Remedies are mainly prepared in the form of powder, concoction and decoction. The methods of administration of herbal medicines are internal, particularly by oral absorption and external: poultice/topical application or bathing.

Ailments: The remedies are used in the management of many diseases including abdominal irritation, abortion, abscesses, anaemia, arthritis, ascariadid, ascite, asthenia, baby growth delay, chancre, chicken pox, conjunctivitis, constipation, cough, cryptococcal meningitis, dermatitis,

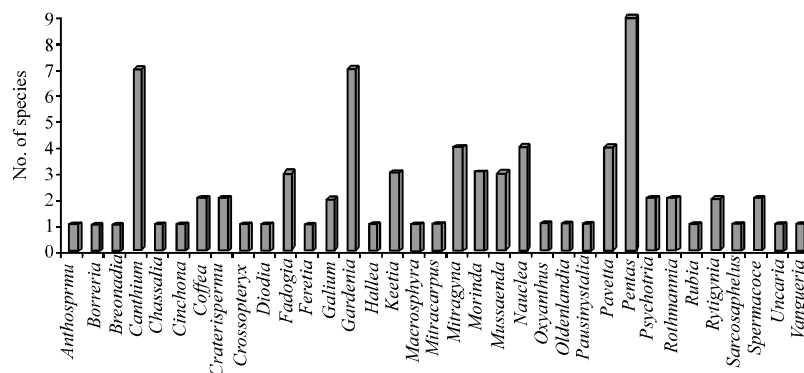


Fig. 1: Rubiaceae members used in Sub Saharan Africa for medicinal purposes

diabetes, diarrhoea, dizziness, dysentery, dysmenorrhoea, eczema, epilepsy, evil eye, evil spirit, fever, filariasis, gastritis, general weakness, gonorrhoea, headache, hemorrhage, hepatitis B, hydrocele, hypertension, itchy rashes, infant umbilical pains, internal inflammation, jaundice, kidney diseases, leprous macular, lumbago, lymphadenitis, madness, malaria, mental disorders, measles, mycoses, obesity, oedema, ovarian cyst, paralysis and nerve diseases, pinworm, poisoning, pubic lice, respiratory infection, rheumatism, ringworm, scabies, sexual impotence, snake bites, splenomegaly, sterility, syphilis, threatened, tapeworm, trypanosomiasis, urinary retention, urinary tract infection, vomiting and wounds (Table 1). Malaria and microbial infections are the main diseases cited. Overall, the cited diseases cover the main of indigenous diseases; indeed, Rubiaceae may be considered as a major component of sub-Saharan folk medicine.

Chemistry of Rubiaceae: Various natural products occur in Rubiaceae plants. Extensive phytochemical investigation has been realized regarding the natural occurrence of terpenoids, anthraquinones and indole alkaloids in the family. The occurrence of alkaloids seems to be a rule in this family, although Leal and Elisabetsky, (1996) demonstrated the absence of alkaloids in *Psychotria carthagenensis*. The alkaloids of Rubiaceae are indolique alkaloids. They may occur in tetracyclic or pentacyclic rings (Fig. 2). The occurrence of alkaloids in some Rubiaceae is well documented. The leaves of *M. inermis* contain tetracyclic and pentacyclic oxindole and indole alkaloids including uncarine D, rhynchophylline, isorhynchophylline, rotundifoline, isorotundifoline, ciliaphylline, speciogynine, pteropodine, uncarine F, mitraphylline, isomitraphylline and mitracilantine (Toure *et al.*, 1996). The proportion of these compounds is variable and depends on the growing

location and the season of harvest. A number of monoterpene indole alkaloids including nauclefine 1 and 2 have been isolated from *Nauclea* species. The main alkaloids of *N. pobeguini* were identified as strictosamide, carboxystritosidine and methylangustoline (Fig. 3). *N. latifolia* contains diverse phytochemicals such as alkaloids, flavonoids, steroids and glycosides. Earlier workers on the plant isolated a series of alkaloids from it. Naucleafoline, nauclechine and naufoline were isolated from the leaves. Other alkaloids isolated from the plant include naucleatine, nauclefine, naucleidinal and epinaucleidinal, augustine and card-ambine (Hotellier *et al.*, 1975, 1979). Naucleidal and epinaucleidal (Fig. 4) have been isolated from an antiviral preparation produced by roasting *Nauclea latifolia* fruits (Morah, 1994); furthermore, five monoterpene indole alkaloids, naucleamides A to E (Fig. 4), were found to occur in the bark and wood of the plant. Naucleamide E was the unique monoterpene indole alkaloid possessing a pentacyclic ring system with an amino acetal bridge (Shigemori *et al.*, 2003). From the stem bark of *Mitragyna africana* collected in Nigeria, seven Corynanthetype oxindole alkaloids, i.e., rhynchophylline, isorhynchophylline, corynoxine, isocorynoxine, ciliaphylline, rhynchociline and isospeciocorynoxine, were isolated. Furthermore, a new indole alkaloid 9-methoxy-3-epi- α -yohimbine (Fig. 4) was isolated as a minor component (Takayama *et al.*, 2004). However, crossopterine was found to be the main alkaloid occurring in the bark of *Crossopteryx febrifuga* (Tona *et al.*, 2000). Chemical compounds isolated from different parts of the plant also include quercetin and non-quercetin containing flavonoids from the leaves and bisdesmonic saponins and triterpene saponin from the stem bark. Similarly, from the bark of *Mitragyna inermis*, Cheng *et al.* (2002) isolated two 27-nor-triterpenoid glycosides, named inermiside I and II (Fig. 2). A

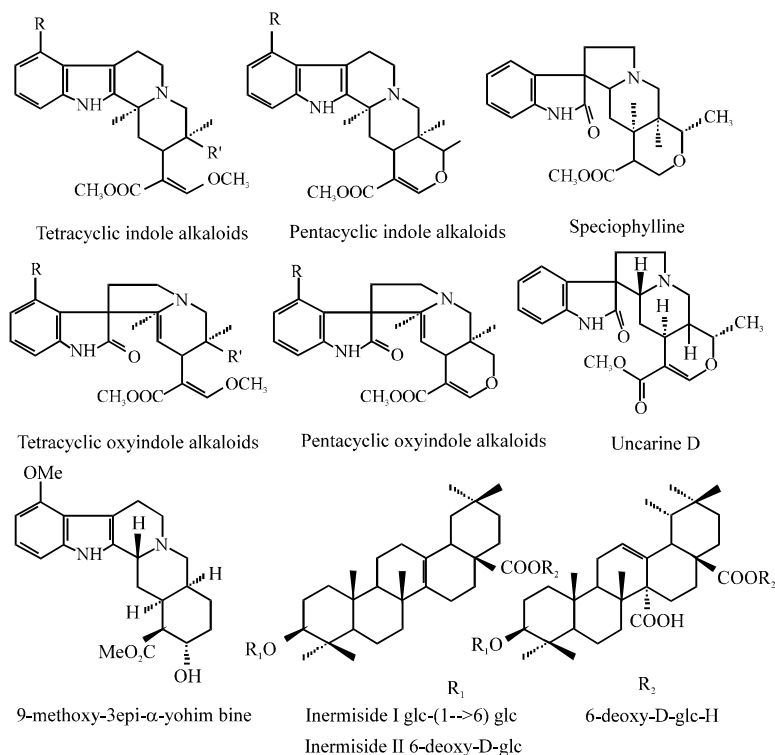


Fig. 2: Chemical structure of inodle alkaloids and terpenoids occurring in Rubiaceae

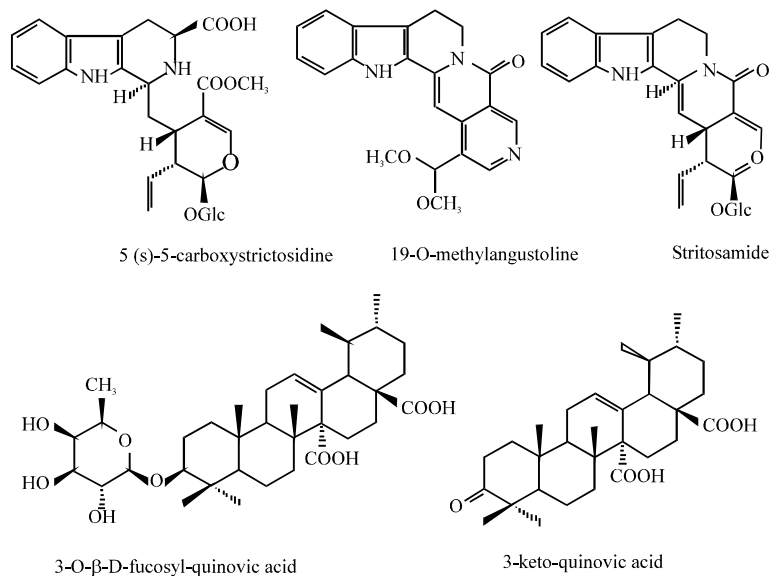


Fig. 3: Chemical structure of compounds isolated from *N. pobeguunii*

detailed phytochemical study of *Pentas longiflora* resulted in the isolation of compounds belonging to chemical families including naphthoquinones, anthraquinones, coumarins and steroids (Fig. 5) (El-Hady *et al.*, 2002). Similarly the investigation of

P. bussei resulted in the isolation and identification of compounds presented in Fig. 6. These were new highly oxygenated naphthohydroquinones e. g., methyl 8-hydroxy-1,4,6,7-tetramethoxy-2-naphthoate methyl 1,8-dihydroxy-4, 6, 7-trimethoxy-2-naphthoate; New

Table 1: Medicinal indications of sub-Saharan Rubiaceae

Scientific names	Local names	Medicinal indications	Region	References
<i>Anthospermum rigidum</i> Eckl. and Zeyh.	Sambulela	Leaves infusion is used to kill pubic lice	Swaziland	Amusan <i>et al.</i> (2007)
<i>Borreria verticillata</i> L.	M'bengbengtuhon	Crushed leaves are directly applied in scarification in case of anaemia	Togo	Adjanohoun <i>et al.</i> (1986)
	Daa si daa dala	Stem bark decoction is used by oral route against infection diseases including sexually transmitted diseases	Guinea	Magassouba <i>et al.</i> (2007)
<i>Breonadia salicina</i> (Vahl) Hepper and Wood	Digel	Ground stem is dispersed in water and drunk against diarrhoea and vomiting in children on breast feeding.	Ethiopia	Flatie <i>et al.</i> (2009)
<i>Canthium glaucum</i> Hiern.	Mhonga, Mronga	The decoction of leaves is used against malaria	Kenya	Nguta <i>et al.</i> (2010)
<i>Canthium multiflorum</i> Schum and Thonn	Laagui Fofana	Decoction of the leaves is used against fever, headache, conjunctivitis, diarrhoea, mycoses and infections	Burkina Faso	Akomo <i>et al.</i> (2009)
<i>Canthium oligocarpum</i> Hiern.	Amshiq	Fresh leaves are crushed and used by dermal application to treat eczema	Ethiopia	Yineger <i>et al.</i> (2008)
<i>Canthiumsetosum</i> Hiern.	Avovoun, Igielera	The leaves decoction is used to treat malaria	Benin	Weniger <i>et al.</i> (2004)
<i>Canthium vulgare</i> Bullock	Ndakalin	Roots bark decoction is used by oral route to treat infectious diseases including sexual transmitted diseases	Guinea	Magassouba <i>et al.</i> (2007)
<i>Canthium zanzibarica</i> Klotzsch.	<i>Omushangati</i>	Root bark is used in the management of Cryptococcal meningitis	Tanzania	Kisangau <i>et al.</i> (2007)
<i>Canthium</i> sp.	NA	Stem is used against ascariasis	Cameroon	Jiofack <i>et al.</i> (2009)
<i>Chassalia kolly</i> Schum.	Diditi	Decoction of leaves is taken orally in case of urinary retention	Togo	Adjanohoun <i>et al.</i> (1986)
<i>Cinchona ledgeriana</i> Moens. ex Trimen	NA	The decoction of the bark is taken orally to treat malaria	Cameroon	Focho <i>et al.</i> (2009)
<i>Coffea arabica</i> L.	Buno	Smoke inhalation of dried leaves and infusion of leaves is taken orally against vomiting	Ethiopia	Mesfin <i>et al.</i> (2009)
	Kahûa/Mûhûa	Boiling root and drinking against cough	Kenya	Njoroge and Bussmann (2006a)
<i>Coffea canephora</i> Pierre ex A. Froehner	NA	Decoction of the flower is used for modification of child birth sex	Cameroon	Jiofack <i>et al.</i> (2010)
(<i>Coffea robusta</i>)	Erwany	Decoction of leaves id drunk to treat Pre-hepatic jaundice	Uganda	Ssegawa and Kasenene (2007)
<i>Craterispermum laurinum</i> Benth.	Gbèghèe	Stem bark decoction is used in the treatment of infectious diseases	Guinea	Magassouba <i>et al.</i> (2007)
<i>Craterispermum schweinfurthii</i> Hiern.	Musekera	Leaves are masticated to give good luck	Uganda	Ssegawa and Kasenene (2007)
<i>Crossoteryx febrifuga</i> (Afzel.) Benth	Golombi	Powder of fruits or bark in maceration is used in case of sterility in women, ovarian cyst, threatened abortion and syphilis	Cameroon	Jiofack <i>et al.</i> (2010, 2009)
	Kèsam	The decoction of stem in association with the bark of <i>Khaya senegalensis</i> by oral administration is antitissuve	Togo	Adjanohoun <i>et al.</i> (1986)
	NA	Preparations of the tree is used for symptomatic relieve of dry cough and for treatment of septic wounds, respiratory infections, fever, dysentery and pain.	Nigeria	Salawu <i>et al.</i> (2008)
<i>Diodia scandens</i> SW.	Belendè	Stem bark decoction treats infectious diseases by oral route	Guinea	Magassouba <i>et al.</i> (2007)
<i>Fadogia agrestis</i> Scheinf ex Hiern	Ehin arigbe	The plant is used in the management of general weakness	Nigeria	Oni (2010)
	Yobè, Dandadanga	Maceration of leaves bark and roots in association with <i>Xylopia aethiopica</i> is used in the treatment of hydrocele. Leaves decoction is used to treat oedema. leaves and root association with <i>Balanites aegyptica</i> and <i>Pteleopsis suberosa</i> is used against rheumatism	Togo	Adjanohoun <i>et al.</i> (1986)
<i>Fadogia cienkowski</i> Schweinf	Baakin gagai	The stem of the plant is used as aphrodisiac	Nigeria	Yakubu <i>et al.</i> (2007)
	NA	Stem bark powder in case of impotence	Cameroon	Jiofack <i>et al.</i> (2010)
<i>Fadogia erythrophloea</i>	NA	Stem in association with <i>Carrisa edulis</i> , <i>Khaya senegalensis</i> and Other plants is used against pinworm K. Schum and K Krause	Togo	Adjanohoun <i>et al.</i> (1986)
<i>Feretia apodanthera</i> Del.	Nassisolok	Leaves decoction is used against constipation of babies. It is used by external application against headache	Togo	Adjanohoun <i>et al.</i> (1986)
	Gigiree	Powdered root bark is mixed with water and used as a wash or the powder is applied against infective wounds	Mali	Inngjerdigen <i>et al.</i> (2004)
<i>Galium asparine</i> Linn	Njikuba	Fresh juice of the whole plant is taken orally after every 4 h for 7 days to fight against gonorrhoea and internal inflammation. Infusion is taken orally in the case of obesity.	Cameroon	Focho <i>et al.</i> (2009)
<i>Galium simense</i> Fresen.	Jiddha	Fresh or dried roots are chewed and used by oral administration to treat abdominal irritation, gastritis, acute stomach illness	Ethiopia	(Yineger <i>et al.</i> , 2008)
<i>Gardenia aqualla</i> Stapl and Hutch	Baou	Stem bark powder in case of impotence, the roots are used against dysmenorrhoea	Cameroon	Jiofack <i>et al.</i> (2010, 2009)
	NA	Leaves and roots and roots of <i>Vitex doniana</i> and the stem of <i>Gewia mollis</i> in decoction by oral route against jaundice	Togo	Adjanohoun <i>et al.</i> (1986)
<i>Gardenia cornuta</i> Hemsl.	Umvalasangweni	Stem concoction is used as emetics	Swaziland	Amusan <i>et al.</i> (2007)
<i>Gardenia erubescens</i> Stapl and Hutch	NA	Leaves associated with bark of <i>Anona senegalensis</i> , <i>Carissa edulis</i> and <i>Securidacta longepedunculata</i> in decoction by oral route is used against ascites	Togo	Adjanohoun <i>et al.</i> (1986)

Table 1: Continued

Scientific names	Local names	Medicinal indications	Region	References
<i>Gardenia imperialis</i> K. Schum	Timbaa	Root bark decoction is used in the case of gonococci and male sexual impotence	Cameroon	Jiofack <i>et al.</i> (2010)
<i>Gardenia sokotensis</i> Hutch and Kew Bull	Kpabnyay Tongologala	Decoction of leaves and bark by oral route is used against hypertension Leaves are mixed with <i>Entada africana</i> roots, leaves and butter of <i>Butyrospermum parkii</i> and the decoction is used as a bath, steam, bath and drunk against internal wounds	Togo Mali	Adjanohoun <i>et al.</i> (1986) Inngjerdingen <i>et al.</i> (2004)
<i>Gardenia ternifolia</i> Schumach. and Thonn.	Fefe, Flifé M'bourétié Buren	Decoction of leaves and bark by oral route is used against hypertension Decoction of roots is used against malaria and jaundice Root bark decoction is used in the treatment of infectious diseases including sexual transmitted diseases	Togo Mali Guinea	Adjanohoun <i>et al.</i> (1986) Maiga <i>et al.</i> (2005) Magassouba <i>et al.</i> (2007)
<i>Gardenia triangacantha</i> <i>Hallea rubrostipulata</i> (K. Schum.) J-F. Leroy	Bao Muzik	Root powder is used against lumbago, cough Decoction of bark is drunk to treat pre-hepatic jaundice, malaria, pregnancy-related illnesses, back ache and Salpingitis Roots decoction is drunk to treat diabetes	Cameroon Uganda	Jiofack <i>et al.</i> (2010) Ssegawa and Kasenene (2007)
<i>Keetia gueinzii</i> (Sond.) Bridson <i>Keetia hispida</i> (Benth.) Bridson (Rubiaceae) <i>Keetia leucantha</i> (K. Krause) Bridson <i>Macrosphyra longistyla</i> <i>Mitracarpus scaber</i> Zucc and Hepper	Mugukuma NA NA Zghidigbo Kpozon, Akpeneteti	The plant is used in the management of malaria Leaves of the plant are used in the management of respiratory diseases The plant is used to treat malaria Roots decoction is used against haemorrhage Pulp and crushed roots applied by cataplasm treat dermatitis	Kenya Ivory Coast Benin Togo Togo	Njoroge and Bussmann (2006b) Kone <i>et al.</i> (2004) Bero <i>et al.</i> (2009) Adjanohoun <i>et al.</i> (1986) Adjanohoun <i>et al.</i> (1986)
	Irawo Ile	The extracted juice from aerial parts is topically applied against skin diseases and on wounds. Internally it is used as an antidote to arrow poison, diarrhoea and dysentery	Nigeria	Jegade <i>et al.</i> (2005)
<i>Mitragyna africana</i> (WILLD.) <i>Mitragyna ciliata</i> Aubrév. and Pellegr. <i>Mitragyna inermis</i> (Willd.) O. Kuntze	NA NA Yéluwun, Leppati NA Orerewa, Etiyayya Sadeene	The plant is used in the treatment of bacterial infection, mental disorder and epilepsy Stem bark extract mixed with <i>Garcinia kola</i> is used for the treatment of trypanosomiasis Decoction of leaves and bark is used against diabetes. The same decoction in association with stem and leaves of <i>Gomphena celosioides</i> and the roots and bark of <i>Cocos nucifera</i> is used against jaundice. The burnt roots powder is used against oedema The decoction of the plant is used against diabetes by oral route The decoction of the stem in association with roots of <i>Stereospermum kunthianum</i> is taken three times daily against diabetes. In association with <i>Kigelia Africana</i> , the decoction of the two plants is taken three times daily to treat hypertension. Leaves, bark and roots of the plant are used in the management of epilepsy The vapour of the decoction of leaves is inhaled to treat boils. The decoction of roots or stem with leaves is applied against small boils	Nigeria Nigeria Togo Ivory Coast Nigeria Mali	Aji <i>et al.</i> (2001) Ogbunugafor <i>et al.</i> (2007) Adjanohoun <i>et al.</i> (1986) Konkon <i>et al.</i> (2008) Igoli <i>et al.</i> (2005), Muazu and Kaita (2008) Inngjerdingen <i>et al.</i> (2004)
<i>Mitragyna stipulosa</i> O. Kuntz <i>Morinda geminata</i> DC. <i>Morinda lucida</i> (Benth.)	Pöpö Dyologban Oruwo, Ufu ogile	Stem bark decoction is used in the treatment of infectious diseases by oral route Leaves decoction is used by oral route in the treatment of infectious diseases Leaves are used to treat fever, malaria treating sore, abscesses, chancre, leprous macular, ringworm. The decoction of the bark of the plant in association with the leaves of <i>Zanthoxylum zanthoxyloides</i> (Lam) Waterm is taken two times daily against diarrhoea. The concoction of the leaves, in association with roots of <i>Parkia biglobosa</i> and leaves of <i>Dracaena perrotetii</i> is taken once daily to treat infertility	Guinea Guinea Nigeria	Magassouba <i>et al.</i> (2007) Magassouba <i>et al.</i> (2007) Lawal <i>et al.</i> (2010a), Oni (2010), Adomi (2008), Igoli <i>et al.</i> (2005), Odugbemi <i>et al.</i> (2007)
<i>Morinda morindoides</i> (Baker) Milne-Redh. <i>Mussaenda arcuata</i> Poir.	NA Mazzi g'abaana	Leaves of the plant is used to treat malaria Root decoction is drunk to treat pre-hepatic jaundice and bathed to baby skin rash	Ivory coast Uganda	Zirih <i>et al.</i> (2005) Ssegawa and Kasenene (2007)

Table 1: Continued

Scientific names	Local names	Medicinal indications	Region	References
<i>Mussaenda elegans</i> Schumach. and Thonn.	Odo omode	NA	Nigeria	Oni (2010)
<i>Mussaenda angolensis</i> Wernh	Ntuabala	Leaves infusion is taken orally against madness and epilepsy.	Cameroon	Focho <i>et al.</i> (2009)
<i>Nauclea didderichii</i> (Merill)	Opepe Opepe, Uburu, Tafashiya	Arthritis, malaria	Nigeria	Lawal <i>et al.</i> (2010a), Kubmarawa <i>et al.</i> (2007)
<i>Nauclea latifolia</i> (Sm)	Merrill Kusia	Decoction of roots is used with bitter against sexual weakness	Ghana	Addo-Fordjour <i>et al.</i> (2008)
	Egbesi, Uche	The plant is used to treat bacterial infections, stomach ache and diabetes mellitus. The fruits are used to treat measles the drug is prepared by roasting the succulent ripe fruits in a pot over a hot firewood flame until the whole fruit is charred. When eaten in excess the fruits act as emetic. In association with <i>Annona senegalensis</i> , maceration or decoction of the mixture of the leaves of the two plants is taken three times daily against dysentery. In association with, <i>Piliostigma thomningii</i> the decoction of leaves treats Filariasis and Chicken pox by oral route. Leaves maceration is taken orally and used to bathe against measles.	Nigeria	Lawal <i>et al.</i> (2010a) Kubmarawa <i>et al.</i> (2007), Gidado <i>et al.</i> (2005), Okwu and Uchenna (2009), Igoli <i>et al.</i> (2005), Odugbemi <i>et al.</i> (2007)
	NA	Eating fruit enhances the digestion	Cameroon	Jiofack <i>et al.</i> (2010)
	Gong, Veveti Kussinyon	Roots decoction in association with <i>Peliocarpa mutica</i> by oral route treats ascariasis. Infusion of roots treats malaria and male infertility. Crushed roots in association with palm nuts are used in beginning of abortion. Powder of burnt roots in association with turtle carapace by oral route treat infant umbilical pains	Togo	Adjanohoun <i>et al.</i> (1986)
	Baro	Decoction of roots is used against abdominal pains and malaria	Mali	Koudouvo <i>et al.</i> (2010) Maiga <i>et al.</i> (2005)
	Badi	Stern bark steep is used in the treatment of infectious diseases including sexually transmitted diseases by oral route	Guinea	Magassouba <i>et al.</i> (2007)
<i>Nauclea pobeguini</i> (Pob. ex. Pell) Petit	NA	The bark is used for threatened abortion	Cameroon	Jiofack <i>et al.</i> (2009)
	Use-ogo	The boiled stem bark is drunk freely against stomach ache	Nigeria	Igoli <i>et al.</i> (2005)
	Doundoukhè	Stern bark decoction is used by oral route to treat infectious diseases	Guinea	Magassouba <i>et al.</i> (2007)
	Tyangol			
<i>Nauclea vanderghouchtii</i>	NA	Leaves and bark decoction and plasters are used to treat dermatitis and wounds	Cameroon	Jiofack <i>et al.</i> (2010)
<i>Oxyanthus speciosus</i> DC	Atidjonu	Roots decoction with palm wine by oral route and crushed roots with salt by external application are used against haemorrhoids	Togo	Adjanohoun <i>et al.</i> (1986)
<i>Oldenlandia monanthos</i> (A.Rich.)Hiern	Matane Ilbisa	Leaves and stem, dried or fresh are decocted and used by dermal application against evil spirits	Ethiopia	Yineger <i>et al.</i> (2008)
<i>Pausinystalia johimbe</i> (K. Schum)	Yohimbe	Bark maceration is used against constipation and sexual weakness	Cameroon	Jiofack <i>et al.</i> (2010)
<i>Pavetta abyssinica</i> Fresen.	Bootha Bekkaa	Crushed fresh leaf homogenized in water drunk and the residue soaks the whole body to treat mitch and evil eye	Ethiopia	Bekalo <i>et al.</i> (2009)
<i>Pavetta corymbosa</i> DC	Sifafati	Stern decoction by oral route is used to treat jaundice and malaria	Togo	Adjanohoun <i>et al.</i> (1986), Koudouvo <i>et al.</i> (2010)
<i>Pavetta crassipes</i> K. Schum and Engl	NA	Decoction of leaves by oral route and bathing treats malaria	Burkina Faso	Sanon <i>et al.</i> (2003b)
	Pagalagbe	Decoction of leaves in association with leaves of <i>Khaya senegalensis</i> is used to treat asthenia by oral route	Togo	Adjanohoun <i>et al.</i> (1986), Koudouvo <i>et al.</i> (2010)
	Kumufida	Stern bark steep by local washing in the treatment of infections	Guinea	Magassouba <i>et al.</i> (2007),
<i>Pavetta owariensis</i> P. Beauv	kpeiwulu	Leaves decoction is used in the treatment of infectious diseases by oral route	Guinea	Magassouba <i>et al.</i> (2007)
<i>Pentas bussei</i> K. Krause	Mdobe, Mudobe	Decoction of the roots is taken as a remedy for gonorrhoea, syphilis and dysentery.	Kenya	Bukuru (2003)
<i>Pentas decora</i> S.Moore	NA	The roots are pounded, mixed with some ghee and rubbed on the pimples.	Kenya	Bukuru (2003)
<i>Pentas hindsioiodes</i> K.Schum	NA	Pounded roots and leaves are soaked in warm water for bathing against scabies	Kenya	Bukuru (2003)
<i>Pentas lanceolata</i> (Forssk.) Deflers	Tigoch	Root and leaf is use to treat lymphadenitis by topical and oral route	Ethiopia	Giday <i>et al.</i> (2009)
<i>Pentas lanceolata</i> (Forssk.) Defl. Subsp. <i>quartiniana</i> (A. Rich.) Verdc.	Mithaa	Crushed fresh root homogenized in water is drunk in case of snake bite.	Ethiopia	Bekalo <i>et al.</i> (2009)
<i>Pentas longiflora</i> Oliver	Nekilango, Segimbe	Roots of are used as a cure both for tapeworm, itchy rashes and pimples; a decoction of the roots is mixed with milk and taken as a cure for malaria.	Kenya	Bukuru (2003), Njoroge and Bussmann (2006b)
	Muhuha	The powder of the roots of this plant mixed with butter is used as an ointment to treat skin diseases, such as scabies and pityriasis versicolor	Rwanda	Puyvelde <i>et al.</i> (1985)

Table 1: Continued

Scientific names	Local names	Medicinal indications	Region	References
<i>Pentas micrantha</i> Backer	NA	Fresh roots are chewed or boiled or pounded and soaked in water and the infusion drunk to treat cough.	Kerya	Bukuru (2003)
<i>Pentas purpurea</i> Oliv.	NA	Women to initiate the menstruation, whereas the juice of the plant is taken as a remedy for headache, fever and rheumatic pains use a decoction of the roots of, mixed with sugar cane.	Tanzania	Bukuru (2003)
<i>Pentas shimperiana</i> subsp. <i>occidentalis</i> (Hook.f.) Verde.	Kamawong	Leaves concoction with bark of <i>Maesa lanceolata</i> is taken orally to treat Hepatitis B liver infections.	Cameroon	Focho <i>et al.</i> (2009)
<i>Pentas shimperiana</i> (A. Rich)Vatke	Dibexxo	Fresh or dry root bark powder mixed with water is taken orally to treat epilepsy. Root bark fine powder is mixed with water given orally for mental illnesses.	Ethiopia	Mesfin <i>et al.</i> (2009)
<i>Pentas zanzibarica</i> (Klotsch) Vatke	NA	The juice of the pounded leaves mixed with a little water, is drunk as a drastic purgative, whereas a decoction of the roots is taken as a remedy for gonorrhoea and syphilis or given to children as a tonic	Kenya	Bukuru (2003)
<i>Psychotria calva</i> Hiem	NA	Bathing with maceration avoiding contact with the head to treat baby growth delay	Togo	Adjanohoun <i>et al.</i> (1986)
<i>Psychotria camptopus</i> Verdc.	Nchaing	Bark concoction with rhizomes of <i>Dissotis longisetosa</i> is taken orally to treat nerves and partial paralysis.	Cameroon	Focho <i>et al.</i> (2009)
<i>Rothmannia octomera</i> Hook	NA	Leaves and bark are used to treat urinary tract infection	Cameroon	Jiofack <i>et al.</i> (2009)
<i>Rothmannia whitfieldii</i> (Dandy)	Buye nla	Fruits are used as febrifuge, analgesic, emetic and for filariasis and dysentery	Nigeria	Lawal <i>et al.</i> (2010b)
<i>Rubia cordifolia</i> L.	Anqis Loitunenei Kasala bakkesi	Diarrhoea Leaves and roots hot decoction per os against upper respiratory tract infections, Decoction of the whole plant is drunk to treat intestinal worms and haemorrhoids and bathed to treat umbilical cord scar healing	Ethiopia Kerya Uganda	Yineger <i>et al.</i> (2008); Nanyingi <i>et al.</i> (2008) Ssegawa and Kasenene, (2007)
<i>Rytigynia beniensis</i> (De Wild) Robyns.	Kalokola	Ash baked crushed leaves are mixed with cow ghee and applied to infected ear to treat septic ear. The decoction of leaves is drunk to treat sore throat	Uganda	Ssegawa and Kasenene, (2007)
<i>Rytigynia canthioides</i> (Benth.) Robyns	NA	The decoction of leaves is used in the treatment of malaria and infectious diseases		Agassounon <i>et al.</i> (2007)
<i>Sarcosaphehus latifolius</i> (Smith)	Egbesi	Leaf decoction is used to treat stomach upset in children in Igbo land. Root infusion is used to treat stomach upset in adults. Leaf and root infusion is given to improve fertility, also as a febrifuge, to treat jaundice and dizziness.	Nigeria	Lawal <i>et al.</i> (2010b)
<i>Spermacoce princeae</i> K. schum.	Npkekepang	Leaves warmed on fire are pulverized and mixed with salt and red oil and taken orally to treat kidney diseases.	Cameroon	Focho <i>et al.</i> (2009)
<i>Spermacoce saticola</i> K. Schum.	Tekwentejo	Juice extract with leaves of <i>Basella alba</i> mixed with white clay is taken orally in case juvenal pregnancies	Cameroon	Focho <i>et al.</i> (2009)
<i>Spermacoce verticillata</i> L.	NA	Leaves of the plant are used in the management of gonorrhoea, abdominal pain and fever	Ivory Coast	Kone <i>et al.</i> (2004)
<i>Uncaria africana</i> G. Don.	Kirobo	Roots decoction is drunk to treat intestinal worms	Uganda	Ssegawa and Kasenene (2007)
<i>Vangueria apiculata</i> K. Schum.	Tugunda	Infusion/decoction of leaves is drunk and bathed to treat constipation, the same decoction is and poison antidote and gives good luck charm when bathed	Uganda	Ssegawa and Kasenene (2007)

NA: Non available data

naphthohydroquinones of the benzochromene type e.g., methyl 5,10-dihydroxy-7-methoxy-3-methyl-3-(4-methyl-3-pentenyl)-3H-benzo[f]chromene-9-carboxylate methyl 5,10-dihydroxy-7-methoxy-1,1,3a-trimethyl-1a,2,3,3a,10c,10d-hexahydro-1H-4-oxacyclobuta[3,4]indeno[5,6-a]naphthalene-9-carboxylate 9-methoxy-2,2-dimethyl-2H-benzo[h]chromene-7,10-diol, 9-methoxy-2-methyl-2-(4-methyl-3-pentenyl)-2H-benzo[h]chromene-7,10-diol and 7-hydroxy-3,3-dimethyl-10-methoxy-3H-benzo[f]chromene-8-carboxylic acid. Further more the already known α -stigmaterol was isolated from the roots of the plant (Bukuru *et al.*, 2002).

The same study conducted on *P. parvifolia* revealed that the chemistry of the plant was mainly similar to that of *P. bussei* (Bukuru, 2003).

Screened biological activities of Rubiaceae plants:

Rubiaceae species have been screened for various biological activities both *in vitro* and *in vivo* using animal models. The main biological activities were antiplasmodial, antibacterial, antiinflammatory and antidiabetic activities.

Antiplasmodial activities: The antimalarial activity is the biological property that received great attention by

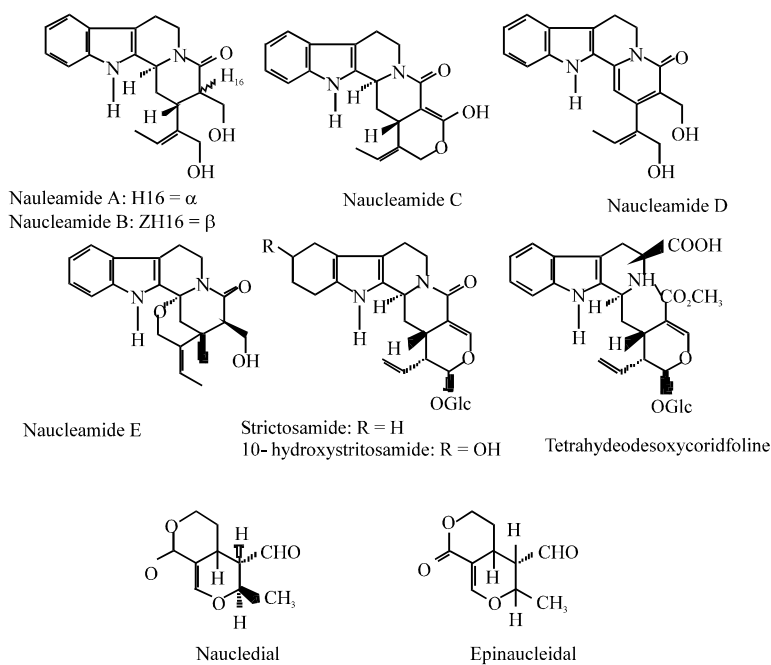


Fig. 4: Chemical structure of compounds isolated from *N. latifolia*

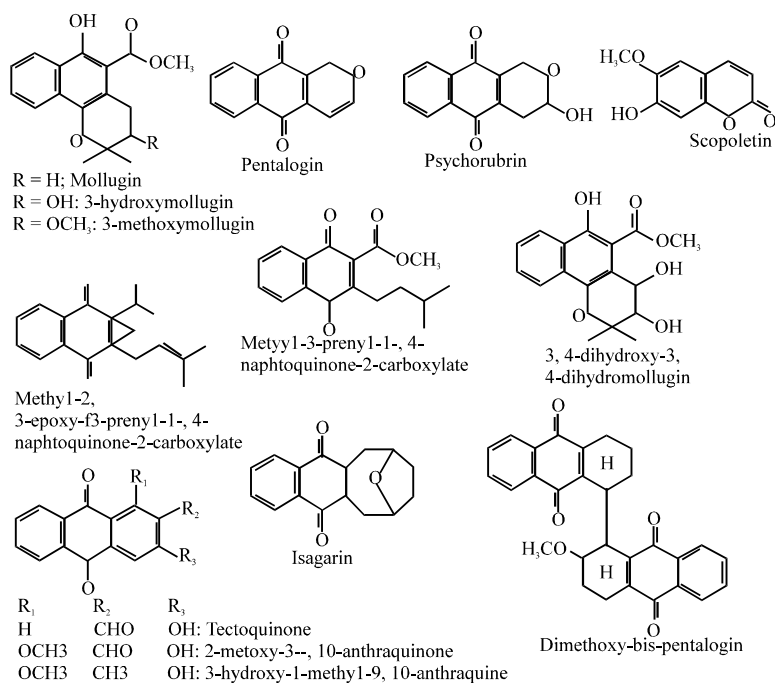


Fig. 5: Chemical structure of compounds isolated from *Pentas longiflora*

scientists interested in Rubiaceae investigation. Extracts were tested on parasite cultures *in vitro* to check if they affect the viability of the main malaria parasites,

Plasmodium falciparum (Pf). Parasites are often fresh clinical isolates obtained from untreated malaria patients or reference Chloroquine-Sensible *Plasmodium*

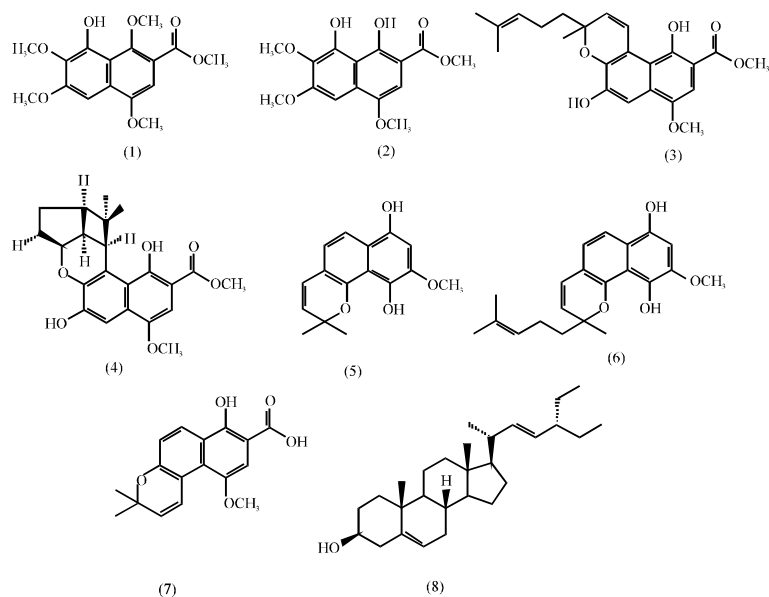


Fig. 6: Chemical structure of compounds isolated from *Pentas bussei*

falciparum (CQSPf) such as strain D6 or Chloroquine-Resistant *Plasmodium falciparum* (CQRPF) strains such as 3D7. Parasites are grown as described by Trager and Jensen, (1976). The quantitative assessment of antimalarial activity *in vitro* is determined by means of the radioisotope technique with incorporation of [3H] hypoxanthine based on the method described by Desjardins *et al.* (1979) and Schulze *et al.* (1997). A light microscopy technique using giemsa-stained smears and colorimetric method that includes 3-acetylpyridine as a substrate for malaria parasite lactate dehydrogenase has been used with the advantage that radio labelled substrates are not required has been developed (Karou *et al.*, 2003; Makler *et al.*, 1993).

A large number Rubiaceae species that are used in TM have been tested *in vitro* for the antimalarial activities. Two main reasons prompted these studies. Firstly, Sub-Saharan Africa possesses many endemic malarious regions and surely the indigenous people have a long experience in antimalarial plant usage. Secondly, since the main antimalarial drug quinine is of Rubiaceae origin, the researchers suppose that similar compounds with similar properties may occur in the family.

Many Rubiaceae crude extracts have been tested with success on *P. falciparum*. Table 2 displays several results recorded with Rubiaceae crude extracts. The antimalarial activity is expressed in terms of IC_{50} , drug concentration causing 50% death of the initial parasite amount. Indeed, (Benoit-Vical *et al.*, 1998) found IC_{50} of

$0.6 \mu\text{g mL}^{-1}$ using aqueous extract of *Nauclea latifolia* on the Columbian multidrug Resistant *Pf*CQRPFcB1, similar IC_{50} value was recorded on Nigerian clinical isolate by Menan *et al.* (2006). However, the ethanol extract of the same plant yielded IC_{50} of $8.9 \mu\text{g mL}^{-1}$ on the same Columbian CQRPF strain (Zirih *et al.*, 2005) (Table 2). Globally IC_{50} values below $5 \mu\text{g mL}^{-1}$ were recorded with chloroform or methylene chloride extracts both on MDRPF or CQSPf or clinical isolates. With *Pavetta crassipes*, chloroform extract yielded 1.02 and $1.23 \mu\text{g mL}^{-1}$ on *Pf*D6 and W2, respectively (Sanon *et al.*, 2003a); 4.36 and $4.82 \mu\text{g mL}^{-1}$ with *Mitragyna inermis* on *Pf*W2 and 3D7 respectively (Traore-Keita *et al.*, 2000). Methylene chloride extract of *Canthium setosum* yielded 2.77 and $4.8 \mu\text{g mL}^{-1}$ on *Pf* (3D7 and K1, respectively) while the methanol extract of the same plant yielded IC_{50} up to $6 \mu\text{g mL}^{-1}$ on the same strains (Weniger *et al.*, 2004). Thus chloroform and methylene chloride appeared to be the best solvents for Rubiaceae antimalarial agent extraction. According to the recorded IC_{50} , *N. latifolia* is the most efficient antimalarial Rubiaceae. Although, interesting IC_{50} values of crude extracts were recorded with other species such as *Enantia pylocarpa* Oliver (Annonaceae) and *Croton lobatus* L. (Euphorbiaceae), Rubiaceae are considered as the main source of antimalarial drugs (Atindehou *et al.*, 2004).

The main chemical group responsible for their antimalarial activity was identified as alkaloids. Indeed alkaloids of *P. crassipes*, *N. latifolia* and *M. inermis* were

tested with success for antiplasmodial activity. Moreover, Ancolio *et al.* (2002) found synergistic effect of the combination of total alkaloids of *M. inermis* and *N. latifolia* on *Pf* D6 and additional effect on *Pf* W2. The activity of Uncarine (Fig. 2) the main alkaloid of *M. inermis* on the CQR*Pf* strain W2 was not correlated with its concentration in the leaves of the plant (Fiot *et al.*, 2005). Mesia *et al.* (2010) investigated for the antimalarial activity of *Nauclea pobeguinii*. Five compounds were isolated in this study: (5S)-5-carboxystrictosidine, 19-O-methylanguistoline, 3-O- β -fucosyl-quinovic acid, 3-ketoquinovic acid and strictosamide (Fig. 4). Only 19-O-methylanguistoline showed a moderate antiplasmodial activity ($IC_{50} = 26.5 \mu\text{g mL}^{-1}$) on a Ghana clinical *Pf*, the other compounds were devoid of antimalarial activity.

Globally Rubiaceae extracts remain active on the clinical isolates according to few screening that used these strains. This is benefit for indigenous people since they are the effective pathogens causing the disease in the concerned zone, in contrast with the reference strains that may have been isolated in other region, thus not reflecting the reality.

The extracts are now being test on animal model for the antiplasmodial activity. Ethanolic extracts of the stem bark of *Crossopteryx febrifuga* was investigated against early, residual and established malaria infections *in vivo* using Swiss albino. Results revealed that an amount of 200 mg kg^{-1} per day appeared to be the effective therapeutic dose for the animals. Indeed, Salawu *et al.* (2008) noted that the administration of 100 mg kg^{-1} of methanolic extract account for 84.7% reduction of parasitemia versus 76.6% for 5 mg kg^{-1} chloroquine phosphate. More recently Mesia *et al.* (2010) found that the aqueous and 80% ethanol extract of *N. pobeguinii* displayed moderate *in vitro* activity with IC_{50} values of 44 and 32 $\mu\text{g mL}^{-1}$, respectively. Daily oral dosing of the extract, containing 5.6% strictosamide, at 300 mg kg^{-1} resulted in 86% reduction of parasitaemia in the 4-day *Plasmodium berghei* mouse model and 75% reduction in the *Plasmodium yoelii* N67 model. Prolonging oral dosing to 2 \times 5 days, with an interval of 2 days and oral administration induced 92% reduction of parasitaemia and a mean survival time of 17 days. Strictosamide, the putative active constituent, may be metabolically activated in the gastrointestinal tract after oral administration.

Antibacterial activity: The crude extracts of the Rubiaceae and their subsequent partitioning gave fractions exhibited a broad spectrum antibacterial activity on several microbial pathogens including reference strains

and clinical isolates. Indeed, reference strains such as *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922 are often used. The extracts are tested using the agar diffusion assay or the broth microdilution assay. In the first case the antimicrobial activity is expressed as inhibition zone diameter around the disk or the well. Using this assay, (Adomi, 2008) screened the aqueous extract of *Morinda lucida*. The recorded inhibition zone diameters with 1000 mg mL^{-1} extract varied from 14 to 25 mm with gram positive and gram negative bacteria (Table 3). The agar diffusion assay is efficient for the quantification of the antimicrobial activity; however, the solubility and the diffusion of some extract in the agar medium can be a limiting factor. Hence, some authors prefer the microdilution assay rather than the agar diffusion. The microdilution allows expressing the activity in term of drug concentration killing microorganisms. The Minimal Inhibitory Concentration (MIC) is then recorded as lowest extract concentration demonstrating no visible growth in the broth and the Minimal Bactericidal Concentration (MBC) as a lowest extract concentration killing 99.9% of bacterial inocula. MBC/MIC ratios can be calculated to appreciate the effect of the extract on the tested microorganisms; indeed MBC/MIC ratios greater than 1 indicate microbiostatic effect of extract, while ratios under 1 indicate microbicide effects of extracts (Karou *et al.*, 2005).

Using the broth microdilution assay, Asase *et al.* (2008) found good inhibition of both gram positive and gram negative bacteria by the acetone extract of *Mitragyna inermis* rather than the n-hexane extract. Okoli and Iroegbu (2004) combined the microdilution and the agar diffusion to screen the antibacterial activity of ethanolic and aqueous extracts of *N. latifolia*. Four references strains, *Staphylococcus aureus* ATCC 12600, *Bacillus subtilis* ATCC 6051, *Pseudomonas aeruginosa* ATCC 10145 and *Escherichia coli* ATCC 11775; in addition with clinical isolates of *S. aureus* and *E. coli* were tested. The ethanol extract was found to be more active on the tested microorganisms. In the agar diffusion assay the inhibition zone diameters recorded ranged from 6.60 to 17 mm while MIC varied from 12.50 to up to 50 mg mL^{-1} in microdilution assay (Table 3). Further, the extract was found to be bacteriostatic to both Gram positive and Gram negative strains. Working on the same plant for the same purposes, Okwori *et al.* (2008) found that the alcoholic and aqueous extracts exhibited both bactericidal and bacteriostatic activities on gram positive bacteria while the gram negative ones seemed to resist to the extract. Another way to appreciate the antimicrobial activity is the

Table 2: Antimalarial activities of sub-Saharan Rubiaceae

Plants	Extraction solvent: IC ₅₀ of antimalarial plants (µg mL ⁻¹) (<i>Plasmodium falciparum</i> strain)	IC ₅₀ of cytotoxicity test (µg mL ⁻¹) test (µg mL ⁻¹)	Selectivity index: ratio cytotoxicity/activity	References
<i>Canthium multiflorum</i>	Acetone: 16.62 (Burkina Faso*)	Nt	-	Akomo <i>et al.</i> (2009)
	Methanol: 4.69 (Burkina Faso*)	Nt	-	
	Water: 9.49 (Burkina Faso*)	Nt	-	
<i>Cathium setosum</i>	Methylene chloride: 2.7 (3D7); 4.2 (K1)	Nt	-	Weniger <i>et al.</i> (2004)
	Methanol: 6.21(3D7); >20 (K1)	Nt	-	
<i>Crossopteryx febrifuga</i>	Dichloromethane: 56.85 (3D7)	Nt	-	Jansen <i>et al.</i> (2010)
	Methanol: 100 (3D7)	Nt	-	
	Water: 100 (3D7)	Nt	-	
<i>Feretia apodanthera</i>	Methanol: <25(W2)	>25(TPH1 cells)	-	Ancolio <i>et al.</i> (2002)
<i>Gardenia sokotensis</i>	Dichloromethane: 14.01 (3D7); 6.75 (W2)	12.67 (WI-38 Human fibroblasts)	0.9 (3D7); 1.9 (W2)	Jansen <i>et al.</i> (2010)
	Methanol: 27.62 (3D7)	Nt	-	
	Water: >100 (3D7)	Nt	-	
<i>Keetia leucantha</i>	Dichloromethane:11.3 (3D7); 15.8 (W2)	50.5 (J774); >100 (W128)	>8.8 (W138/J774)	Bero <i>et al.</i> (2009)
<i>Mitragyna inermis</i>	Water: >500 (W2, 3D7)	Nt	-	Traore-Keita <i>et al.</i> (2000)
	Methanol: >100 (W2, 3D7)	Nt	-	
	Chloroform: 4.36 (W2); 4.82 (3D7)	Nt	-	
	Water: 1.59 (FcM29-Cameroon); 57.45 (Cameroon FcB1-Columbia); 2.43 (Nigeria*)	Nt	-	
	Methanol: >25 (W2)	>25(TPH1)	-	
<i>Morinda citrifolia</i> (Benth)	Chloroform : >25 (W2)	31.5 (TPH1)	-	Addae-Kyereme <i>et al.</i> (2001)
<i>Morinda morindoides</i>	Methanol : >100 (K1)	>250 (BrSh)	-	
<i>Nuclea diderrichii</i>	Ethanol: 3.54 (K1)	42.2 (MRC-5 mammalian cells)	3.6	Atindehou <i>et al.</i> (2004) Zirih <i>et al.</i> (2005) (Mustofa <i>et al.</i> (2000)
	Ethanol: 11.6 (FcB1/Colombia)	Nt	-	
	Water: 312.14 (FcM29-Cameroon); 434.32 (FcB1/Columbia); >500 (Nigeria*)	Nt	-	
<i>Nuclea latifolia</i>	Water: 0.6 (FcB1/Columbia)	400 (Human melanoma)	666.67	Benoit-Vical <i>et al.</i> (1998) Menan <i>et al.</i> (2006)
	Water: 0.7 (FcB1); 1.3 (FcB1); 1.7 (FcB1)			
	Water: 0.7 (Nigerian*) Water: 0.8 (Nigerian*)			
	Ethanol : 8.9 (FcB1/Columbia) (Zirih <i>et al.</i> , 2005)	>50 (L-6 and MRC-5 mammalian cells) >5.6 (L-6 and MRC-5 mammalian cells)		
	Water: >500 (W3, 3D7)	Nt	-	
<i>Nuclea pobeguini</i>	Methanol: >250 (W2, 3D7)	Nt	-	Mesia <i>et al.</i> (2010)
	Chloroform 5.36 (W2); 6.20 (3D7)	Nt	-	
	Water: 44 (Ghana*)	>64 (MRC-5 mammalian cells)	-	
<i>Pavetta corymbosa</i>	Ethanol: 32 (Ghana*)	>64 (MRC-5 mammalian cells)	-	Weniger <i>et al.</i> (2004)
	Dichloromethane: >20 3D7); 5.54 (K1)	Nt	-	
<i>Pavetta crassipes</i>	Methanol: >20 (3D7); 1.7.50 (K1)	Nt	-	Sanon <i>et al.</i> (2003a)
	Chloroform: 1.02 (D6)	Nt	-	
K. Schum.	Chloroform: 1.23 (W2)	Nt	-	Gansane <i>et al.</i> (2010)
<i>Sarcocephalus latifolius</i>	Methanol: >50 (W2)	>125 (K562S)	-	
	Water: >50 (W2)	>125 (K562S)	-	
<i>Rothmannia longiflora</i>	Alkaloids: >50 (W2)	90.2 (K562S)	-	(Addae-Kyereme <i>et al.</i> (2001)
	Dichloromethane: >50 (W2)	52.9 (K562S)	-	
	Methanol: >100 (K1)	>250 (BrSh)	-	
<i>Vangueria acutiloba</i> Robyns	Methanol: 13.36 (D6); 33.98 (3D7)	661.5 (Vero E6)	49.5 (D6)	Muthaura <i>et al.</i> (2007)
	Water:178.14 (D6); >250 (3D7)	3457 (Vero E6)	-	

*: Clinical isolates of *Plasmodium falciparum*; Nt: Not tested; -: Non available data

time-kill assay. This allows monitoring the decrease of bacterial amount as a function of the time. The assay consists of exposing bacteria to a drug concentration greater than the MIC and to perform cell enumeration at regular time interval. This assay was used by Akomo *et al.* (2009) who demonstrated that no viable microorganism remained in the medium for *Enterococcus*

faecalis CIP 105150 and *Escherichia coli* CIP 105182 after 9 h and 11 h exposition to 1.25 and 2.50 mg mL⁻¹ methanol extract of *Canthium multiflorum* respectively. Similarly, Zongo *et al.* (2009) found that 9 h exposition to 3 mg mL⁻¹ alkaloids of *M. inermis* killed the total inoculums.

According to results recorded with Rubiaceae, main authors found greatest activity of ethanol extracts,

Table 3: Antimicrobial activities of sub-Saharan Rubiaceae

Plants	Extract	Gram positive	Gram negative	Fungi	References
<i>Canthium multiflorum</i>	Methanol	0.312 to 2.5 mg mL ⁻¹	0.625 to 1.25 mg mL ⁻¹	Nt	Akomo <i>et al.</i> (2009)
<i>Keetia hispida</i>	Ethanol	0.023 to 0.375 mg mL ⁻¹	Nt	Nt	Kone <i>et al.</i> (2004)
<i>Mitragyna inermis</i>	alkaloids	0.625 to 1.25 mg mL ⁻¹	0.625 to 2.5 mg mL ⁻¹	Nt	Zongo <i>et al.</i> (2009)
<i>Morinda lucida</i> Benth	Water	14mm (1000 mg mg ⁻¹)*	0 to 25mm (1000 mg mL ⁻¹)*	Nt	Adomi (2008)
<i>Nauclea latifolia</i>	Ethanol	0.5 mg mL ⁻¹	1 mg mL ⁻¹	1 mg mL ⁻¹	Kubmarawa <i>et al.</i> (2007)
	Water	100 mg mL ⁻¹	100 mg mL ⁻¹	Nt	Okwori <i>et al.</i> (2008)
	Chloroform	150 mg mL ⁻¹	150 mg mL ⁻¹	Nt	
	Diether	150 mg mL ⁻¹	150 mg mL ⁻¹	Nt	
	Ethanol	12-50 mg mL ⁻¹	6.25 to <50 mg mL ⁻¹	Nt	Okoli and Iroegbu (2004)
	Water	12.5 to <50 mg mL ⁻¹	<50 mg mL ⁻¹	Nt	

Data are the value of minimal inhibitory concentration for broth microdilution assay and values of inhibition zone diameter in for agar diffusion assay *: Assay performed using agar diffusion method, Nt: Not tested

showing the strong capacity of this solvent to extract the antibacterial compounds of Rubiaceae. This is in accordance with literature reports; in fact phenolic compounds are the main chemical group responsible for the antimicrobial activity of plants including Rubiaceae and it well known that acetone or alcohol are the solvents of choice for the extraction of such components. Referring to Table 3 which displays some results recorded with Rubiaceae, available data do not show clearly whether the gram positive bacteria or the gram negative ones are more susceptible to the extract; but in general, the gram positive ones are found to be most susceptible (Karou *et al.*, 2006). This selective susceptibility may be due to the biochemical composition of the cell wall. The gram positive bacteria have only an outer peptidoglycan layer which is not an effective barrier (Scherrer and Gerhardt, 1971). The Gram-negative bacteria have an outer phospholipidic membrane that make the cell wall impermeable to lipophilic solutes, while the porines constitute a selective barrier to hydrophilic solutes with an exclusion limit of about 600 Da (Nikaido and Vaara, 1985).

Cytotoxic activity: Medicinal plants are often assumed to be efficient and safe; however, there are some reports on poisonings consecutive to plant based-medicine administration (Fennell *et al.*, 2004). Thus renewed interest is accorded to toxic effects of plant extracts. Many assays have been used to evaluate the toxicity plants. The main assays are based on the reduction of cell amount in cell culture and the results are expressed as IC₅₀ the drug concentration killing 50% of the cells. In a screening of some Nigerian antimalarial plants for *in vitro* cytotoxicity using brine shrimp IC₅₀ of 2.6, 383.9 and 9368 µg mL⁻¹ were recorded for *Morinda lucida* bark, *Morinda lucida* leaves and *Nauclea latifolia* bark extracts respectively, versus 449.1 µg mL⁻¹ for chloroquine phosphate. Indeed *M. lucida* was found to be less toxic than chloroquine phosphate and *N. latifolia* (Ajaiyeoba *et al.*, 2006). The methanol extract obtained from *Feretia apodanthera* leaves, fractionated

by silica gel chromatography and tested on TPH1 cells exhibited lower cytotoxicity with an IC₅₀ between 20 and 40 times higher than the IC₅₀ obtained on *P. falciparum*. The results of the effect on cell cycle and protein synthesis showed a decrease of cells in S phase and an accumulation in G2M phase, probably due to an inhibition of total protein synthesis Ancolio *et al.* (2002). Moreover using *Allium cepa* test, (Akintonwa *et al.*, 2009) demonstrated that *Morinda lucida* at higher concentrations exhibited mitostatic effect and this may be due to the effect of the plant on the mitotic cell division process. However, the results of modified Ames test showed alteration of at least three biochemical characteristics of the normal organism, thus demonstrating mutagenicity.

Scientists now often associate the toxicity tests when looking for a particular biological activity; although some reports are systematically focussed on toxicology studies. The antimalarial activity is the main activity that has been associated with the cytotoxic activity. The activities are conducted on human cell or mammalian cell lines. Great IC₅₀ values have been recorded with crude extracts. Benoit-Vical *et al.* (1998) found 400 µg mL⁻¹ with aqueous extract of *N. latifolia* on human melanoma cells. According to Table 2, all IC₅₀ recorded were up to 40 µg mL⁻¹ except for the dichloromethane extract of *Gardenia sokotensis* which was found to be very toxic on W1-38 human fibroblasts (Jansen *et al.*, 2010). The selective index is calculated by the ratio of the IC₅₀ and the IC₅₀ of the antimalarial test. This suggests the opportunity to continue the study with the fractionation of the extract.

Rubiaceae are continuously screened for their safety to ensure rational use in folk medicine. Some studies used animal models to better understand the *in vivo* manifestations of the toxic effects of the plants. Globally all results demonstrated the safety of tested Rubiaceae species supporting the continuous use of these plants in folk medicine. The *in vivo* toxicity of *Mitracarpus scaber*, *Mitragyna inermis*, *Morinda lucida* and *Crossopteryx febrifuga* are well documented. Looking for the possible

hepatoprotective effect of *Mitracarpus scaber* decoction on carbon tetrachloride-induced acute liver damage in the rat Germano *et al.* (1999) found that treatment with the extract resulted in significant hepatoprotection against carbon tetrachloride-induced liver injury both *in vivo* and *in vitro*. *In vivo*, *Mitracarpus scaber* pretreatment reduced levels of serum Glutamate-Oxalate-Transaminase (GOT) and serum Glutamate-Pyruvate-Transaminase (GPT) previously increased by administration of carbon tetrachloride. *In vitro* the addition to the culture medium of *Mitracarpus scaber* extracts significantly reduced glutamate-oxalate-transaminase and lactate dehydrogenase activity resulting in a good survival rate for the carbon tetrachloride-intoxicated hepatocytes. A similar study previously conducted with *Mitragyna inermis* alkaloids extract resulted in the isolation of speciophylline as the main alkaloids of the leaves of the plant. The biological investigation showed that both speciophylline and total alkaloids extract were found to enhance biliary flow in female Wistar rats. In addition total and conjugated bilirubin were increased significantly, while GOT, GPT, alkaline phosphatase and total cholesterol decreased indicating an obvious hepatic cellular activity induced by the alkaloids without cellular necrosis. The authors concluded that alkaloid extract and particularly speciophylline may act as choleric drugs (Toure *et al.*, 1996).

Acute and chronic toxicity of the hydroethanolic extract of *Mitragyna inermis* leaves were performed in rats, according to the recommendations the French Drug Office. No animal died and no behavioral signs of acute toxicity were observed after two dosages (300 mg kg⁻¹ and 3 g kg⁻¹) were administered to animals. In addition, no changes in body weight and no macroscopic abnormality in examined organs after 28 days chronic toxicity follow up (Monjanel-Mouterde *et al.*, 2006). However, Konkon *et al.* (2008) demonstrated that the administration of 300, 2000 and 5000 mg kg⁻¹ aqueous extract of leaves of the plant was lethal for the inoculated animals. Indeed the aqueous leaf extract of *M. inermis* should be used with some degree of safety by oral route. The maximal dose seems to be 300 mg kg⁻¹. However, the methanolic extract of *C. febrifuga* seemed to be less toxic, since the extract did not produce severe toxicity at dose lower than 500 mg kg⁻¹ body weight (Salawu *et al.*, 2009). Recently, the aqueous extract of *N. pobequinii* was found to be non toxic in mice model. Thus levels of creatinin, urea, GOT and GPT remained unchanged after treatment; in addition, no acute toxicity was observed in mice and no significant macroscopic or microscopic lesions were observed in organs neither after a single 2 g kg⁻¹ oral dose, nor after 4 weekly doses (Mesia *et al.*, 2010).

Antioxidant activity and anti-inflammatory activity:

Antioxidant and radical scavenging properties of plants are subject to intensive research. Indeed Rubiaceae are continuously screened for these pharmacological properties. Maiga *et al.* (2006) found that the methanol extract of the seed of *C. febrifuga* had a moderate free radical scavenging using the stable free radical diphenylpicrylhydrazyl. However, the lipophilic fraction that was found to have no scavenging activity highly inhibited the soybean 15-lipoxygenase. In a similar study, Dongmo *et al.* (2003) demonstrated that the methanolic extract of *Mitragyna cilita* had not inhibitory effect on the 5-lipoxygenase, although the extract reduced carrageenin-induced paw oedema in rat showing an effective anti-inflammatory effect. The author suggested that the active compounds may exert the activity on another sites implicated in the anti-inflammatory process. This was confirmed by the observed analgesic activity of the same methanol extract through significant increase of the threshold of sensitivity to pain in the rats with salicylates as standard analgesic. Similar results were recorded with methanolic extract of *C. febrifuga*; indeed the extract significantly diminished acetic acid-induced writhes in mice and increased the pain threshold in rats dose-dependently. It also demonstrated significant antipyretic and anti-inflammatory activities in mice and rats in a dose-related manner (Salawu *et al.*, 2008). Aqueous extract of the root bark of *N. latifolia* was evaluated for its anti-nociceptive, anti-inflammatory and anti-pyretic activities in mice and rats. The results showed that the extract significantly attenuated writhing episodes induced by acetic acid and increased the threshold for pain perception in the hot-plate test in mice, dose-dependently. The product also remarkably decreased both the acute and delayed phases of formalin-induced pain in rats and also caused a significant reduction in both yeast-induced pyrexia and egg-albumin-induced oedema in rats. These effects were produced in a dose-dependent manner (Abbah *et al.*, 2010).

Antidiabetic activity: Following the traditional usage, some Rubiaceae species including *Morinda lucida* and *Nauclea latifolia* have been screened for antidiabetic activity. Gidado *et al.* (2008) screened *N. latifolia* for its fasting blood glucose lowering effect in normoglycaemic and streptozotocin-diabetic Wistar albino rats. The aqueous and ethanolic extracts significantly lowered the fasting blood glucose levels of the diabetic rats in a dose-dependent manner; however, the aqueous extract did not significantly lower the glucose levels of normoglycaemic rats. The hypoglycaemic and antihyperglycaemic potentials of the aqueous and

ethanolic extracts were comparable to that of glibenclamide supporting the traditional use of the plant in the treatment of diabetes mellitus. Olajide *et al.* (1999) previously found that the methanol extract of the *Morinda lucida* exerted a dose-dependent hypoglycaemic activity in normal rats within 4 h after oral administration. In hyperglycaemic rats, the extract produced a significant anti-diabetic effect from day 3 after oral administration. Furthermore, the aqueous extract of the roots of the plant, exhibited potent hypoglycaemic effects in both normoglycemic and alloxan-induced diabetic mice by oral administration. This effect was dose-dependent and more potent than that observed with chlorpropamide (1-(p-chlorobenzene-sulphonyl)-3-propylurea) (Kamanyi *et al.*, 1994).

Other biological activities: Rubiaceae species have been screened for many other pharmacological properties including antispasmodic, antihyperthermic, anticonvulsive and antipyretic activities. The *in vitro* antispasmodic activity of *Morinda morindoides* leaves extracts was evaluated on acetylcholine and the depolarized KCl solution induced contractions on guinea-pig isolated ileum. The issue of the study revealed that *M. morindoides* leaves possess spasmogenic and spasmolytic properties that can at least explain and support its traditional use against constipation and diarrhoea, respectively (Cimanga *et al.*, 2010). This property was already described for *C. febrifuga* and *N. latifolia*. Polyphenol extracts of these plants exhibited more than 70% inhibition of contractions on isolated guinea-pig ileum; in addition to inhibit *Entamoeba histolytica* growth (Tona *et al.*, 2000).

Extract *Morinda lucida* was screened with 12 other Congolese medicinal plants for their antidrepanocytary activity through the ability of the extracts to normalize the SS blood erythrocytes. The results showed normalization rate (45%) of the methanol extract of leaves and bark, however, the aqueous extract failed in normalizing the cells (Mpiana *et al.*, 2007). The leaf extract of the plant investigated for possible antispermatogenic activity did not cause any changes in body and somatic organ weights, but significantly increased the testis weight. The sperm motility and viability and the epididymal sperm counts of rats treated for 13 weeks were significantly reduced. Sperm morphological abnormalities and serum testosterone levels were significantly increased. There were various degrees of damage to the seminiferous tubules. The extract also reduced the fertility of the treated rats by reducing the litter size. Reversal of these changes, however, occurred after a period of time (Raji *et al.*, 2005). Similar effects were observed with the

aqueous extract of *Fadogia agrestis*. In addition, the extract induced significant increases in the prostrate/body weight ratio, citric acid concentration and acid phosphatase activity at all the dose regimen and only at 50 and 100 mg kg⁻¹ body weight dose regimen for calcium and phosphate, while pH was not altered. There was no recovery on prostatic parameters except the citric acid content at 18 mg kg⁻¹ body weight (Yakubu *et al.*, 2007).

The decoction from the bark of *N. latifolia* tested for its anticonvulsant, anxiolytic and sedative activity in mice was found to increase the total sleep time induced by diazepam in mice model and to protect mice against maximal electroshock-, pentylenetetrazol- and strychnine-induced seizures. In addition, turning behaviour induced by N-methyl-D-aspartate was inhibited. The extract antagonized, in a dose-dependent manner, stress-induced hyperthermia and reduced body temperature (Ngo Bum *et al.*, 2009). The anthelmintic efficacy of aqueous extract of stem bark of the plant was investigated in sheep with natural acute and sub-acute parasitic gastro-enteritis due primarily to mixed nematode species. Graded doses of the extract improved haemoglobin and leucocytosis values in worm-infected sheep and significantly reduced faecal egg counts in infected animals. The percentage reduction by 1600 mg kg⁻¹ of the extract was comparable to that of 5 mg kg⁻¹ of albendazole (Ademola *et al.*, 2007; Onyeyili *et al.* (2001). Njamen *et al.*, (2008) evaluated the *in vitro* estrogenic activity of the methanol extract of the plant using the yeast test-system. The extract yielded interesting activity and was then further investigated on alkaline Phosphatase induction in Ishikawa cells. The results showed significant stimulatory effects at 10 and 100 mg mL⁻¹ doses. *In vivo* the extract had not effect on the uterine epithelial height on ovariectomised rats, although the administration of 200 mg kg⁻¹ increased vaginal epithelial height by 15.64%, confirming the estrogenic activity of the plant.

The evaluation of the neuropharmacological effects of the aqueous extract of *N. latifolia* root bark in rodents were assayed by measuring the effects on the Spontaneous Motor Activity (SMA), exploratory behaviour, pentobarbital sleeping time, apomorphine-induced stereotypic behaviour and motor coordination (rota-rod performance). The extract significantly decreased the SMA and exploratory behaviour in mice and prolonged pentobarbital sleeping time in rats dose-dependently. The intensity of apomorphine-induced stereotypy was also attenuated dose-dependently in mice, but no effect on motor coordination as determined by the performance on rota-rod was recorded indicating the presence of psychoactive substances in the aqueous extract of the root bark of *N. latifolia* (Amos *et al.*, 2005).

Looking for possible hypotensive, cardiotropic and vasodilatory properties *M. inermis*, Ouedraogo *et al.* (2004) found that the aqueous extract of the plant produced a concentration-dependent *ex vivo* increase in cardiac contractile response and coronary flow but did not modify heart rate in the rat. Adverse effects were observed with the extract of *N. latifolia* which was found to reduce systolic, diastolic and mean arterial pressure in normotensive and in one kidney one clip hypertensive rats in a dose dependant manner. The extract also reduced the heart rate of normotensive and hypertensive rats. The reduction in blood pressure and heart rate was not affected by prior treatment with atropine or promethazine (Nworgu *et al.*, 2008). In the case of *M. inermis*, the extract produced relaxation in isolated porcine coronary artery at concentration up to 3 mg mL⁻¹ that was exclusively dependent on the presence of endothelium. This relaxation involved partial depolarization and NO synthase inhibitor-sensitive mechanisms but was not sensitive to the blockade of cyclo-oxygenase pathway. However, the relaxant effect was not dependent on the presence of endothelium in rat tail artery.

CONCLUSION

The present review discussed the significance of Rubiaceae as a valuable source of new leads for medical purposes. Reports for biological activity of Rubiaceae species are numerous, but phytochemical investigations have been conducted only on a few species such as *N. latifolia*, *N. pobeguinii*, *M. inermis*, *P. bussei* and *P. longiflora*. Indole alkaloids seem to be typical of the family as they were detected in several species. Correlation between the traditional uses and the pharmacological activities has been observed and described in the present review. Significant activity of the alkaloids isolated from certain species against *Plasmodium* has been reported. Crude extracts of these plants have been found to have antibacterial, antidiabetic, anti-inflammatory, antioxidant activities and the lack of toxicity have been reported in some cases. However, referring to current situation, HIV is the main major public health problem and much effort is made by scientists in this topic. HIV control efforts may include the attempt to seek for effective agents able to kill the virus itself, agents able to boost up the immune system and agents able to treat opportunistic infections. According to online published data Rubiaceae exhibited antimicrobial activity against several pathogens including AIDS opportunistic ones. Indeed, antimicrobial property of Rubiaceae may be useful tool in treating opportunistic infection. Therefore, the new challenge is the investigation for immunomodulatory and antiviral activities of Rubiaceae, considering the lack of published data in this matter.

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