Journal of
Plant Sciences

Vol. 5, No. 1 March 2011 p. 7-14
ISSN No. 0974 6927

Antifungal and antiprotozoal activity of some members of Rubiaceae-a review

Katyayani Dutta Choudhury*, Manabendra Dutta Choudhury
Ethnobotany & Medicinal plant research laboratory, Department of Life Science and Bioinformatics, Assam University, Silchar, 788011.

Abstract
The Rubiaceae is the largest and most popularly known woody plant family in the wet tropics and subtropics. It contains approximately 13,200 species in 660 genera, some of the species having ethno medicinal significance and reported to possess a wide range of medicinal practices. Some of the important genera belonging to the family are *Coffea, Rubia, Cinchona, Uncaria, Gardenia, Hedyotis, Morinda, Mitragyna, Oldenlandia, Ixora*, etc, having used by traditional peoples in curing various diseases and reported to be used as antimicrobials, antioxidants, antifeedants, analgesics, antivenomous and also found to play roles in hepatoprotection and activity against tumour formation.
The review paper deals with the present status of the family Rubiaceae being used as antifungals and antiplasmoidals and the chemical constituents investigated till date showing bioactive principles against various pathogenic fungi and protozoan. Literature survey reveals that only 35 plants have been investigated to possess antifungal properties and 22 have been reported to be used as antiplasmoidals out of 660 genera of Rubiaceae.

Keywords: Rubiaceae, antifungal, antiplasmoidal, protozoan

Although Rubiaceae are found on in every major region of the world except for continental Antarctica, diversity is highest in the humid tropics (Davis *et al* 2009). The Rubiaceae is one of the five largest plant families. According to the World Rubiaceae checklist, 660 genera and 13,200 species have been recognised (Davis *et al* 2009). A large number of members belonging to the family are ethno medicinally important and also reported to have a wide variety of biological activities such as antimicrobial, antimalarial, hepatoprotective, antioxidant, and so many other interesting biological activities. Investigations have been carried out on various members of this family regarding their antimicrobial activities and found to be active against large number of pathogenic microorganisms. Some of the important genera of this family are *Cinchona, Coffea, Randia, Ixora, Borreria, Gardenia, Morinda, Mitragyna, Uncaria, Mussaenda, Nauclea, Psychotria, Rubia*, etc which have been reported to possess antimicrobial properties and their ethnomedicinal practices are well documented.

Cinchona or quinine bark is one of the rainforest's most famous plants and most important discoveries. Out of about 40 species of plants of *Cinchona* the most important are *C. officinalis, C. succirubra, C.calisaya* and *C. ledgeriana*. The alkaloids obtained from the bark extracts of *Cinchona sp* used for curing malaria, have a long historical background. By 1820, researchers were able to isolate quinine from the bark. This led to the commercial production of quinine starting 1827. Quinine was the principal remedy for malaria until World War I. Soon thereafter pharmacologists created a successful synthetic drug, chloroquinine. However, from the 1960s on, resistance of the malarial parasite to chloroquinine, the synthetic drug has brought about a need for quinine once again in preventing and treating malaria. Cinchona in a highly processed form, along with quinine and quinidine, are commonly used in drug therapies for heart disease (Substances & Homeopatic Remedies, Homeovision. info@homeovision.org). The concentrations of quinine alkaloids in the bark extracts of *C. officinalis, C. calisaya, C. ledgeriana* and *C. succirubra* are 1.75-10.6%, 4%, 4.13% and 0.82-1.37% respectively and their antimalarial actions are concentration and species dependant (Kanjilal 2005). Two new alkaloids, myrionidine and myrionamide obtained from *Myrioneuron nutans*. Showed a significant antimalarial activity against *Plasmodium falciparum* (Pham *et al* 2008).

Some important Phytochemicals obtained from *Coffea arabica* and *C. robusta* such as caffeine, organic acids, phenols and aromatic compounds are reported to have antimicrobial activity. Caffeine reduces the growth rate of some fungus by inhibiting the production of their characteristic mycotoxins (Buchanan *et al* 1983).

Morinda tinctoria is widely distributed throughout Southeast Asia, commercially known as Nunaa, is indigenous to tropical countries and is considered as an important folklore medicine. In the traditional system of medicine, leaves and roots are used as astringent, deobstrent, emmengogue and to relive pain in the gout (Kumaresan & Saravanan 2009). It has been reported to

*Corresponding author:
E-mail: katyayanidc@gmail.com

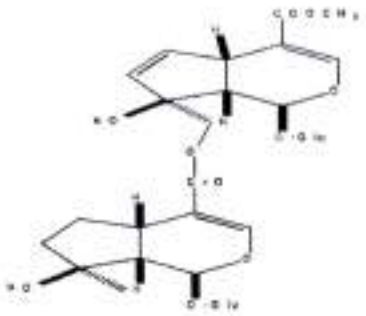
Table 1:- Anti fungal activities of some plants belonging to Rubiaceae

Plants	Parts used	Extract	Fungal pathogens	Zone of inhibition (mm)	References
Benkara malabarica (Lam.) D.D.Tirvengadum	Bark	Hexane	*Saccharomyces cerevisiae*	11	Jayasinghe, 2001
		Dichloromethane	*Saccharomyces cerevisiae*	13	
Borreria latifolia (Aubl.) K.Schum.	Leaf	Methanol	*Aspergillus ochraceous*	25	Ali *et al* ,1995
			Cunninghamella elegilns	24	
			Candida lipolytica	13	
			C. albicans	20	
			C. intermedia	19	
Canthium coromandelicum (Burm.f.) Alston	Bark	Dichloromethane	*Saccharomyces cerevisiae*	13	Jayasinghe, 2001
Haldinia cordifolia (Roxb.) Hook.f.	Bark	Dichloromethane	*Saccharomyces cerevisiae*	23	Jayasinghe, 2001
Hedyotis nudicaulis (Roth) Wight & Arn.	Whole plant	Methanol	*Aspergillus niger*	19	Ali *et al* ,1995
			Candida lipolytica	10	
			C. albicans	17	
			C. intermedia	18	
Hedyotis diffusa Willd.	Whole plant	Methanol	*Aspergillus niger*	20	Jayasinghe, 2001
Ixora coccinia L.	Leaf	Ether	*Candida albicans*	12	Annapurna *et al*, 2003
			Saccharomyces cerevisiae	12	
Hymenodictyon parvifolium Oliv.	Stem bark	Methanol(800mg/ disc)	*C. albicans*	14	Kariba, 2002
Ixora calycina Thw.	Bark	Dichloromethane	*Saccharomyces cerevisiae*	17	Jayasinghe, 2001
Morinda eclipta L.	Root	Methanol	*Aspergillus niger*	13	Ali *et al* ,1995
			C. albicans	13	
			C. intermedia	19	
Morinda tinctora Roxb.	Leaves	Dichloromethane	*Saccharomyces cerevisiae*	12	Jayasinghe, 2001
Morinda tinctora Roxb.	Bark	Dichloromethane	*Saccharomyces cerevisiae*	13	Jayasinghe, 2001
Mussaenda frondosa L.	Leaves	Dichloromethane	*Saccharomyces cerevisiae*	15	Jayasinghe , 2001
Neonauclea pallida Merr.	Stem bark	Methanol	*C. albicans*	8	Verma, 2007
Psychotria gardneri (Thw.) Hook.	Leaves	Methanol	*Saccharomyces cerevisiae*	14	Jayasinghe, 2001
Psychotria nigra (Gaert.) Als.	Bark	Methanol	*Saccharomyces cerevisiae*	17	Jayasinghe, 2001
Psychotria stemophylla(Thw.)Hook.	Bark	Dichloromethane	*Saccharomyces cerevisiae*	16	Jayasinghe, 2001
Saprosma foetans (Wight.) K.Schum.	Bark	Dichloromethane	*Saccharomyces cerevisiae*	13	Jayasinghe, 2001
Wendlandia bicuspidate	Leaves	Dichloromethane	*Saccharomyces cerevisiae*	11	Jayasinghe, 2001

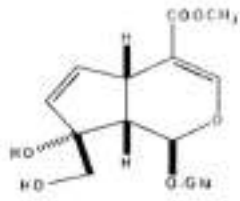
have a broad range of therapeutic and nutritional values (Levand & Larson 1979).There is a greater demand for fruit extract of *Morinda* in treatment for arthritis, cancer, gastric ulcer and other heart disease (Narayanasamy *et al*, 2006). The major components have been identified in the plant which includes octoanic acid, potassium, vitamin C, terpenoids, scopoletin, flavonesglycosides, linoleicacid, anthraquinones, morindone, rubiadin and alizarin (Moorthy & Reddy 1970; Singh & Tiwari 1976; Duduku *et al* 2007).

Ixora coccinea have been used in the Ayurvedic system of medicine for a variety of ailments: leaves in diarrhoea; roots in hiccough, fever, sores, chroniculcersand skin diseases; flowers in catarrhal bronchitis and dysentery (Sivarajan 1941).

Randia spinosa commonly known as 'Mainphal' have been documented to possess medicinal properties in ethno botanical surveys conducted by ethno botanists and in traditional systems of medicine such as Ayurveda

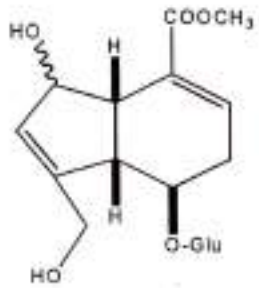


Randinoside

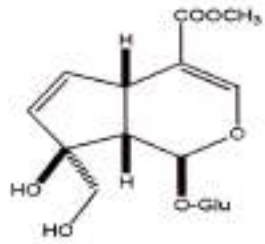


Galioside

Figure 1: Structure of some Phytoconstituents isolated from leaves of *Randia spinosa*



Deacetylasperulosidic acid methyl ester



Scandoside methyl ester

(Chopra *et al* 1956). As per Ayurvedic claim, Mainphal is bitter, aphrodisiac, emetic, antipyretic, carminative, alexiteric and cures abscesses, ulcers, diarrhoea, dysentery, inflammations, tumors, skin-diseases, piles etc and used as insect repellent (The Wealth of India, 1999; Nadkarni, 1954; Gustafsson &Persson 2002).

There are about 35 species of plants belonging to the genus *Nauclea*, including *N. officinalis*, *N. latifolia* and *N. diderrichhii*, which are used in folk medicine. Their extracts have been reported to exhibit antimicrobial and antiparasitic activities (Lamidi *et al* 1996). *Nauclea officinalis*, a traditional Chinese Herb, is widely used to cure colds, pink eye, and other ailments (Editorial Committee of Chinese Herbs 1999). Several indole alkaloids like naucleaorine, epimethoxynaucleaorine, etc have been isolated from this plant are reported to exhibit antimalarial properties (He *et al* 2005). Report reveals that *N. pallida* is used as tonic (Burkill 1935).

Antifungal and Antiprotozoal Activities of Rubiaceae

An antimicrobial is a substance that kills or inhibits the growth of microorganisms such as bacteria, fungi or protozoan (Merriam-Webster Online Dictionary 2009). Antimicrobial drugs either kill microbes or prevent the growth of microbes. A wide range of chemical and natural compounds are used as antimicrobials. Traditional healers long have used plants to prevent or cure infectious diseases. Many of these plants have been investigated scientifically for antimicrobial activity and a large number of plant products have been shown to inhibit the growth of pathogenic microorganisms. A number of these agents appear to have structures and modes of action that are distinct from those of the antibiotics in current use, suggesting that cross-resistance with agents already in use may be minimal. Within the recent years, infections have increased to a great extent and antibiotics resistance becomes an ever-increasing therapeutic problem (Austin *et al* 1999).

Fungal pathogens are becoming much more prevalent in systemic infections in immune compromised patient populations like transplant patients, AIDS sufferers, cancer patients (San & Calderone, 2008).The most common pathogenic species of *Aspergillus* are *Aspergillus fumigatus* and *Aspergillus flavus*. *Aspergillus flavus* produces aflatoxin which is both a toxin and a carcinogen. *Aspergillus fumigatus* and *Aspergillus clavatus* can cause allergic disease. Aspergillosis is the group of diseases caused by *Aspergillus*. The symptoms include fever, cough, chest pain or breathlessness. Usually, only patients with weakened immune systems or with other lung conditions are susceptible (San & Calderone 2008; dEnfert & Hube 2007; Machida & Gomi 2010). Candidiasis is by far the most common type of yeast infection. There are more than 20 species of *Candida*, the most common being *Candida albicans*. These fungi live on all surfaces of human bodies. Under certain conditions, their overgrowth cause infections, particularly vaginal tract infections, thrust (infection of tissues of the oral cavity), skin and diaper rash, and nail bed infections (e Medicine

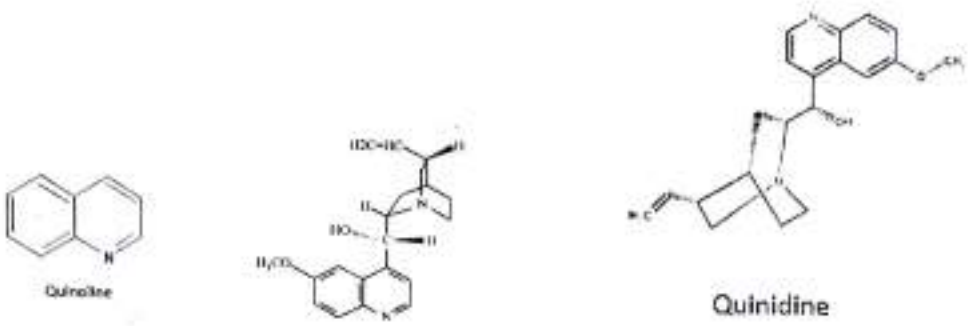


Figure 2: Structure of some Phyto constituents isolated from bark *Cinchona sp.*

Health 2011).

Plasmodium sp. are protozoan parasites responsible for malaria, an illness killing about 1–2 million people per year (WHO 2005). It is estimated that 62% of *P. falciparum* around the world presents with mono or multiresistant drug profile (Khan *et al* 2004). The World Health Organization estimates that there are between 300 and 500 million new cases of malaria worldwide, every year, mostly in Africa, Asia, South Pacific Islands and South America, which causes, at least, 3 million deaths (Heggenhougen *et al* 2003). The very high prevalence of this disease and the resistance of parasites to cheap treatments have led to the search for new antimalarial compounds, particularly in plants used in traditional medicine, as a source of new leads with new mechanism of action (Bero *et al* 2009).

Leishmaniasis is a tropical disease caused by *Trypanosomatidae* of the *Leishmania* genus spread in Africa, Asia, Europe, North and South America, with an estimated 12 million people infected worldwide (http://www.who.int/zoonoses/diseases/leishmaniasis/en/). Cutaneous leishmaniasis affects the skin and mucus membranes. Systemic or visceral leishmaniasis affects the entire body damaging the immune system by decreasing the numbers of lymphocytes (Jeronimo *et al* 2007).

The genera of Rubiaceae on which antifungal screening have been conducted till date are *Agathisanthemum* (Deborah *et al* 2006), *Alibertia* (Viviane *et al*, 2008), *Bathysa* (Alexandros, 2007), *Borreria* (Ali *et al*, 1995), *Benkara* (Jayasinghe, 2001), *Breonadia* (Salome, 2009),

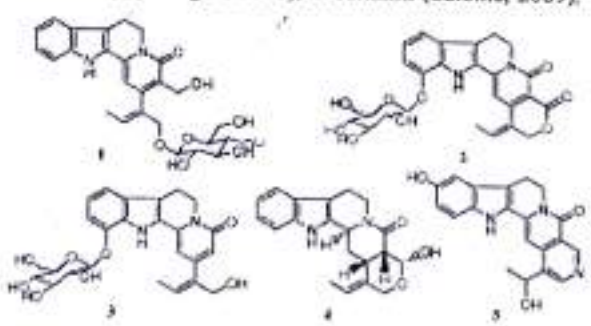


Figure 3: Structure of indole alkaloids isolated from the stems of *Nauclea officinalis*

Canthium (Jayasinghe, 2001), *Coffea* (Buchanan *et al*. 1983), *Diplospora* (Mia *et al*, 2007), *Diodia* (Ojo *et al*, 2010), *Fadogia* (Taresa *et al*, 2010), *Gardenia* (Lenono *et al*, 2009), *Gonzalagunia* (Jaime *et al*, 2006), *Genipa* (Ojeda, 1966), *Guettarda* (Philippine Medicinal Plants), *Haldina* (Jayasinghe, 2001), *Hedyotis* (Ali, *et al* ,1995), *Hydnophytum* (Prachayasittikul *et al*, 2008), *Hymenodictyon* (Kariba, 2002), *Ixora* (Annapurna *et al*, 2003), *Mitracarpus* (Gbaguidi *et al*, 2005), *Morinda* (Jayasinghe, 2010), *Mussaenda* (Jayasinghe, 2001), *neonauclea* (Verma R.K., 2007), *Palicaurea* (Sette *et al*, 2004), *Phyllanthus, Prismatomeris* (Kanokmedhakul *et al*, 2005), *Psychotria* (Jayasinghe, 2001), *Randia* (Gustafsson &Persson, 2002), *Rubia* (Sabrina *et al*, 2005), *Saprosma* (Jayasinghe, 2001), *Tarenna* (Nishanta *et al*, 2002), *Uncaria* (Milata, 2008) and *Wendlandia* (Jayasinghe, 2001).

The plants of Rubiaceae on which antiprozoal activities have been reported are *Aidia* (Bradacs *et al*, 2010), *Bathysa* (Costa DAM, 1885), *Cinchona* (Kanjilal, 2005), *Capiriona* (Estevez *et al*, 2007), *Coffea* (Revista da Flora Medicinal, Nov. 1942), *Couteria* (Revista de Flora Medicinal, July 1945), *Mitracarpus* (Fabri *et al*, 2009), *Myrionuron* (Pham *et al*, 2008), *Fadogia* (Taresa *et al*, 2010), *Heinsia* (Jude *et al*, 2009), *Nauclea* (Jingyong *et al*, 2008), *Pagamea* (Roumya *et al*, 2007), *Pavetta* (Blade *et al*, 2010), *Porterandia* (Mbatchia *et al*, 2006), *Prismatomeris* (Kanokmedhakul *et al*, 2005), *Randia* (Gustafsson &Persson, 2002), *Remijia* (Revista de Flora Medicinal, July 1945), *Urophyllum, Sabicea* (Roumya *et al*, 2007), *Schumanniophyton* (Jean *et al*, 2007), *Isertia* (Esteveza *et al*, 2007) and *Warszewiczia* (Esteveza *et al*, 2007).

Some recent publications have shed substantial light on the anti-microbial activities of some useful medicinal plants of this family Rubiaceae. Plant parts like root, stem, bark, leaf or whole plant in case of small herbs are powdered and extracted with various solvents like petroleum ether, ethyl acetate, methanol, ethanol, etc and their antimicrobial activities were found out against various pathogenic strains of fungi (Jayasinghe, 2001; Algia, 1966; Annapurna *et al*, 2003; Verma, 2007; Kariba, 2002). The method employed by most of the workers for anti fungal investigations is modification of Filter Paper Disc Diffusion Method (Vincent & Vincent

Table 2: Anti-protozoal activities of some plants belonging to Rubiaceae

Plants	Parts used	Active against Protozoa	Reference
Aidia racemosa (Cav.) Tirveng	Leaves	*Plasmodium falciparum*	Bradacs *et al*, 2010
Bathysa cuspidata (St. Hil.) Hook.f.	Barks	*Plasmodium falciparum*	Costa DAM, 1885.
Capirona decorticans Spruce		*Leishmania sp*	Estevez *et al*,2007
Cinchona calisaya Wedd.	Barks	*Plasmodium falciparum*	Costa DAM, 1885.
Cinchona succirubra Vahl.	Barks	*Plasmodium falciparum*	Khare C.P., 2007
Coffea arabica L.	Leaves and seeds	*Plasmodium falciparum*	Revista da Flora Medicinal, Nov 1942
Coutarea hexandra (Jacq.) Schum		*Plasmodium falciparum*	Revista de Flora Medicinal, July 1945
Heinsia crinata (Afz) G.	Leaf	*Plasmodium berghei*	Jude *et al*, 2009
Isertia hypoleuca Benth.	Stem	*Leishmania amazonensis*	Esteveza *et al*, 2007
Mitracarpus frigidus (Roem. & Schult.) K. Schum.	Aerial parts	*Leishmania sp*	Fabri *et al*, 2009
Myrionuron nutans Van.	Leaves	*Plasmodium falciparum*	Pham *et al*, 2008
Nauclea officinalis (Pierre) Pitard	Stem	*Plasmodium falciparum*	Jingyong *et al*, 2008
Pagamea guianensis Aubl.	Stem	*Plasmodium falciparum*	Roumya *et al*, 2007
Paverta crassipes K. Schum.	Leaves	*Trypanosoma cruzi, and Trypanosoma brucei Leishmania infantum Plasmodium falciparum*	Blade *et al*, 2010
Porterandia cladantha (K. Schum.) Keay	Leaves	*Plasmodium falciparum*	Mbatchia *et al*, 2006
Prismatomeris fragrans E.T. Geddes	Roots and stems	*Plasmodium falciparum*	Kanokmedhakul *et al*, 2005
Randia spinosa (Thunb.) Poir	Stems	*Plasmodium falciparum Leishmania sp*	Tandon *et al*, 1991
Remijia ferruginea A. St. Hil	Barks	*Plasmodium falciparum*	Revista de Flora Medicinal, July 1945
Sabicea villosa (Willd.) Roem. & Schult.	Aerial parts	*Plasmodium falciparum*	Roumya *et al*, 2007
Warszewiczia cordata (Spruce)K. Schum	Stem	*Leishmania amazonensis*	Esteveza *et al*, 2007

1944). Values of Minimum Inhibitory Concentration also have been reported by some workers by using several methods like Serial Dilution Technique (Hufford *et al* 1975; Ali *et al* 1995). Antimalarial evaluations have been conducted using modification of the reported method (Trager & Jensen 1976) on animal model and IC 50 values also have been reported in most of the research papers (Sun *et al* 2008; Roumya *et al* 2007; Pham *et al* 2008; Jingyong *et al* 2008).

Table 1 and Table 2 represent some of the important medicinal plants of the family Rubiaceae and their reported antifungal and antiprotozoal activities respectively against some specific fungal pathogenic strains and protozoans.

Discussion

Anti-microbial properties of several plants have been investigated as alternatives with low toxicity for the prevention and treatment of infectious diseases. Almost all the plants mentioned above are multi resistant against a number of fungal pathogens and protozoans and may have the potentiality for broad range of clinical practices.

Rubiaceae is a family of flowering plants which possess a large collection of medicinal plants. Literature survey reveals that research works on anti fungal activity have been conducted on only 35 genera of Rubiaceae out of 660 genera. Most of the plants under investigation have shown significant activity against multiple pathogenic microorganisms. Available data regarding the zone of inhibitions indicate that the fungal pathogens whose activities have been inhibited most by the plant secondary metabolites present in crude extracts are *Candida albicans, Aspergillus niger and Saccharomyces cerevisiae*. Maximum inhibitions have been observed in case of dichloromethane extract obtained from bark of *Haldina cordifolia* executing 23 mm zone diameter against *Saccharomyces cerevisiae*. In all the research papers studied, zone of inhibition of the plant extracts against fungal inoculums have been compared with the zone of inhibition executed by the standard antibiotics to find out their level of significance. Anti protozoal activity studies have been carried out against different pathogenic strains of *Plasmodium, Leishmania* and *Trypanosoma*. The activity of various plant extracts against the above mentioned fungal strains and protozoans clearly indicates the presence of potent bioactive principles in these crude extracts which might be very useful as antimicrobial. Alkaloids with active antimalarial and antifungal principles have been isolated and well documented with their structural elucidations in case of various species of *Cinchona officinalis, C. succirubra, C. Calisaya, C. ledgeriana, Nauclea officinalis, Randia spinosa, Randia dumatorum, Mitragyna speciosa, Mitragyna tubulosa, Mitragyna ciliate, Mitragyna parvifolia, Myrionuron nutans, Uncaria sp.* etc.

Now-a-days there is a worldwide movement towards finding out chemical constituents from various plant sources and the bioactivity studies of the novel drugs isolated. As significant anti microbial activities have been displayed by some of the members of the family

Rubiaceae, they need special attention by researchers for isolating their chemical backgrounds and their related biological applications.

During the past decades, the number of drugs consistently effective for the treatment and prophylaxis of malaria infection has decreased as a result of the progressive emergence of *Plasmodium falciparum* resistance to chloroquine, pyrmethamine-sulfadoxine, and quinine. Among some of the major antimalarial drugs, most of them belonging to the quinoline group, cross resistance have been described, particularly between chloroquine and quinine (Chonsuphajaisiddhi 1981). One possible way to face this situation is to use combinations of antimalarial drugs like quinine tetracyclines (Cowell 1973) which are now increasingly applied in multi resistant areas.

As antifungal activity screenings have been performed on only 35 genera and antiprotozoal on 2 genera of Rubiaceae out of 660 genera, data from a large number of genera are lacking in this field. Attention should be paid by the workers to carry out extensive research on those genera which may enrich the area of medicinal chemistry by providing valuable drugs with better efficacy. Attention should also be paid for implementation of proper protection strategies to conserve all these valuable medicinal plants in nature and their proper utilisation in the field of medical sciences.

Conclusion

Thirty-five genera belonging to the family Rubiaceae out of 660 genera have been recorded to show anti fungal properties and 22 genera have been documented to show anti protozoal activities. Extensive studies should be carried out on isolation and characterization of pure chemical constituents from these plants and their successful clinical application in curing various infectious diseases.

References

Alexandros, S.B. 2007. The archives of Flora Medicinal *Journal of Ethnobiology and Ethnomedicine* (3):18.

Ali, A.M. *et al 1995*. Antimicrobial Activity of Selected Malaysian Plants. *Pertanikaj. Trop. Agric. Sci.* 18(1): 57 – 61.

Austin, D.J.; Kristinsson, K.G. & Anderson, R.M. 1999. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance, *Proceedings of the National Academy of Sciences of the United States of America* 96: 1152 – 1156.

Bero, J.; Ganfon, H.; Jonville, M.C.; Frédérich, M.; Gbaguidi, F.; DeMol, P.; Moudachirou, M. & Leclercq, J.Q. 2009. *In vitro* antiplasmodial activity of plants used in Benin in traditional medicine to treat malaria. *Journal of Ethnopharmacology*. 122 (3): 439 – 444.

Balde, E.S.; Megalizzi, V.; Traore, M.S.; Cos, P.; Maes, L.; Decaestecker, C.; Pieters, L. & Balde A.M. 2010. In vitro antiprotozoal, antimicrobial and antiturbor activity of *Pavetta crassipes* K. Schum leaf extracts. *Ethnopharmacol.* 130(3): 529 – 535.

Bradacs, G.; Maes, L. & Heilmann, J. 2010. *In vitro* cytotoxic, antiprotozoal and antimicrobial activities of medicinal plants from Vanuatu. *Phytotherapy Research*. 24(6): 806-809.

Buchanan, R.L.; Harry, M.A. & Gealt, M.A. 1983. Caffeine inhibition of sterimagtocystin, citrinin and patulin production. *J. Food Sci.* 48 (4): 1226-1228.

Burkill, I.H. 1935. *Dictionary of the economic products of the Malay Peninsula*, Crown Agents for the Colonies, London.

Chonsuphajaisiddhi, T.; Sabchareon, A & Attanath, P. 1981. In vivo and in vitro sensitivity of falciparum malaria to quinine chloroquine Fansidar resistant falciparum malaria in East Africa. *Am. J. Trop. Med. Hyg.* 32: 217-220.

Chopra, R.N.; Nayar, S.L. & Chopra, I.C. 1956. *Glossary of Indian Medicinal Plants. New Delhi*. Council of Scientific and Industrial Research.

Costa, D.A.M. 1885. *A Malaria e Suas Diversas Modalidades Clinicas*. Rio de Janeiro: Lombaerts & Co.

Cowell, E. J.; & Hickman R.L. 1973. Quinine-tetracycline and quinine-bactrim treatment of acute falciparum malaria in Thailand. *Ann. Trop. Med. Parasitol.* 67: 125.

Davis, A.P.; Govaerts, R.; Diane, M.B.; Ruhsam, M.; Moat, J. & Neil A. B. 2009. A global assessment of distribution, diversity, endemism, and taxonomic effort in the Rubiaceae. *Annals of the Missouri Botanical Garden. 96 (1): 68–78*.

Deborah, K.B.; Runyoro, I.N.; Olipa, D.; Cosam, C. & Zakaria, H. 2006. Screening of Tanzanian medicinal plants for anti-Candida activity. *BMC Complementary and Alternative Medicine*.6:11.

DEnfert, C. & Hube B. 2007. *Candida: Comparative and Functional Genomics*. Caister Academic Press.

Duduku, K.; Rosalam, S. & Lee N.J. 2007. Recovery of phytochemical components from various parts of *Morinda citrifolia* extracts by using membrane separator. *J. Appl. Sci.*, 7(15): 2093-2098.

Editorial Committee of Chinese Herbs, 1999. *Chinese Herbs*. Shanghai Science and Technology Press, Shanghai 6: 456.

eMedicineHealth 2011. WebMD. www.emedicinehealth.com/candidiasis yeast.../article em.htm

Esteveza, Y.; Castillob, D.; Tangoa, M.; Arevalob, J.; Rojasb, R.; Albanc, J.; Deharoa, E. & Bourdya, G. 2007. Evaluation of the leishmanicidal activity of plants used by Peruvian Chayahuita ethnic group. *Journal of Ethnopharmacology* 114(2): 254-259.

Fabri, R.L.; Nogueira, M.S.; Braga, F.G.; Coimbra, E.S. & Scio, E. 2009. *Mitracarpus frigidus* aerial parts exhibited potent antimicrobial, antileishmanial, and antioxidant effects. *Bioresour Technol.* 100(1): 428-33.

Foster, S. & Duke, J. A. 1990. *A Field Guide to Medicinal Plants. Eastern and Central N. America*. Houghton Mifflin Co.

Gbaguidi, F.; Accrombessi, G.; Moudachirou, M. & Quetin-Leclercq, J. 2005. HPLC quantification of two isomeric triterpenic acids isolated from Mitracarpus scaber and antimicrobial activity on Dermatophilus congolensis. *J Pharm Biomed Anal.* 39(5): 990-995.

Gustafsson, C. & Persson, C. 2002. Phylogenetic relationships among species of the neotropical genus Randia (Rubiaceae, Gardenieae) inferred from molecular and morphological data. *Taxon* 51: 661–674.

He, Z.D.; Ma, C.Y.; Zhang, H.J.; Tan, G.T.; Tamez, P.; Sydara, K.; Bouamanivong, S.; Southavong, B.; Soejarto,

D.D.; Pezzuto, J.M. & Fong, H.S. 2005. Antimalarial constituents from *Nauclea orientalis* (L.). *L. Chem. Biodiversity* 2: 1378–1386.

Heggenhougen, H.K.; Hackethal, V. & Vivek, P. 2003. The behavioural and social aspects of malaria and its control. In *Special Programme for Research & Training in Tropical Diseases (TDR)*. Geneva: UNDP/World Bank/WHO. 12 (52): 79–90.

Jayasinghe, U. L. B. *et al* 2002. Antimicrobial Activity of some Srilankan Rubiaceae and Meliaceae. *Fitoterapia* 72: 424-427.

Jean, B.; Guy, R.F.T.; Jean, C.T. & and Etienne, T. 2007. Antimalarial activity in crude extracts of some cameroonian medicinal plants. *African J. Trad., Compls. Altern. Med.* 4(1): 107 – 111.

Jeronimo, S.M.B.; DeQueiroz-Sousa, A. & Pearson, R.D. 2007. Leishmaniasis. *Cecil Medicine*. Philadelphia, Pa: Saunders Elsevier 23: 369.

Jingyong, S.; Hongxiang, L.; Shengjun, D.; Hui, X.; Feng, Z. & Ke, L. 2008. Indole alkoloids from *Nauclea officinalis* with weak antimalarial activity. *Phytochemistry* 69(6): 1405-1410.

Jude, E.O.; Emem, E.U.; Emmanuel, I.E. & Clement, L.J. 2009. *Journal of Medicinal Food* 12(1): 131-136.

Kanjilal, U.N. 2005. *Flora of Assam, Caprifoliaceae to Plantaginaceae*. Omsons Publication. 3: 11-95.

Kanokmedhakul, K.; Kanokmedhakul, S. & Phatchana, R. 2005. Biological activity of Anthraquinones and Triterpenoids from *Prismatomeris fragrans*. *Journal of Ethnopharmacology* 100(3): 284-288.

Khan, M.A.; Smego, R.A.; Razi, S.T. & Beg, M.A. 2004. Emerging drug-resistance and guidelines for treatment of malaria. *J Coll Physicians Surg Pak* 14: 319-324.

Khare C.P. 2007. *Indian Medicinal Plants : An Illustrated Dictionary*. Springer- Verlag Berlin/ Heidelberg.

Lamidi, M.; Gasquet, E.; Ollivier, L.; Nze-Ekekang, G.; Balansard G. & Boudon G. 1996. Antiparasitic studies of *Nauclea diderrichhii* bark, *Pharm. Pharmacol. Lett.* 6: 31–33.

Lelono, R.A.A.; Tachibana, S. & Itoh, K. 2009. Isolation of antifungal compounds from *Gardenia jasminoides*. *Pak. J. Biol. Sci.*, 12: 949-956.

Levand, O. & Larson, H.O. 1979. Some chemical constituents of Morinda species. *Plant Med.* 36: 186-187.

Machida, M. & Gomi, K. 2010. Aspergillus: *Molecular Biology and Genomics*. Caister Academic Press.

Mbatchia, S.F.; Mbatchia, B.; Banzouzia, J.T.; Bansimbsa, T. & Nsonde, G.F. 2006. In vitro antiplasmodial activity of 18 plants used in Congo Brazzaville traditional medicine. *Journal of Ethnopharmacology* 104(1-2): 168-174.

Mia, Y.S.; Kong, F.; Feng, X.; Marshall, M. S.; Jeffrey, E. J.; Edmund, L. G. & Guy T. C. 2007. Septocylindrins A and B: Peptaibols Produced by the Terrestrial Fungus *Septocylindrium* sp. *J. Nat. Prod.* 70: 391-396.

Milata, V. (2008). Naturally occurring enolethers. *Acta Chimica Slovaca*. 1(1):221 – 237.

Moorthy, N.K. & Reddy, G.S. 1970. Preliminary phytochemical and pharmacological study of *Morinda tinctoria* Linn. *Antiseptic*. 67:167-171.

Mourice, M.; Jacqueline, C. & Wootton, J. 2002. *Ethnomedicine and Drug Discovery*. p- 315.

Nadkarni, A.K. 1954. *The Indian Materia Medica*. Mumbai: ThePopular Prakashan. Revised edition. P- 184.

Narayanasamy, M.; Gangadharan, S.; Krishnamurthy, S. & Malarvizhi, K. 2006. *Morinda pubescens J. E. Smith (Morinda tinctoria* Roxb.) Fruit Extract Accelerates Wound Healing in Rats. *J. Med. Food.* 9(4): 591–593.

Nishanta, R.;Cory, S. H. & Towers,G.H.N. 2002. Antimicrobial Activity of Plants Collected from Serpentine Outcrops in Sri Lanka. *Pharmaceutical Biology* 40(3): 235 –244.

Ojo, S.K.S; Idemudia, A.J; Alikwe, P.C.N. & Awokoya O.O. 2010. ANTIMICROBIAL POTENCY OF *DIODIA SCANDENS* AND *PHYLLANTHUS AMARUS* ON SOME CLINICAL ISOLATES. 2(2): 321-334.

Ojeda, A.M. 1966. Antimicrobial activity of Genipa Americana. *Bios.* 37(3): 108-110.

Pham, C.; Jossang, A.; Grellier, P.; Svenet, T.; Hung N.V. & Bodo, B. 2008. Structure and Total Synthesis of (−)-Myrionadine and (−)-Schoberine, Antimalarial Alkaloids from *Myrioneuron nutans*.Van *J. Org. Chem.*, 73 (19): 7565–7573.

Prachayasittikul, S.; Buraparuangsang, P.; Worachartcheewan, A.; Ruchirawat, S. & Prachayasittikul, V. 2008. Antimicrobial and Antioxidative Activities of Bioactive Constituents from *Hydnophytum formicarum* Jack. *Molecules*. 13: 904-921.

Rasoanaivo, P.; Petitjean, A.; Ratsimamanga-Urverg, S. & Rakoto-Ratsimamanga, A. 1992. Medicinal plants used to treat malaria in Madagascar. *Journal of Ethnopharmacology*, 37(2): 117-127.

Revista de Flora Medicinal, July 1945.

Revista da Flora Medicinal, Nov. 1942.

Roumya, V.; Garcia, G.; Gutierrez, A.L. & Rauch, D.L. 2007. Amazonian plants from Peru used by Quechua and Mestizo to treat malaria with evaluation of their activity. *Journal of Ethnopharmacology* 112(3): 482–489.

Sabrina, K.; Claude M.H. & Claude H. 2005. Ethnomedicinal and bioactive properties of plants ingested by wild chimpanzees in Uganda. *Journal of Ethnopharmacology* 101: 1–15.

San-Blas, G.& Calderone, R.A. 2008. *Pathogenic Fungi: Insights in Molecular Biology*. Caister Academic Press.

Sette L.D.; _Passarini, M.R.Z.; Delarmelina, C.; _Salati, F. & Duarte M.C.T. 2004. Molecular characterization and antimicrobial activity of endophytic fungi from coffee plants. *World Journal of Microbiology and Biotechnology*. 22(11): 1185-1195.

Singh, J. & Tiwari, R.D. 1976. Flavone glycosides from the flowers of *Morinda* species. *J Ind. Chem. Soc.*, 53:424.

Sivarajan, V.V. & Balachandran, I. 1941. *Ayurvedic drugs and their plant sources*. NewDelhi: Oxfordand IBH Publishing Co.

Substances & Homeopatic Remedies.Homeovision. info@homeovision.org.

Tandon, J.S.; Srivastava, V. & Guru, P.Y. 1991. Iridoids—a new class leishmanicidal agents from *Nyctanthes arbortristis*. *Journal of Natural Products* 54: 1102–1104.

Teresa, M.; Patrizia, P.; Pasquale, D.G.; Michela, F. Anna, C. & Rita, A. 2010. Saponins and Polyphenols from *Fraxinus*

ancylantha (Makoni Tea). *J. Nat. Prod.* 73 (2): 247–251.

The Wealth of India Volume (F-G). 1999. *A Dictionary of Indian Raw Materials & Industrial Products.* Vol. 4 New Delhi: council of Scientific and Industrial Research.

Thirupathy, P. & Saravanan, A. 2009. Anticonvulsant activity of *Morinda tinctoria* Roxb. *Afr.J. Pharmacy Pharmacol.*, 3 (2): 063-065.

Vietinck, A.J.; Van, N.; Hoof, L. & Tott, J. 2005. Screening of Hundred Rwandese Medicinal Plants of Antimicrobial and Viral Properties. *J. Ethnopharmacol* 46: 31-47.

Vincent, J.G. & Vincent, H.W. 1944. Filter Paper Disc Modification of Oxford cup Penicillin determination. *Proc Soc. Exp. Med* 55: 162-164.

Viviane, C.S.; Maria, J.S.; Virginia C.; Sonia, P.; Cosimo, P. & Nasser, L. 2008. New Antifungal Terpenoid Glycosides from Alibertia edulis(Rubiaceae). *Helvetica Chimica Acta* 91: 1335-1362.

Williams, L.A.D. 2006. Ethnomedicine. West Indian Medical Journal *versão impressaWest Indian med. j.* 55(4): 23-34.

Zoonoses and veterinary public health. World Health Organization. http://www.who.int/zoonoses/diseases/leishmaniasis/en/