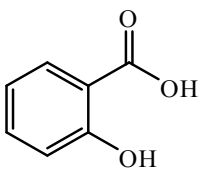
CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Some Pioneer Potent Plant Chemotherapeutics

Drug discovery is embedded on the ethnobotanical information and is as old as history (Rossato *et al.*, 1999). Prior to the development of modern science, medicines from natural sources were discovered through trial and error in the form of clinical observations that were gradually refined and improved over the centuries (Rogers and Pegel, 1976; Heinrich, 2004). Thus, the discovery of the plant-based antimalarial drug quinine (**33**) from *Cinchona officinalis* from Peru in 1662 accounts for the beginning of malaria chemotherapy (Rozman, 1973). Similarly, the leaves and flowers of the meadowsweet were the original source of salicyclic acid (**34**) which is the prototype of aspirin, a well known analgesic (Walter, 2000).

Search for drugs and dietary supplements derived from plants have accelerated in recent years making ethnopharmacologists and natural products chemists to comb the earth for phytochemicals and "leads" to be developed for treatment of fungal infections (Cowan, 1991). Plants are rich in a wide variety of secondary metabolites, such as tannins, terpenoids, alkaloids, and flavonoids, which have been found to have antimicrobial properties (Cowan, 1991). Thus 25-50% of current pharmaceuticals are derived from plants (Cowan, 1991). For example eugenol (**35**) from *Pimenta dioica*, phlorentin (**36**) from *Malus sylvestris* and warfarin (**37**) from *Medicagon sativa* have proved to be highly potent in managing topical and systemic fungal infections (Cowan, 1991).



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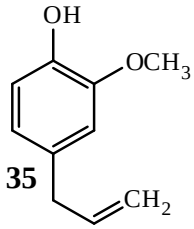

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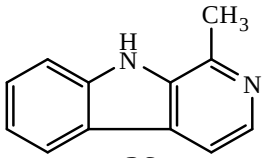

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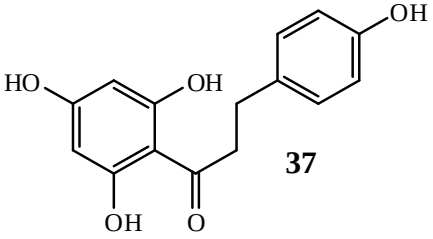

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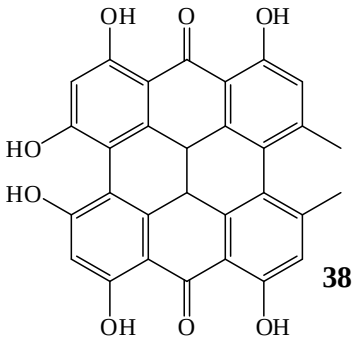
The discovery of penicillin (**23**) in 1928 (Drew, 2000) was a milestone in the development of antibacterial agents in the history of natural products, and marked a new era of drug discovery (Garrod, 1960). Over the years, increasing incidence of drug-resistant-bacteria has renewed interest in studies on the potential antimicrobial activity of plant-derived substances as an untapped source of antimicrobial chemotypes. This is based on the fact that many of these compounds, which have been used for centuries, are a source of new drugs and useful therapeutic tools to manage bacteria (Aiyegoro and Okoh, 2009). In line with this, hypericin (**38**) isolated *Hypericum penforatum* and capsaicin (**39**) from *Capsicum annum* are antimicrobial compounds from medicinal plants whose mechanism of action have been studied and their efficacy proved (Aiyegoro and Okoh, 2009). This represents scientific evidence that plant-derived antibiotics are still effective in managing bacteria (Aiyegoro and Okoh, 2009).



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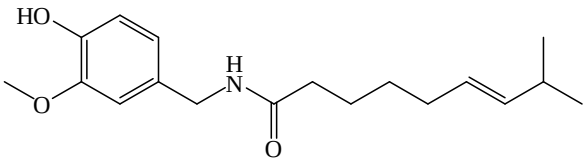

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2.2 The intransigence of pathogens

2.2.1 Malaria resistance

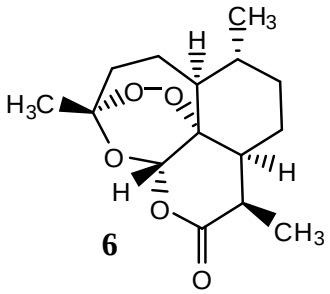
Malaria remains a global health problem with 3.2 billion people at risk (KMIS, 2015). The causative factor is the *Plasmodium* parasites which are spread to people through the bites of infected *Anopheles gambie* mosquito (WHO, 1997a). There are four reported types of human malaria parasites namely; *P. vivax*, *P. malariae*, and *P. ovale* and *P. falciparum* of which the last two are the most common and most lethal (WHO, 1997a). Some human cases of malaria have also been reported with *P. knowlesi* which is a malaria parasite that originated from monkeys in south-East Asia (WHO, 1997a, 2010b).

In Africa, malaria is a major public health problem and a leading cause of morbidity and mortality thus inflicting huge economic burden making it a major hindrance to economic growth and development (Worrall *et al.*, 2005). Countries with the lowest gross national income (GNI) per capita register the highest mortality rates (Worall *et al*., 2005; WHO, 2010a and b; Ricci, 2012). Malaria is one of the greatest threats to realizing the millennium development goal (MDG) number 4 (Nadjm and Behrens, 2012). Although a lot of research has been done with respect to its control and management, drug and insect resistance is still major challenge (WHO, 2015). This has led to the advocacy for use of medicinal plants to manage malaria-related illnesses (Prakash, 2009). In a case study in India, 5-10 times reduction in malaria related deaths have been reported among communities using guduchi (*Tinospore coeditdia*); native to India (Prakash, 2009). Plants are therefore a potential source of alternative antimalarial drugs.

In Kenya, malaria is the leading cause of morbidity and mortality and accounts for 30-50% of all outpatient attendance and 20% of admissions to health facilities (KMIS, 2015). Out of a

population of about 41.6 million, 25 million are at risk of malaria and an estimated 170 million working days are lost to the disease each year explaining the reason for low GDP (KNBS, 2010). It is hence recognized as a serious health and socio-economic burden by the Government (KMIS, 2015). The most vulnerable groups prone to malaria infections are pregnant women and children under five years of age and it is estimated that it causes 20% of all deaths as well as causing impaired cognitive and motor development, besides creating anaemic conditions (Juma and Zurovac, 2011).

The greatest challenge in the treatment of malaria is multi-drug and mosquito-resistance (Enayati and Hemingway, 2010). The first case of chloroquine (**2**) resistance in Kenya was reported in 1977 (Fogh *et al.*, 1979) and by 1993, resistance levels had reached 70% (Anabwani, 1996). In 1998, the Ministry of Health in Kenya changed the first line of treatment from chloroquine to sulfadoxine (**14**) and pyrimethamine (**5**) (SP; Fansidar®) (Shreta *et al.*, 2000). Due to resistance to these first line drugs and related side effects, the Ministry of Health officially changed the first-line drug to artemether (**40**) , in 2004 (Amin *et al.*, 2007). Validation of traditional medicinal practices could lead to new plant -derived drugs like artemisinin (**6**) from *Artemesia annua*, one of the best plant-derived drugs ever developed to combat malaria.



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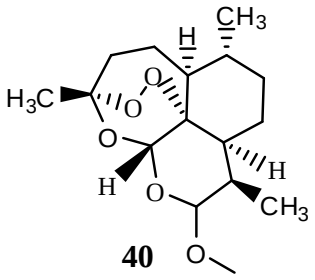

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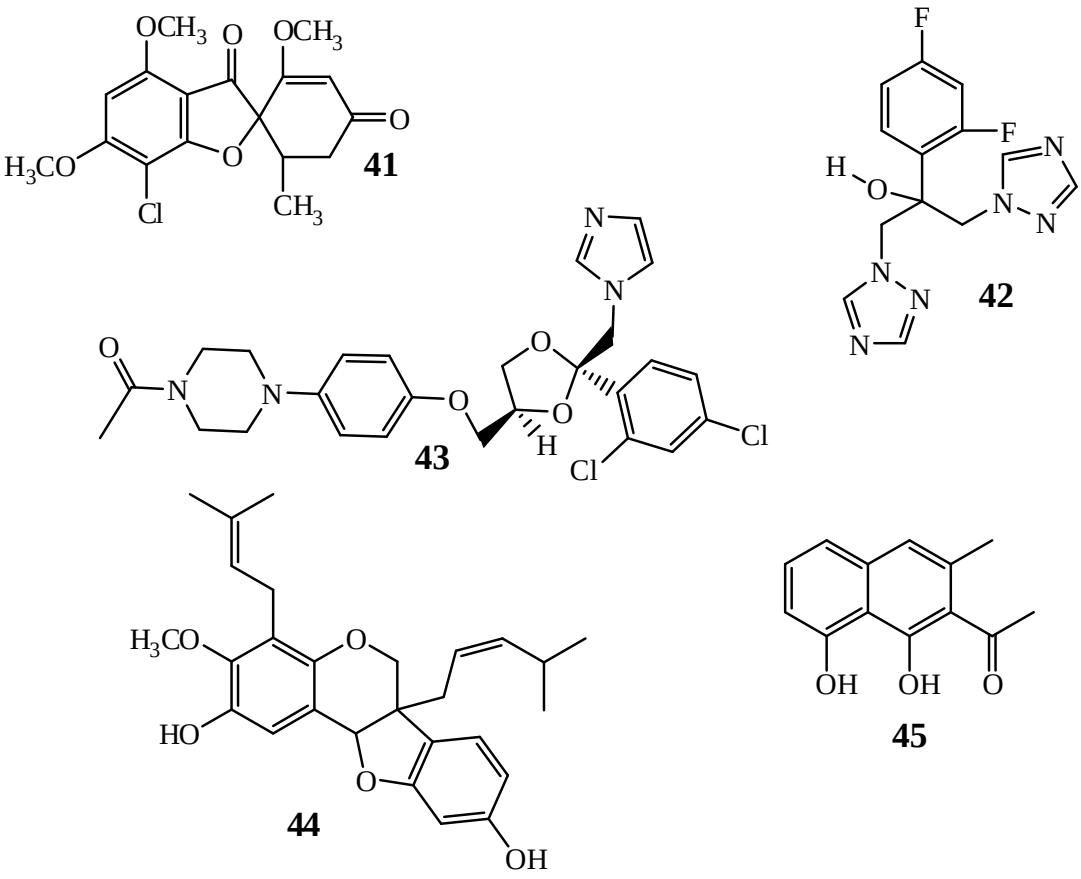
2.2.2 Fungal Infections

Since 1940s, a drastic rise in fungal infection has been observed, and it is now a global threat (Brown *et al.*, 2012). This increasing incidence of infection is influenced by the growing number of immunodeficient cases related to HIV and AIDS, cancer, old age, diabetes, cystic fibrosis, organ transplants and other invasive surgical procedures (Vandeputte *et al.*, 2012). Globally, the infections are estimated to occur in over a billion people every year (Hsu *et al.*, 2011; Di Santo, 2010). Although several species of fungi are potentially pathogenic in humans, *Candida albicans* is the organism responsible for most fungal infections (Merck Manual, 2008). Despite extensive research dedicated to the development of new antifungal agents, only four molecular classes are currently used in clinical practice to treat all manner of fungal infections. These include fluouropyridine analogs, polyenes, azoles and echinocandins (Vandeputte *et al.*, 2012). Fungi are intrinsically developing resistance to once effective drugs like griseofulvan (**41**) (Taghreed and Refai, 2007), diflucan/fluconazole (**42**) (Pranab *et al.*, 2003) and ketoconazole (**43**) (Espinel, 2008; Frank-Michael *et al.*, 2000; Klepser *et al.*, 1997; Maenza *et al.*, 1996). Recent biological evaluation of *Vatairea marcarpa* Benth. (Fabaceae), a plant used to treat superficial mycoses in Amazonia led to the isolation of vatacarpan (**44**) and musizin (**45**). Compound **44** showed antifungal activity against *C. albicans* with MIC value of 0.8 μg/mL; an activity that was superior to fluconazole (Dandara *et al*., 2015).



L. eriocalyx, *A. ovalifolius* and *E. abyssinica* have been used traditionally in the management of fungus-related illnesses hence a potential source of lead antifungals. However, there is little information on the phytochemical and biological evaluation of these plants for antifungal activities.

2.2.3 Bacterial infections

When antibiotics were discovered in the 1940s, they were very effective in management of bacterial and offered a powerful tool against bacterial infections worldwide (Jacobs, 1999). This led to a dramatic decline in mortality rates from bacterial infections (Spellberg *et al.*, 2011). Over the time, many antibiotics have lost effectiveness against common bacterial infections (Shah, 2013). The spread and aggregation of antibiotic-resistant genes into multi drug-resistant

pathogens is therefore challenging the existing life-saving antibiotic therapies (Arias and Murray, 2009; Udwadia *et al.*, 2012). However, there is hope that the three plants being investigated for antibacterial activities in this study could provide alternative compounds which could be modulated into potent antibiotics.

Bacteria infections are generally managed by antibiotics whose classification is done according to their chemical structures. Some pathogenic bacteria are highlighted in **Table 1**.

Table 1: Some pathogenic bacteria, disease they cause and mode of transmission

Species	**Nature**	**Disease caused**	**Mode of Transmission**	**Reference**
Bacillus anthracis	Gram-positive, rod-shaped	Anthrax	Cutaneous infection by tissues of animals (sheep, goat, cattle, horses, pigs) dying of the disease	Chun *et al*., 2012
Escherichia coli	Gram-negative, rod-shaped	Urinary tract infection (UTI), Bloody diarrhea, Anaemia, Kidney failure	Part of gut, spreading extraintestinally/prolife rating in the GI tract, eating undercooked meat, contaminated fruits or vegetables, as well as by drinking unpasteurized (raw) fruit juices or milk, sewage-contaminated water. Infection spread from person to person.	Schwaber *et al*., 2011
Klebsiella pneumoniae	Gram-negative, non-motile	Pneumonia, blood stream infections, wound/surgical site infections, Meningitis	Exposure via respiratory tract, skin contact, faecal	Schwaber *et al*., 2011
Mycobacterium tuberculosis	Gram-positive rope-like	Tuberculosis	Person-to-person: Microscopic droplets that contain the bacteria may be expelled when a person who has infectious TB coughs or sneezes.	Frieden and Sbarbaro, 2007
Neisseria	Gram-	Gonnorrhoea,	Sexually transmitted,	Anderson

gonorrhoeae	negative Coffee bean-shaped diplococci	Ophthalmic neonatorum, Septic arthritis	Vertical birth	*et al*., 2014
Pseudomonas aeuriginosa	Gram-Negative rod-shaped	urinary tract infections, Diffuse bronchopneumonia, respiratory system infections, dermatitis	Airborne transmission, contaminated water, lung exposure from inhaling aerosols discharged from infected respiratory tracts	Mena and Gerba, 2009
Staphyloccocus aureus	Gram-Positive Spherical and occur in clusters	Soft-tissue skin infections, abscesses, respiratory infections, sinusitis, food poisoning (diarrhoea),	Ingestion of food containing enterotoxins, person-to-person through contact with a purulent lesion/carrier	Stevens *et al*., 2010
Salmonella typhimurium	Gram-negative rod-shaped	Typhoid fever diarrhoea	Cross-contamination in food products: poultry, eggs, and beef, unwashed fruit	Okoro *et al*., 2012
Streptococcus faecalis	Gram-positive oval-shaped	UTIs, endocarditis, bacteremia, catheter-related infections, wound infections, intra-abdominal and pelvic infections	Nosocomial and person-to-person transmission, transmitted on food products	Smith *et al*., 2015

In Africa, antibiotic resistance poses a catastrophic threat to modern medicine and is quickly creating "discovery void" (Klevens *et al*., 2007). Since only a handful of new antibiotics have been developed and brought to market in the past few decades, it is a race against time to find more effective antibiotics that will fight the superbugs (Klevens *et al*., 2007; Schrier *et al*., 2009). Some strains that are resistant to the current antibiotics, including vancomycin (**46**), have emerged in the United States and Japan (Gonzalel *et al*., 2005). Antibiotic resistance has evolved over the years as summarized in **Table 2**

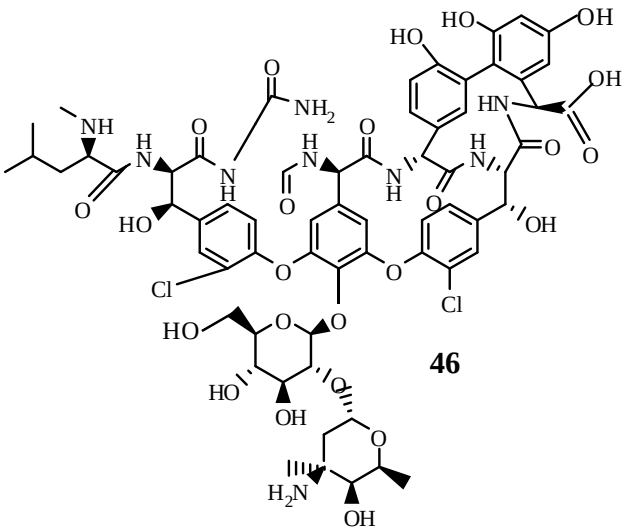


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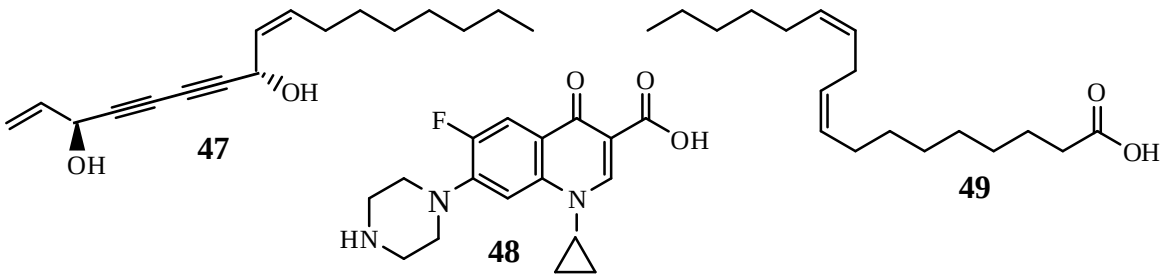
Table 2: Evolution of resistance to antibiotics (Palumbi, 2001)

S/N	Antibiotic	Year launched	Year resistance observed
1	Sulphonamides	1930s	1930s
2	Penicillin	1943	1946
3	Streptomycin	1943	1959
4	Chloramphenicol	1947	1959
5	Teracycline	1948	1953
6	Erythromycin	1952	1988
7	Vamomycin	1956	1988
8	Methcillin	1960	1961
9	Ampicillin	1960	1973
10.	Cephalosporins	1960s	Late 1960s

However, phytochemicals from plants have found their way into the arsenal of antibacterial drugs prescribed by physicians; several of which are already being tested in humans and it is reported that, on average, two or three antibiotics derived from plants are launched each year (Clark, 1996). From *Levisticum officinale*, a medicinal plant used as a herbal remedy for bacterial infections, falcarindiol (**47**) and linoleic acid (**48**) were isolated and they showed inhibitory activity against Gram-negative bacteria *Salmonella enterica* serotype *Typhimurium*, *Enterobacteriaceae* and *Pseudomonas aeruginosa* (Clark, 1996). The activity of these two

compounds compared very well with ciprofloxacin (**49**). This shows that medicinal plant extracts may provide suitable lead antibiotics (Kemp, 1978).



L. eriocalyx, *A. ovalifolius* and *E. abyssinica* are used to treat bacteria related infections, but the phytochemicals have not been fully explored. Although tests against *S. aureus, P. aeruginisa* and *Sacharomyces cerevisae* are reported for *E. abyssinica* extracts ((Irungu, 2012; Taniguchi and Kubo, 1993), the studies were mainly done on the stem and root barks. Phytochemical and biological evaluation of isolates from these three plants could generate lead antibiotic drug candidates for derivatisation to support interventions aimed at addressing resistance of bacteria such as *K. pneumaoniaie, S. typhimurium, S. faecalis, B. anthracis,* and *E. coli*. This has not been done.

2.3 The family Fabaceae

The family Fabaceae commonly known as Leguminosae represents the largest family of flowering plants (Haegnauer and Grayer-Barkmaijer, 1993). Plants in this family are characterized by the pod; technically known as the legume (Schrire, *et al.*, 2005). The family consists of about 20,000 species in 650 genera and is rich in flavonoids, anthraquinones, nitrogen containing compounds, terpenoids, lipids and polysaccharides (Yenesses *et al.*, 2004; Wojciechowski, *et al.*, 2004). Today, it is one of the most economically important families for the provision of medicines, ornaments, dyes, timber,

fodder, tannins, resins, essential oils, flavours, insecticides, piscicides and even human food (Kokwaro, 2009). In addition, they impact on the environment as nitrogen-fixing legumes (Bentjee, 1994; Mannetje, 2002).

2.3.1 Ethnomedical information on the family Fabaceae

Several plants belonging to the family Fabaceae have been used traditionally in various communities for the treatment of many ailments to remedy fever, general body weakness and microbial infections as highlighted in **Table 3** (Kokwaro, 2009).

Table 3: Ethnomedical uses of some Kenyan Fabaceae species

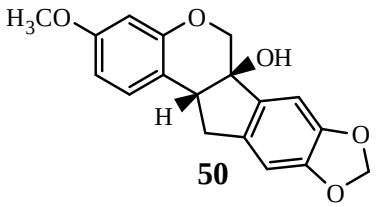
Species	**Plant part, preparation and use**	**Refences**
Abras precatorius	Roots, leaves decoction used for the treatment of gonorrhoea	Kokwaro, 2009
Acacia albida	Stem bark decoction drunk for coughs and diarrhoea	Kokwaro, 2009
Acacia mmellifera	Stem bark boiled and used for stomach discomfort, pneumonia, malaria and sterility	Kokwaro, 2009
Caesalpinia volkensii	Leaves boiled in soup or tea for malaria treatment	Kokwaro, 2009
Cassia abbreviate	Leaves, stem and root barks used to cure fever, malaria, stomach troubles and uterus complications	Kokwaro, 2009
Cassia didymobotrya	Leaves, stem and root bark decoction used as a purgative	Kokwaro, 2009
Dalbergia vacciniifolia	Root decoction is used as a purgative	Kokwaro, 2009
Erythropheleum suaveolens	Root decoction is used as an antihelminth	Kokwaro, 2009
Mucuna pruriens	Root bark decoction used to enhance male fertility	Amri and Kisangau, 2012
Pterocarpus angolensis DC.	Root bark decoction used to treat hernia	Amri and Kisangau, 2012
Sesbania aegyptiaca Poir	Seeds, leaves and root bark used in birth control	Meghendra and Ashwani, 2013
Vicia faba Linn.	Shoot and beans are used to treat skin diseases	Shaoyun, *et al*., 2012

2.4 Phytochemistry of the family Fabaceae

A large number of crude drugs used in traditional health care system employ plants from the family Fabaceae. It is known to be a rich source of flavonoids, alkaloids, terpenoids, steroids, phenols, phenylpropanoids, glycosides and a number of essential oils (Xueqin *et al*., 2011).

2.4.1 Phytoallexins

These are antimicrobial agents synthesised by plants *via* a metabolic sequence induced either biotically or in reponse to chemical or environmental stressor factors (Grayer and Kokubun, 2001; Ingham, 1973). The most common phytoallexins found in this family include, pterocarpans, coumestans and coumaranochromones (Grayer and Kokubun, 2001). These phytoallexins include pisatin (**50**) from *Pisum* species, 6α-hydroxyisomedicarpin **(51**) from *Melilotus alba* and lupinisiflavone **(52**) from *Lupinus albus* which are known to have fungicidal activities (Tahara, *et al.,* 1984).



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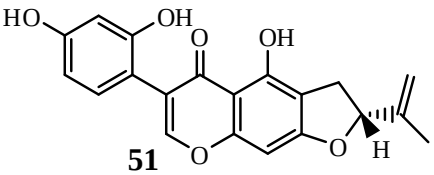

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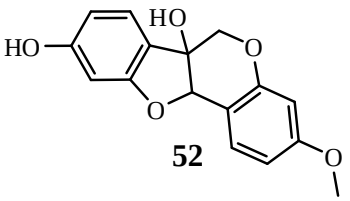

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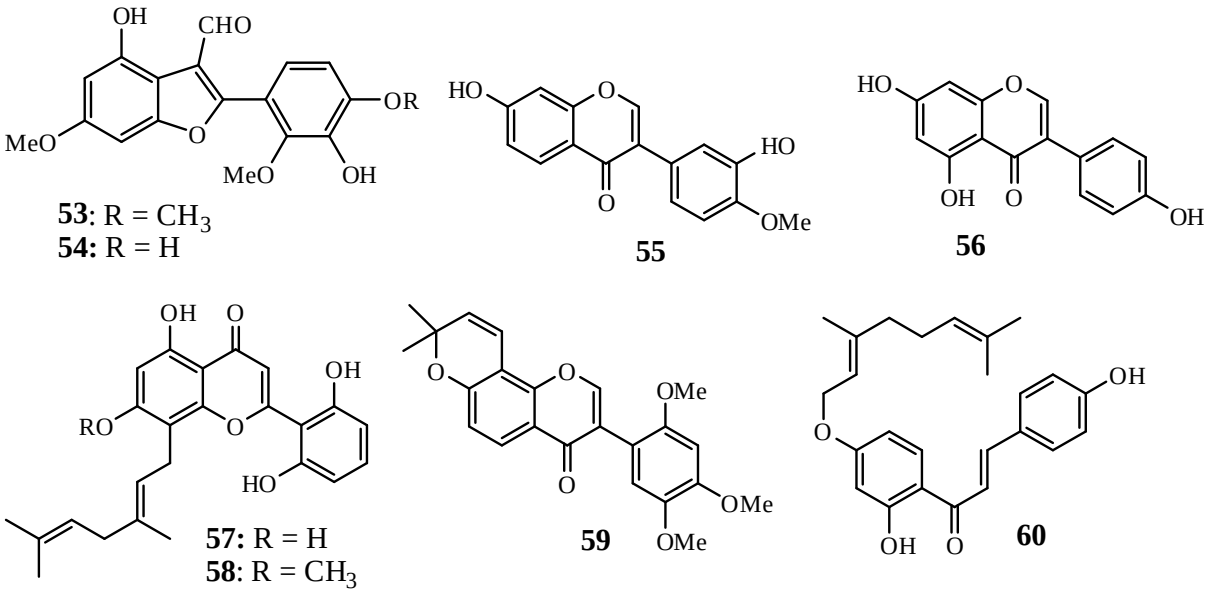
2.4.2 Antiplasmodial flavonoids

From *Andira inermis*, andidermal A (**53**) and C (**54**) were isolated together with isoflavone calycosin (**55**) and genistein (**56**) as the antimalarial principles (Schwikkard and Heerden, 2002). Other antimalarial flavonoids isolated from *Artemisia indica* species include exiguaflavanone A (**57**) and B (**58**) which showed activities of IC_{50} values of 4.6 and 7.1 μg/ml against *P. falciparum* respectively. More flavonoids which have been obtained from this family include the pyranoisoflavone barbigerone (**59**) from *Tephrosa barbigeria* which showed an IC_{50} value of 27.0 and 27.3 μM against W2 and D6 strains of *P. falciparum* respectively. Similarly, the 4'*O*-

geranylisoliquiritigenin (**60**) was isolated from *T. barbigeria* and had IC_{50} values of 8.7 and 10.6 μM against W2 and D6 respectively (Yenesew *et al*., 2003a, Yenessew, 1997).



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57: R = H
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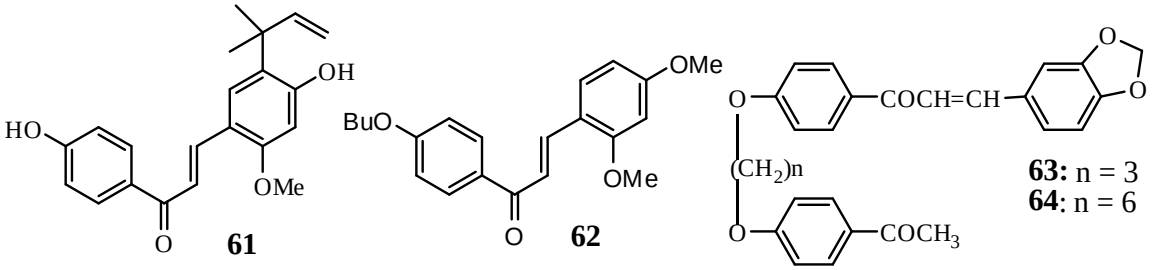
2.4.3 Antiplasmodial chalcones

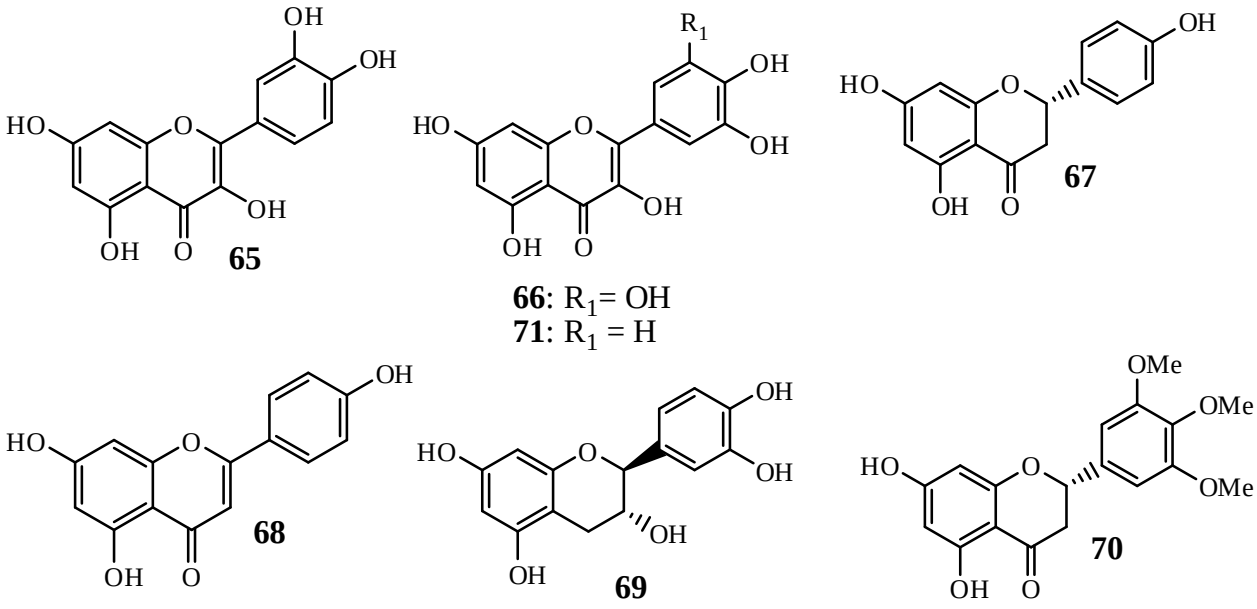
Several chalcones have also been obtained from this family. These include licochalcone A (**61**) from *Glycyyrrhiza* species which exhibited *in vivo* activity against *P. yoelli* in mice; on oral doses of 100 mg/kg. It resulted in the complete eradication of malaria parasite with no measurable toxicity noted (Nielsen, 1997). This compound also showed antileishmanial activity as well as high *in vitro* efficacy against W2 strain of *P.falciparum* (Kharazami *et al*., 1998). It was also considered as a lead compound to design and synthesise several derivatised chalcones and bischalcones in order to improve antiplasmodial potency. An example is 2,4-dimethoxy-4'-butoxychalcone (**62**) which is its analogue (Ram, *et al*., 2000). Other compounds derivatised from licochalcone A (**61)** include bischalcones (**63**) and (**64**) whose antiplasmodial efficacy

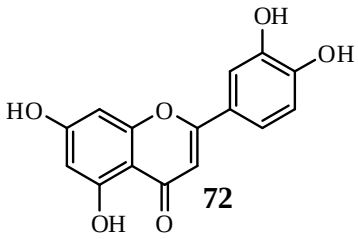
confirmed that the sites and nature of substituents in the aromatic ring greatly influence the activity profile (Ram, *et al*., 2000).



2.4.4 Antioxidant flavonoids

The main structural feature in plant phenolics responsible for the antioxidant activity is the hydroxyl group (Bors *et al*., 1990). The most studied natural antioxidant quercetin (**65**) is common in this family (Rietjens *et al*., 2002). Other antioxidant polyphenols include myricetin (**66**), naringenin (**67**), apigenin (**68**), catechin (**69**), 5.7-dihydroxy-3',4'5'-trimethoxyflavone (**70**), kaempferol (**71**) and Luteolin (**72**) (Chaturvedula and Prakash, 2011).





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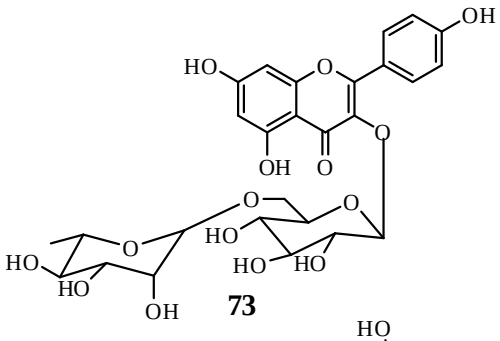
From *Vigna subterranea* (Fabaceae) the glycoside kaempferol-3-*O*-rutinoside (**73**) was isolated together with the flavonoids kaempferol-3-*O*-glucoside-7-rhamnoside (**74**) and genistin (**75**) and they also showed radical scavenging activities (Onyilagha *et al*., 2009, Baek *et al*., 1994).



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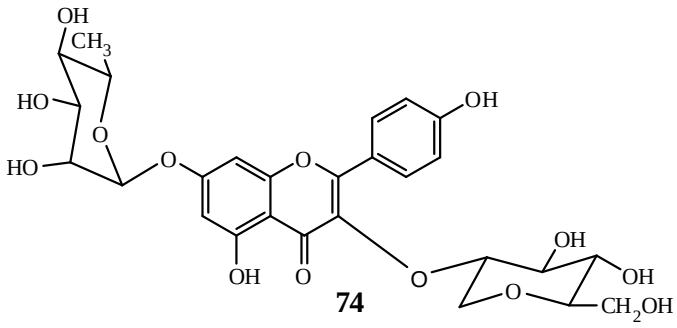

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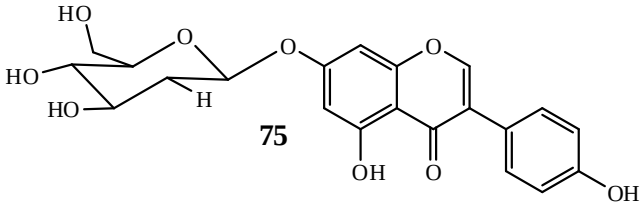

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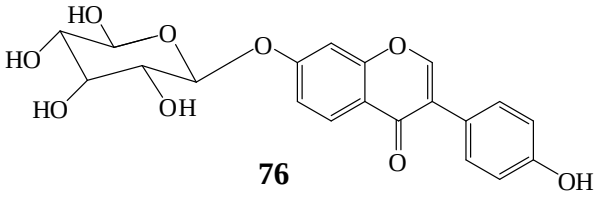
Similarly, phytochemical studies of *Bituminaria bituminosa* L. (Fabaceae) revealed the presence of isoflavone daidzein (**76**) and flavone iso-orientin (**77**) which had antibacterial and significant antioxidant activity (Azzouzi *et al*., 2014).



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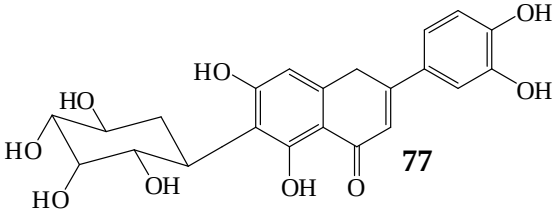

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2.5 The genus *Erythrina*

The genus *Erythrina* belongs to the family Fabaceae/Leguminosae and consists mainly of trees but some are shrubs and a few are perennial herbs. *Erythrina* comes from the Greek word 'erythros'- red, alluding to the showy red flowers of the *Erythrina* species and is known to have showy, mostly pink, red, orange or yellow flowers (Yenesew *et al*., 1997, 2003a, 2004, Machumi *et al*., 2006). It has close to 130 species distributed throughout the tropics and warm zones of the temperate areas. There are 31 *Erythrina* species in Africa with five occurring in Kenya. These are *E. abyssinica, E. sacleuxii, E burttii. E. excelsa,* and *E. melancantha*. *E. abyssinica* is the most widespread species in Africa, found in savannahs throughout eastern and southern Africa (Bentjee, 1994).

2.5.1 Ethnomedical uses of *Erythrina* species

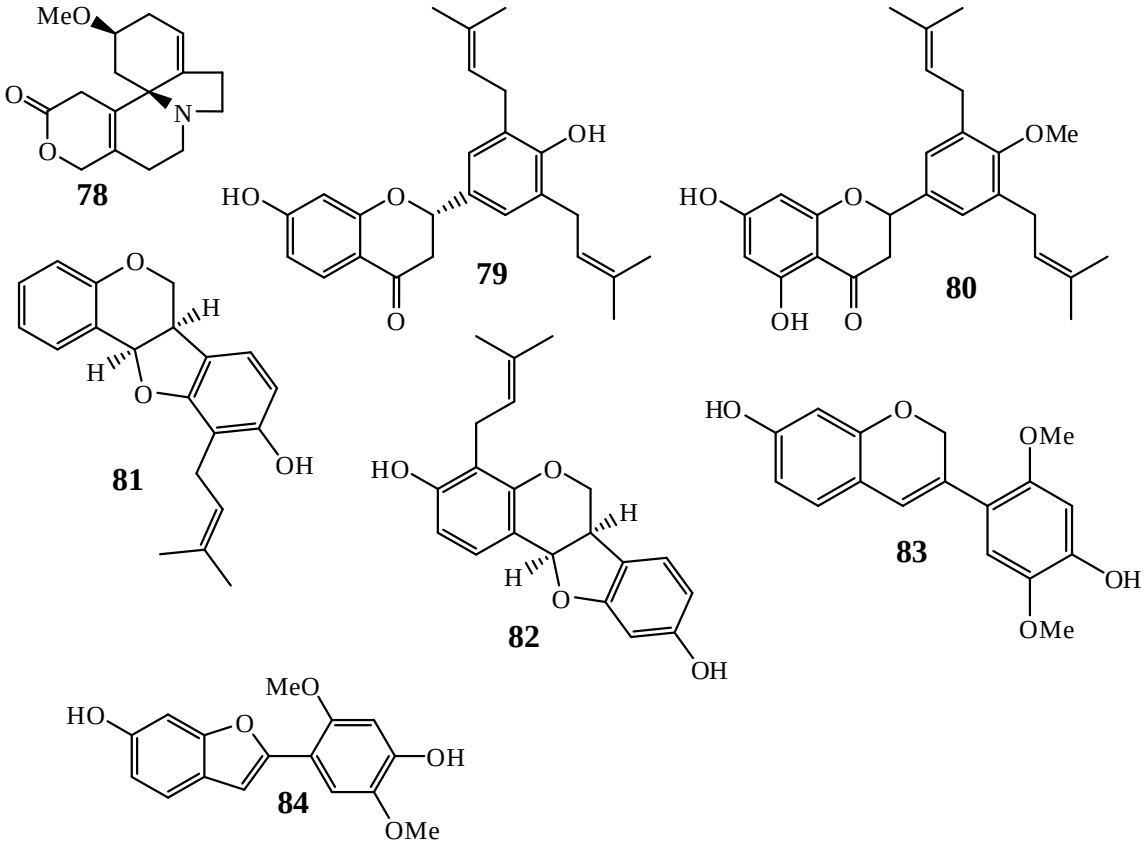
Worldwide *Erythrina* species are of importance in indigenous medicinal practice (Kamat *et al*., 1981). Plants in this genus are used in the management of various health conditions as highlighted in **Table 4**.

Table 4: Some *Erythrina* species and their Ethnomedical Uses

Species (Plant part)	Use	Reference
Erythrina abyssinica Stem bark Root bark	Malaria, fever, syphilis, trachoma, leprosy, ring worms, elephantiasis, stomach-ache	Ichimaru *et al*., 1996 Kokwaro, 2009
Erythrina arborescens Leaves Stem bark	Anthelminthic, ear-ache reliever Skin diseases, Anti-HIV	Manandhar, 1995 Rao, 1981
Erythrina buttii	Malaria, fever	Yenesew *et al*., 2002
Erythrina coralloides	Measles, gonorrhoea	Hastings, 1990
Erythrina sacleuxii	Fever, stomach disorder	Kokwaro, 2009
Erythrina variegata	Malaria, ring worms	Gilman and Watson, 1993
Erythrina sigmoidea	Fever, thrush	Promsattha, *et al*., 1998
Erythrina milbraedii	elephantiasis, stomach	Mitscher, *et al*., 1988

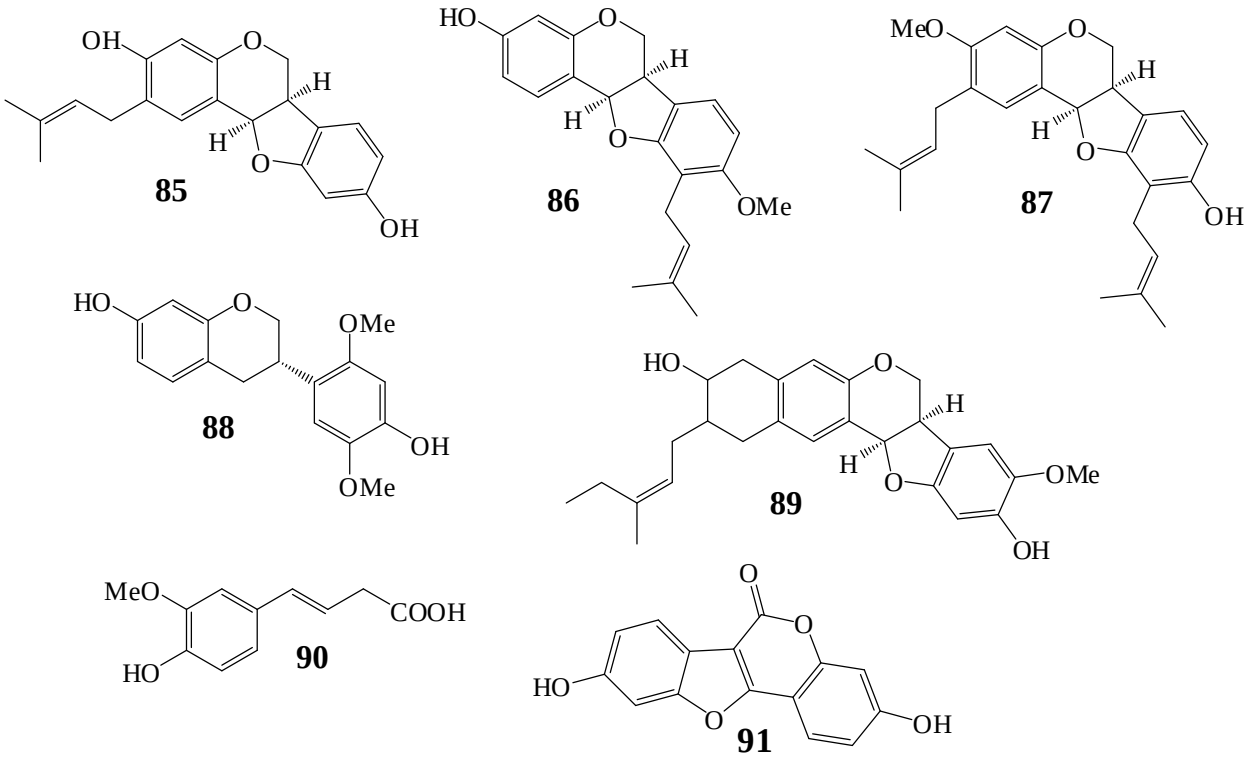
2.5.2 Biological activities of compounds from *Erythrina* species

The petroleum ether extract of the root bark of *E. sacleuxii* showed antimalarial activity against *P. falciparum* (Gessler *et al*., 1994), whereas the curare-like action of *E. americana* was due to the erythroidene-like alkaloid-erythroidine (**78**) (Folkers and Koniuszy 1993). The DCM extract of the same plant yielded flavanones; 7,4'-dihydroxy-3'5'-diprenylflavanone (**79**), 5,7-dihydroxy-4'-methoxy-3',5'-diprenyl-flavanone (**80**), 3,9-dihydroxy-2,10-diprenylpterocarpan (**81**) and 3,9-dihyroxy-4-prenylpterocarpan (**82**); 7,4'-dihydroxy-2',5'-dimethoxyflav-3-ene (**83**) and 6-hydroxy-2',5'-dimethoxy-2-arylbenzofuran (**84**). Compounds **81 and 82** showed antiplasmodial activity against W2 and D6 clones of *P. falciparum* (Tuwei, 2006).



Flavonoids and isoflavonoids from *Erythrina* species have shown antiplasmodial activities e.g calocarpin (**85**) from the stem bark *E. abyssinica* (Yenesew, *et al*., 2003b; 2004). The anti-HIV activity of the organic bark extract from a Guatemalan *E. galuca* was attributed to the pterocarpans sandwiscensin (**86**) and 3-*O*-methylcalocarpin (**87**) (Inamura *et al*., 2000). Isoflavonoids isolated from *E. variegata, E. sigmoidea, E.milbraedii* and *E.latissima* showed antibacterial activities against thirteen strains of methicillin (**24**)-resistant *Staphylococcus aureus* (Inamura *et al*., 2000). These compounds were the isoflavan eryvarin H (**88**), the pterocarpans eryvarin K (**89**) among others (Tanaka *et al*., 2003). Antioxidant flavonoids namely; isoflavones, flavans, flavanols, flavanones, and ferulic acid **(90**) derivatives have also been reported (Inamura *et al*., 2000). Among the isoflavones isolated from *Eyrthrina* species include genistein (**56**),

daidzein (**76**) coumestrol (**91**) from the stem bark of *E. cristagalii* (Redko *et al*., 2007, Inamura *et al*., 2000).

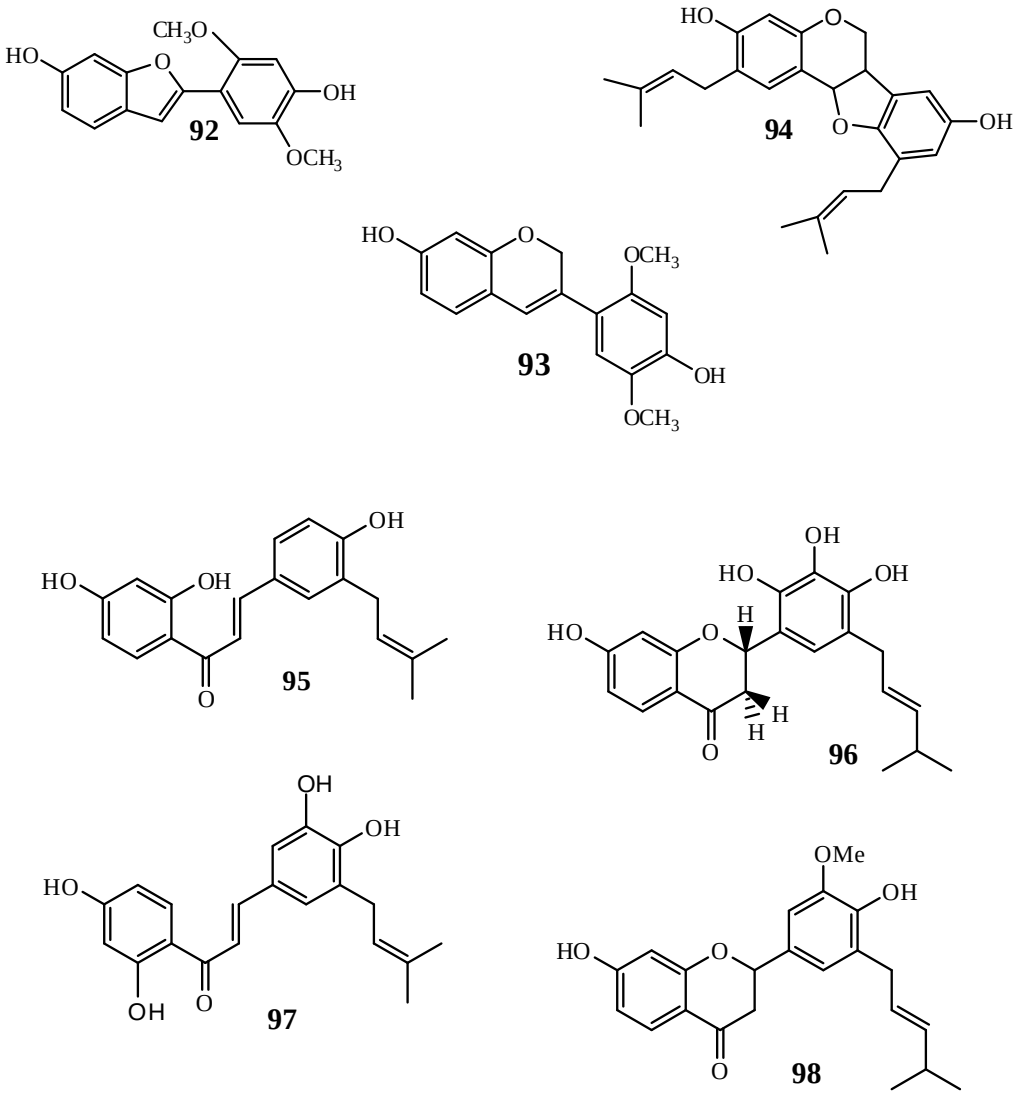


2.5.3 *Erythrina abyssinica* (DC)

Erythrina abyssinica belongs to the family Fabaceae/Leguminosae and is distributed in warm regions of southern as well as the savannah of eastern Africa (Yenesew *et al*., 1997, 2003a, 2004, Machumi *et al*., 2006). It is medium-sized tree, usually 5-15 m in height, deciduous, leaves are compound, trifoliolate, and alternate leaflets almost as broad as long, 5.5-15 x 6-14 cm. Flowers are spectacular, in strong, sturdy racemes on the ends of branchlets, orange-red, up to 5 cm long; calyx joined to form a tube (Inamura *et al*., 2000).

Figure 1: Aerial part of *Erythrina abyssinica* (Photo taken by myself [14.01.2011]

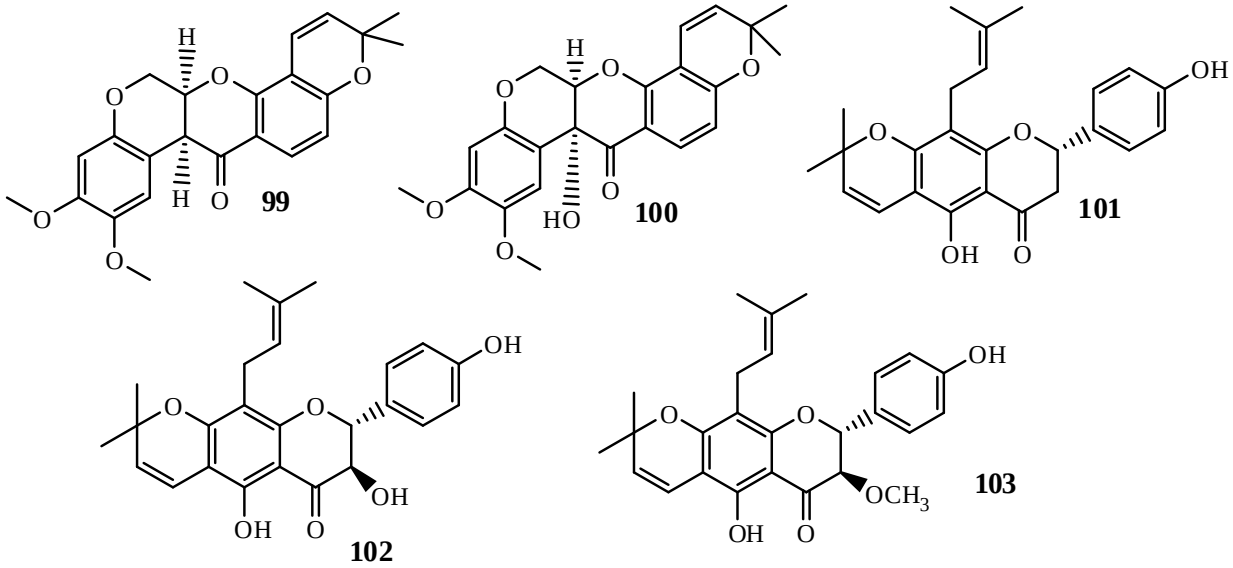
Previous phytochemical studies on *E. abyssinica* yielded 8-methoxyneoratenol (**25**), eryvarin L (**92**), eryvarin H (**93**), erycristagallan (**94**) and 5-hydroxy-9-methoxy-10-(3,3-dimethylallyl)pterocarpene (**24**) which showed antifungal activity against *Trichophyton mentagrophytes* and antiplasmodial activity against the chloroquine-sensitive (W2) and chloroquine-resistant (D6) strains of *P. falciparum* (Yenesew *et al.*, 2003b). Similarly, 1,5,4'-trihydroxy-5'-prenylchalcone (**95**), 2',3',4',7-tetrahydroxy-5'-prenylflavanone (**96**), 2',3,4,4'-tetrahydroxy-5-prenylchalcone (**97**) and 4',7-dihydroxy-3'-methoxy-5'-prenylflavanone (**98**) have also been isolated from *E. abyssinica*. Compounds **95** and **96** were mildly active against *S. aureus*, whereas **97** and **98** showed antiplasmodial activity against W2 and D6 strains of *P. falciparum* with IC_{50} values of 7.9±1.1 and 5.3±0.7 µg/mL (Irungu, 2012; Yenesew *et al*., 2004). Although *E. abyssinica* has been investigated, there is little report on the phytochemical and biological evaluation of the leaves. Use of the leaves to address health issues would lead to its conservation.



2.6 The genus *Lonchorcarpus*

The genus *Lonchocarpus* (family Leguminosae) is also classified in the legume family Fabaceae (Raynolds *et al.*, 2007). In Kenya, it is indigenous to Kenya-Coast Province, Embu, Ukambani and Mwala regions (Kokwaro, 2009). In Africa, it is common to Zimbabwe and Botswana (Coastes, 2002). Phytochemical analyses have revealed that this genus is a rich source of many different classes of polyphenolic compounds. These classes include aurones, chalcones, dibenzoylmethane derivatives, pterocarpans, rotenoids, flavanones, flavanols, flavans, flavones,

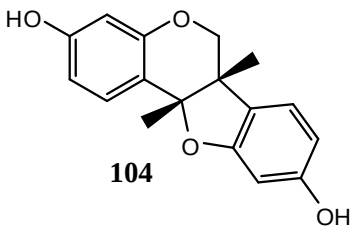
flavonols, and isoflavones (Cassidy *et al*., 2011). The rotenoids; rotenone **(14)** and deguelin **(99)** are common in this genus and they have exhibited insecticidal and piscicidal activities (Caboni *et al.*, 2004). Deguelin is useful in cancer therapy and can be applied directly into tumors (Hebert *et al.*, 2004). Rotenone **(14)**, one of the most extensively used natural insecticides, was highly toxic to the 4th instar larvae of *Aedes aegypti* (Abe *et al*., 1985). The insecticidal activities of rotenone and some other rotenoids including deguelin and tephrosin **(100)** against a variety of insect species are known (Fukami and Nakajima, 1971). Commercially, rotenone is mainly extracted from the roots of *Derris* species in Asia and *Lonchocarpus* species in South America (Fukami and Nakajima, 1971). Similarly, the methanolic extract of the root bark of *Lonchocarpus guatamalensis*, native to Central America, yielded flavanones lupinifolin (**101**), lupinifolinol (**102**) and 3-*O*-methyl-lupinifolinol (**103**) (Igham *et al.*, 1973).



Recently, two flavonoids novel to *Lonchocarpus araipensis* (Benth.) namely; benzofuran-3-ol (**104**) and furanoflavan (**105**) were isolated. These flavonoids have been reported to have antiviral, anti-allergic, anti-platelet, anti-inflammatory, anti-tumour and antioxidant activities

(Lima *et al*., 2014). 3,6-dimethoxy-6”,6”-dimethyl-(7,8,2”,3”)-chromeneflavone (DDF) (**106**) was also obtained from this plant and it showed antinociceptive activity ($p < 0.001$) in mice (Almeida *et al*., 2015).

Lonchocarpu laxiflorius is widely distributed in West Africa, Central Africa and Northern Africa. Although it is little investigated, two isoflavones; lonchocarpene (**107**) and laxiflorane (**108**) have been isolated from its stem bark (Okello and Ssegawa, 2007, Neuwinger, 1996). Similarly, 3-hydroxyflavanones jayacanol (**109**), mundulinol (**110**) together with mundulin (**111**) and minimiflorin (**112**) were obtained from *L. oaxacensis* and they showed antifungal activity (Alavez-Solano *et al*., 2000).



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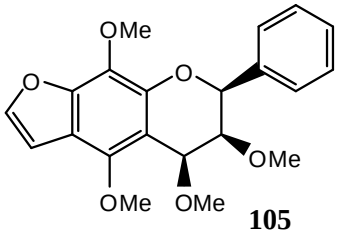

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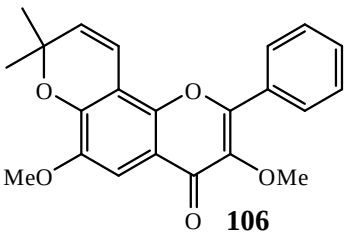

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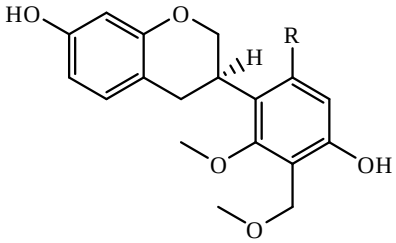
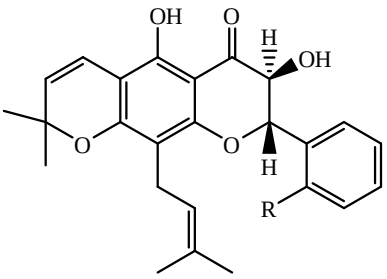


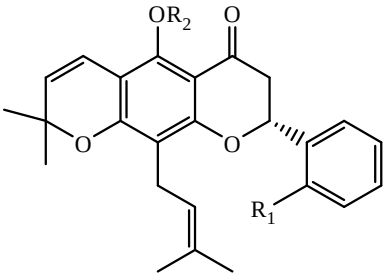
107: R = OMe

108: R = H



109: R = OH

110: R = H



111: R_1= H, R_2 = H

112: R_1 = OH, R_2 = H

2.6.1 Ethnomedical uses of *Lonchocarpus* species

Plants in this genus have are used to manage various health conditions as shown in **Table 5**

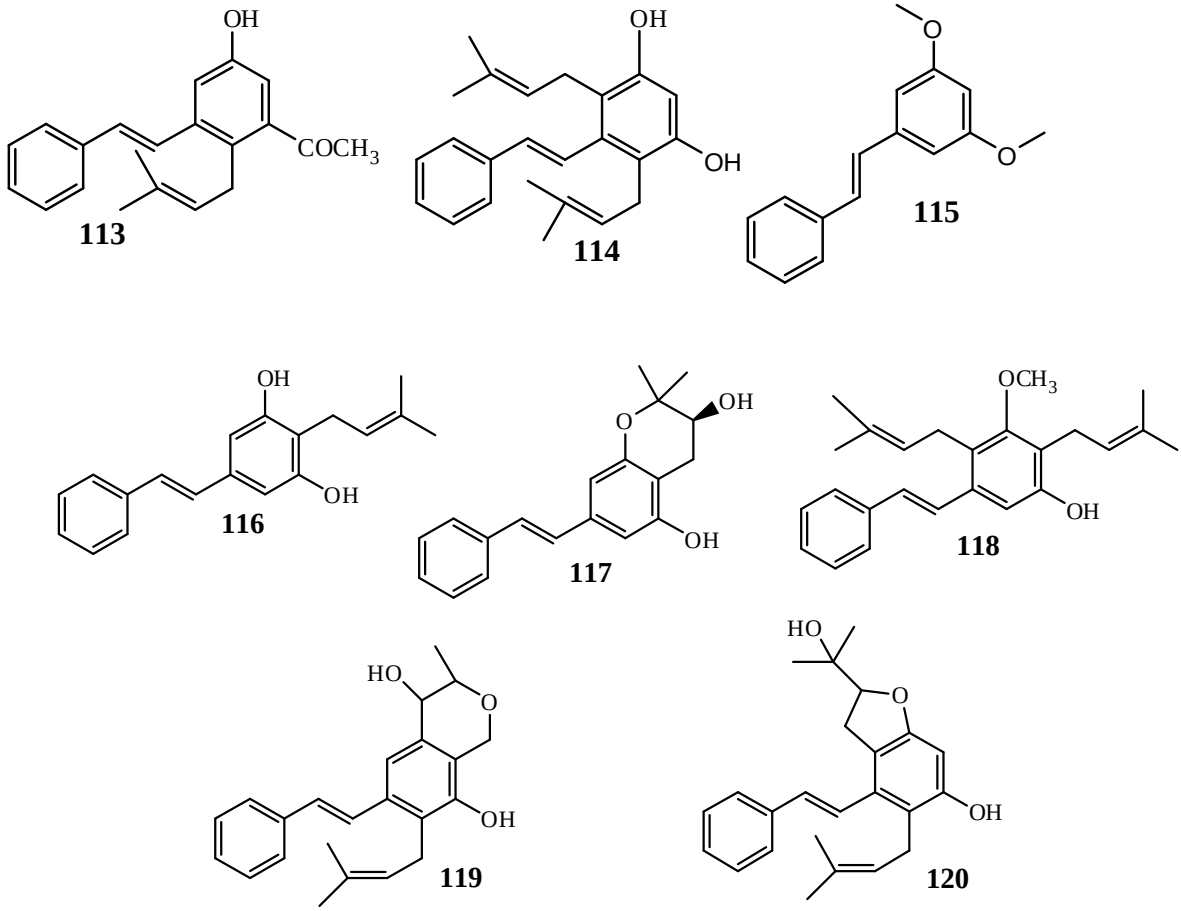
Table 5: Some *Lonchocarpus* Species and their ethnomedical Uses

Species (Plant Part)	**Use**	**Reference**
Lonchocarpus eriocalyx	Headache relief, fever, malaria, skin disorder, thrush, ringworms, mosquito repellant	Kareru *et al*., 2007 Yenesew *et al*., 2013a
Lonchocarpus violaceus (Balche) Stem bark Root bark	Stress relief, alternative alcoholic beverage and an intoxicating agent Fish poison, insecticide, anticancer Mosquito repellant	Udeani *et al*., 1997 Correa, 1984
Lonchocarpus urucu (Barbasco) Stem bark Root bark	Antitumour, anti-HIV, headache relief, skin disorders Insecticide, piscicide and pesticide	Udeani *et al.*, 1997 Correa, 1984
Lonchocarpus costaricensis	Insecticide, Treatment of thrush	Caboni *et al.*, 2004
Lonchocarpus oliganthus	Insecticide	Herbert *et al.,* 2004
Lonchocarpus araripensis	Rheumatism, arthritis and diabetes, skin diseases	Julianeli *et al.*, 2011
Lonchocarpus cyanescens	Ulcers, arthritis, Antioxidant	Samwel, *et al*., 2014
Lonchocarpus guatamalensis	Fever, headache	Igham, *et al*, 1973
Lonchocarpus castilloi	Anti-termitic, antifungal	Alavez-Solano *et al*., 2000
Lonchocarpus chiricanus	Insecticide	Jean-Robert *et al*., 2001
Lonchocarpus xuuul	Fever, headache	Borqes- Arga'ez *et al*., 2007
Lonchocarapus yucatenesis	Fever, headache	Borqes- Arga'ez *et al*., 2007
Lonchocarpus laxiflorus	Headache, mental illness, dermatitis, intestinal worms, back pain, paralysis, ulcers	Neuwinger, 1996 Okello and Ssegawa, 2007

2.6.2 Biological activities of compounds from *Lonchocarpus* species

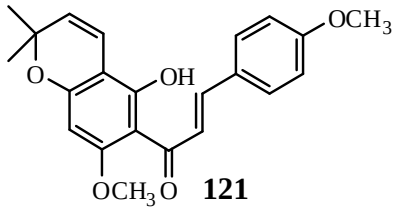
Longistylines C (**113**), D (**114**), and 3,5-dimethoxystilbene (**115**) and five prenylated stilbenes, named chiricanines **A**–**E** (**116-120**), were isolated from the root bark of *Lonchocarpus chiricanus* (Jean-Robert *et al.*, 2001). Compound **115** showed antifungal effects against

Cladosporium cucumerinum. Four of the isolated compounds showed toxicity against the larvae of the yellow fever-transmitting mosquito *Aedes aegypti*. Compound **116** was as potent as rotenone in the larvicidal dilution tests (Jean-Robert *et al.*, 2001).



In previous investigations (Borqes-Arga'ez *et al.*, 2007), a number of flavonoids with antioxidant activities were isolated from leaves, stem and root barks of *Lonchocarpus xuuul* and *Lonchocarapus yucatenesis* from Yucatan Peninsula. The flavonoids were also evaluated for antiprotozoal and cytotoxic activities and were moderately active (Borqes-Arga'ez *et al*., 2007). These flavonoids included; 2',4-dimethoxy-6'-hydroxylonchocarpin (**121**), 5,4'-dihydroxy-3'-methoxy-(6:7)-2,2-dimethylpyranoflavone (**122**) and 5,4'-dimethoxy-(6:7)-2,2-dimethylpyranoflavone (**123**) and carpachromene (**124)**. Those isolated from root bark of both species were: xuulanin (**125**) and 3β-methoxyxuulanin (**126**). The chalcones **125** and **126** were

the most active against Leishmania parasites and also cytotoxic against cell cultures of leukemia P388DI and adenocarcinoma prostate PC-3 cell (Borqes-Arga'ez *et al*., 2007).



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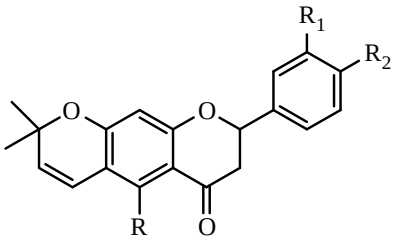
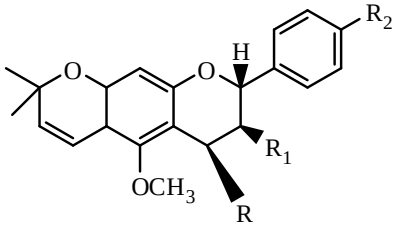


	R	R_1	R_2
122:	OH	OCH_3	OH
123:	OCH_3	H	OCH_3
124:	OH	H	OH



	R	R_1	R_2
125:	OCH_3	H	H
126:	OCH_3	OCH_3	H

2.6.3 *Lonchocarpus eriocalyx* (Harms)

Lonchocarpus eriocalyx belongs to the family Fabaceae, which synthesizes a wide range of flavonoids with insecticidal and other antimicrobial activities (Ceres *et al.*, 1981). In a previous study, the crude extract of the root bark of *L. eriocalyx* showed antiplasmodial activity against chloroquine-sensitive (W2) and chloroquine-resistant (D6) strains of *P. falciparum* (Tuwei, 2006). This extract also showed larvicidal activity against the mosquito the larvae of *A. aegypti*. Only one compound, the lupane-type triterpene lupeol (**27**) has been isolated from *L. eriocalyx* and it showed good antiplasmodial activity (Yenesew *et al.*, 2003a, Tuwei, 2006). There is no report on any phytochemical analysis of the stem.

Figure 2: Aerial part of *Lonchocarpus eriocalyx* (Photo taken by Mathenge, S. [24.11.2012]

2.7 The genus *Alysicarpus*

The genus *Alysicarpus* also belongs to the family Fabaceae and includes 83 plant names of which 34 are accepted as distinct taxa (Taylor *et al.*, 2001). In Kenya, it is found in Mount Kenya regions Shimba Hills and Ukambani areas (Kokwaro, 2009).

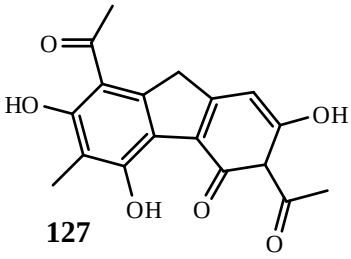
2.7.1 Ethnomedical uses of the genus *Alysicarpus*

Plants from this genus have been used in indigenous system of medicine as anti-inflammatory agents, for stomach-discomfort (Rao and Haridasan, 1991), an antidote to snake bite (Jain and Sahu, 1993), for skin diseases and as a diuretic agent (Singh and Prakash, 1994). The leaves of *Alysicarpus gautalensis* are used in fever (Radhakrishnan, 1996) and jaundice (Purvi *et al.*, 2011). Some ethnomedical uses of plants from this genus is shown in **Table 6**.

Table 6: Some *Alysicarpus* Species and their ethnomedical Uses

Species (Plant part)	Use	Reference
Alysicarpus ovalifolius Leaves Stem and root	Fever, acute and chronic troubled bleeding piles, skin disease, thrush wound medicine, to control cough, treatment of ring worms	Gillett *et al.*, 1971
Alysicarpus glumaceus Leaves Oil from fruits	A stimulating wash for babies Massaging glandular swellings in the neck and jaws	Kokwaro, 2009, 1976
Alysicarpus vaginalis Root bark Leaf sap and root decoction	Stimulant for babies As a mouth wash and cough relief	Kokwaro, 2009
Alysicarpus rugosus	Haemoaglutinating activity	Siddhuraju *et al.*, 1992
Alysicarpus monilifer L. (DC.) Aerial part	Leprosy, cough, purgative, anti-pyretic, stomach pain, anti-inflammatory activity	Purvi *et al.*, 2011
Alysicarpus poklianus	Purgative	Gholami and Pandey, 2016-1
Alysicarpus gautalensis	Ulcers, thrush, fever, jaundice	Gholami and Pandey, 2016-2 Radhakrishnan, 1996

From *Alysicarpus monolifer*, alysinol (**28**) usnic acid (**127**), methyl-2,4-dihydrox-3,6-dimethylbenzoate (**128**), 3-hydroxybenzoic acid (**129**), stigmasterol (**30**), poriferasterol (**130**) and ursolic acid (**131**) have been isolated and the essential amino acid threonine (**29**) (Conolly and Hill, 2005; Riaz *et al.*, 2003; Siddhuraju *et al.*, 1992).



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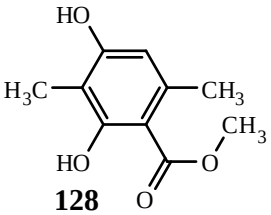

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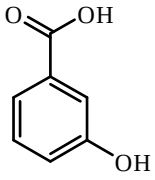

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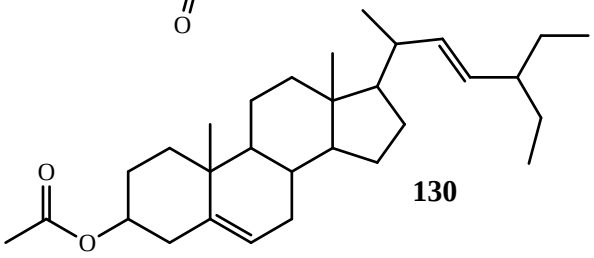

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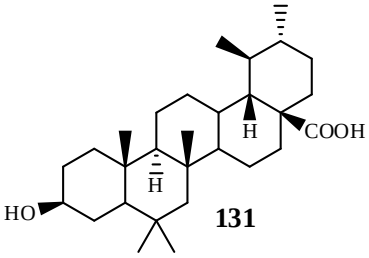

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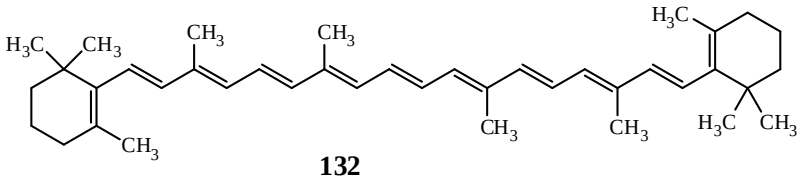

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2.7.2 *Alysicarpus ovalifolius* (Schumach)

Alysicarpus ovalofolius is widespread in West and East Tropical Africa, from Cape Verde and Mauritania, East to Ethiopia and Kenya and south to Angola, Zimbabwe, Mozambique and Madagascar. Elsewhere, it is found in Tropical Asia, Afghanistan, India, Vietnam and Indonesia (Burkill, 1995). It is an erect or spreading annual herb, sometimes woody at the base, 20-60 cm tall; stems are puberulous or pubescent, becoming almost glabrous with age. In a recent study, β-carotene (**132**) was isolated from this plant (Ndiaye, 2016). The phytochemical and biological evaluation of this plant has not been fully explored.

Figure 3: Aerial part of *Alysicarpus ovalifolius* (Photo taken by Mathenge, S. [20.04.2013]