A REVIEW ON THE PHYTOCHEMICAL AND PHARMCOLOGICAL ACTIVITIES OF *Hymenocardia acida* Tul (PHYLLANTACEAE)

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ABSTRACT

Hymenocardia acida (Tul) is a medicinal plant used in folkloric medicine in the treatment of various diseases. This study aimed to review ethno-medicinal uses, biological/pharmacological activities as well as the phytochemical constituents of *Hymenocardia acida* (Tul). The data were searched from electronic databases such as Google Scholar, Pub Med, Wiley and Science Direct. The key word used for searching information is *Hymenocardia acida*. The study has shown that the plant is used in ethno-medicine for the treatment of asthma, snake bite, small pox, pain, trypanosomiasis, cough, eye infections, pulmonary infections, diarrhea, dysentery, diabetes, epilepsy and schizophrenia. Additionally, the plant has been reported to contain various phytochemical constituents such as lupeyl docosanoate, lupine, β-sitosterol, friedelan-3-one, betulinic acid, stigmasterol and oleic acid. Moreover, the study highlighted that, the plant possessed positive analgesic, antidiabetic, anticonvulsant, anticancer, antiplasmodial, antibacterial and antifungal activities. Therefore, *Hymenocardia acida* having various medicinal properties as reported in this study can be used as herbal supplement in the treatment of various diseases.

Key words: *Hymenocardia acida*, phytochemical, pharmacological ethomedicinal, activity

INTRODUCTION

Traditional medicine refers to the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses (WHO, 2000).

The use of traditional medicines continues to expand rapidly across the world with many people resorting to herbal products for the treatment of different health challenges in various national healthcare sectors.(Ajao *et al*., 2017). Almost all cultures from prehistoric times to the present day have used plants as a source of medicines and this includes a considerable percentage of the peoples in both developed and developing countries (Akerele *et al*., 1991). Before the introduction of the orthodox medicine, herbal medicine used to be the commanding medical system available to millions of people in Africa in both rural and urban communities. In fact, it was the only source of medical care available for a greater percentage of the population (Abdullahi, 2011). Medicinal plants are regarded as rich resources of drug ingredients and still remain the basis for development of modern drugs. (Tor-Anyiin *et al*., 2013; Mahtab, 2016).

Hymenocardia acida (Tul), family Phyllantaceae (Tuenter *et al*., 2016) is a very popular plant in African traditional medicine practices. The plant is known commonly in Nigeria as Jan yaro (Hausa), Yawasatoje (Fulfulde), Ikalaga (Igbo), Orupa (Yoruba), Ii-kwarto (Tiv), emela (Etulo), Uchuo (Igede), Enanche (Idoma) and Heart-fruit (English) (Tor-Anyiin *et al*., 2013). This review aimed to highlight ethno-medicinal uses, biological, pharmacological activities as well as the phytochemical constituent of *Hymenocardia acida* (Tul).

METHODOLOGY

In this study, previous scholarly works carried out on *Hymenocardia acida* were reviewed. The data were searched from online electronic databases such as Google Scholar, Pub Med, Wiley and Science Direct using the key word "*Hymenocardia acida*". Only papers published in English were reviewed and there is no limit on the age of the papers or studies.

PLANT DESCRIPTION AND DISTRIBUTION

Hymenocardia acida (Tul) belongs to the plant family Phyllantaceae though it was formerly classified under the families Euphorbiaceae and Hymenocardiaceae (Tuenter *et al*.,2016). It is a small dioecious (male and female flowers occurring on different trees), deciduous savannah tree or shrub about 9 m high, it's branches become rusty brown when the bark peels off and the bark is smooth or flaky and pinkish-brown when they are freshly collected and changes to pale brown or gray after a while (Ahmad *et al*., 2021).

The generic name *Hymenocardia* is derived from the Greek words 'hymen' meaning 'membrane' and 'kardia' meaning ' heart', which is in reference to the heart-shaped fruits that have a transparent covering membrane (hymen). The specific label *acida* describes the sour taste of its fruits (Orwa *et al*., 2009).

Hymenocardia acida is found mostly in savannah, scrub and open woodland in association with *Parinari curatellifolia*, *Isoberlinia* specie, *Stereospermum kunthianum*, *Parkia clappertoniana* and *Protea madiensis*. The plant grows on sandy, loamy and clayey soils. The plant is reported to be native to Angola, Cameroon, Chad, Congo, Cote d'Ivoire, Gambia, Ghana, Guinea-Bissau, Kenya, Mali, Mozambique, Niger, Nigeria, Senegal, Tanzania, Togo, Uganda, Zambia and Zimbabwe (Orwa *et al*., 2009).

PLATE I: Picture of *Hymenocardia acida* in its natural habitat

ETHNOMEDICINAL USES

The leaf, stem bark, and root are commonly used as medicines. Young fruits and leafy shoots of *Hymenocardia acida* are eaten as supplementary food (Burkill, 1985). Infusion made of the leaf is taken to treat small pox, chest pain and oedema caused by malnutrition. Extract obtained from leafy twigs is rubbed on sickly children to strengthen them. Furthermore, Leaf preparations are used either singly or in combination with other parts of the plant (root, bark or stem) in the treatment of stomach ache, trypanosomiasis, cough, eye infections, headache, otitis, fever, haemorrhoids, gall bladder problems, rheumatic pains, toothache, asthma and snake bites. Additionally decoction made of the leaf is used for bathing to treat tetanus, convulsion and fatigue (Schmelzer, 2008).

In some parts of west Africa, the stem bark of *Hymenocardia acida* is chewed with kola to treat dysentery treat, pulmonary infections, syphilitic sores, diarrhea, dysentery, menstrual pains, abdominal pains, painful swellings, infertility, cough, epileptic fits, colic, abscesses and tumours, migraine, skin and eye infections (Schmelzer, 2008). It is reportedly used for bone setting and as an anti-inflammatory agent by traditional bone healers. Furthermore, in Northern Nigeria, the preparations of leaf and stem bark or root bark is used for the treatment of different categories of pain such as sickle cell crisis, menstrual pain and migraine and it is also used among the Idoma and Igede people in the treatment of diabetes (Tor-Anyiin *et al*., 2013).

Root bark is used in treatment of malaria, toothache, stomatitis, pyorrhea and as anti-enteralgic; it is also used in treatment of sterility, prevention of miscarriage and as aphrodisiac. Root and stem barks of the plant are used in combination as an emetic antidote to ordeal poison (Burkill, 1985). The root extracts of the plant have shown insecticidal activity while the leaf, bark and roots of the plant are used either in powdered form or infusion to treat hypotension, diabetes, sickle cell, epilepsy, schizophrenia (Bum *et al*., 2011).

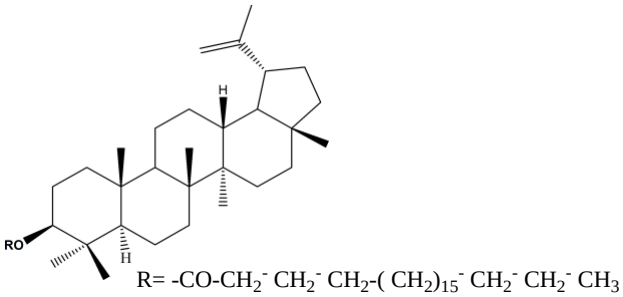
PHYTOCHEMICAL CONSTITUENTS

Based on phytochemical analysis, the stem bark of *Hymenocardia acida* was reported to contain carbohydrates, saponins, tannins, alkaloids, flavonoids, terpenes and steroids where as anthraquinones and glycosides were absent (Olotu *et al*., 2011; Usman *et al* ., 2021). In contrast, however, Ukwe, (1997), Abu and Uchendu, (2010) and Abu *et al*., (2011) reported the presence of glycosides in the stem bark of *Hymenocardia acida*. Additionally, anthraquinones were reported to be present in both aqueous and ethanol leaf extract of the plant (Oshomoh and Idu, 2012). Both the root and stem bark of *Hymenocardia acida* were reported to contain tannins, steroids, terpenes, saponins and alkaloids (Tona *et al*., 1998). On the other hand, the leaves of *Hymenocardia acida* were reported to contain carbohydrates, resins, balsams, flavonoids, flavonols, saponins, alkaloids, anthraquinones, proanthocyanidines, cardiac glycosides, tannins, triterpenoids, phenols and steroidal nucleus (Sofidiya *et al*., 2006; Ibrahim *et al*., 2007; Sofidiya et al., 2009; Sofidiya *et al*., 2010b; Kamba and Hassan, 2011; Obidike *et al*., 2011; Haruna *et al*., 2017; Wada *et al*., 2017; Bafor *et al*., 2018). Similarly, the presence of saponins, terpenes, flavonoids, steroids, tannins, alkaloids, carbohydrates, protein and glycosides in *Hymenocardia acida* timber were reported (Udeozo *et al*., 2017). Furthermore, the leaf and stem bark were found to contain anthraquinones, flavonoids, carbohydrates, saponins, cardiac glycosides, tannins, terpenes and steroids (Iyadi *et al*., 2003). Lastly, the root, stem bark and leaf of *Hymenocardia acida* were all reported to have alkaloids, anthraquinones, flavonoids, carbohydrates, saponins, sugars, tannins and terpenes.

However, steroids were reported to be present in the stem bark and leaf of the plant (Agbidye *et al*., 2020).

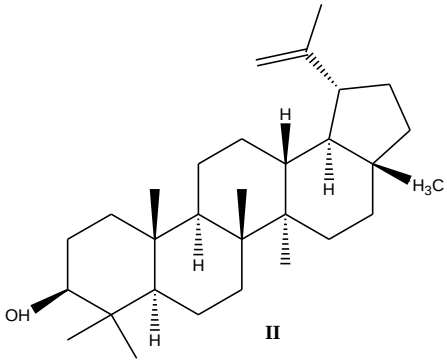
ISOLATED COMPOUNDS

Several phytochemical compounds were isolated from different parts of *Hymenocardia acida*. Lupeyl docosanoate (**I**) a lupane type triterpene along with lupeol (**II**) β-sitosterol (**III**) were isolated from the stem bark of *Hymenocardia acida* (Mahmout *et al* ., 2008). In addition, β-sitosterol (**III**) was reported to be isolated from the roots of *Hymenocardia acida* (Shimbe *et al*., 2016). Also, five triterpenoids namely friedelan-3-one(**IV**), betulinic acid (**V**) and lupeol (**II**), β-sitosterol (**III**), stigmasterol(**VI**) together with oleic acid(**VII**) and hymenocardine(**VIII**) were reported to have been isolated from the stem bark of the plant (Pais *et al* .,1968; John and Alexander, 2008; Mpiana *et al*., 2009).



R= -CO-CH_2- CH_2- CH_2-(CH_2)$_{15}$- CH_2- CH_2- CH_3

I



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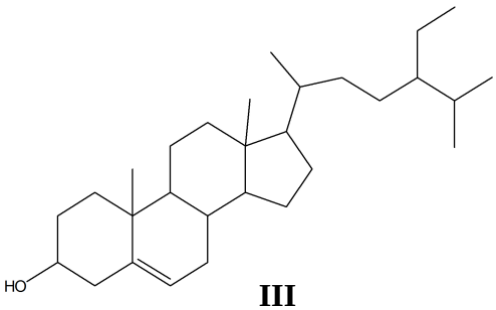
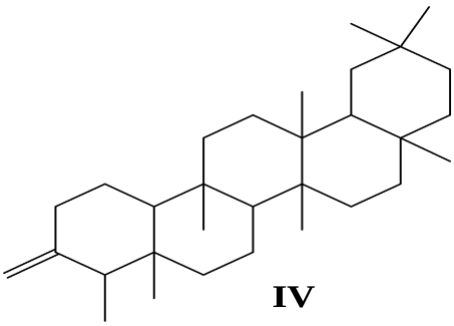


III



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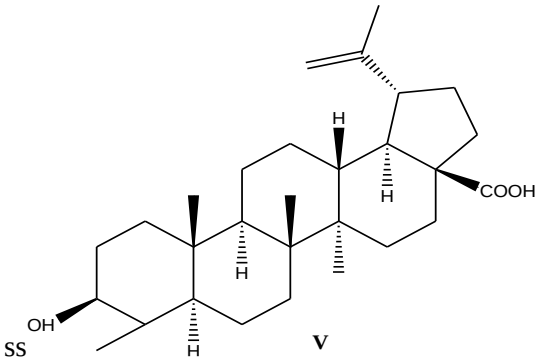

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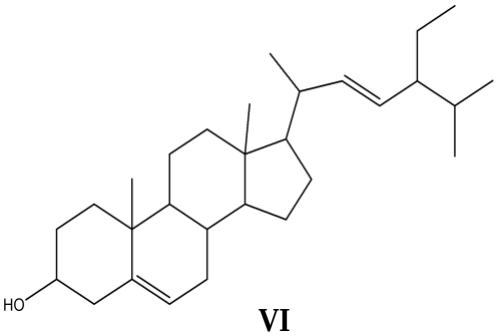

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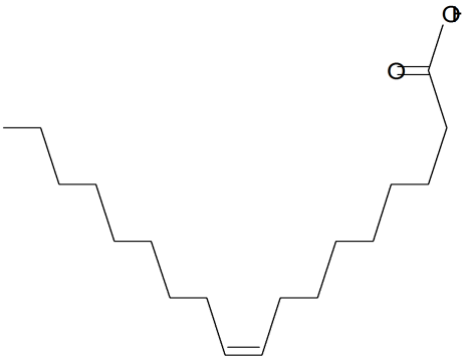
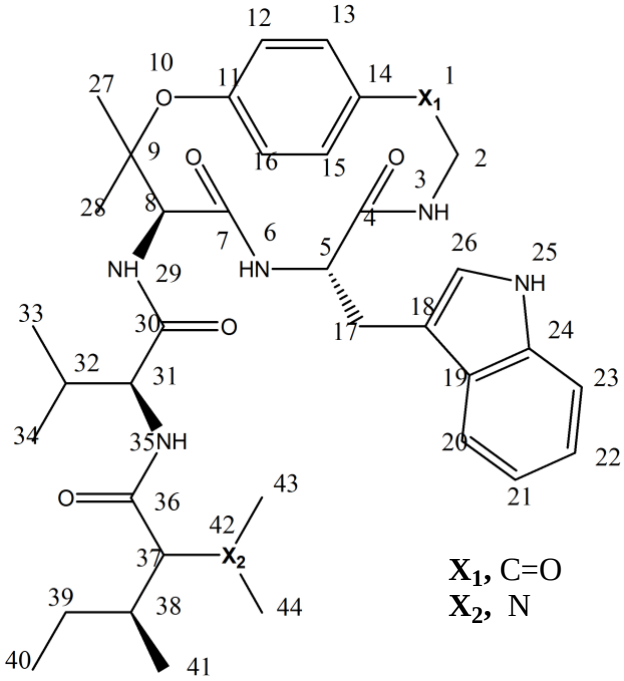
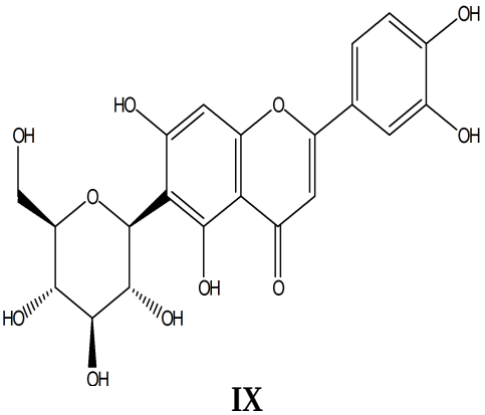


VII

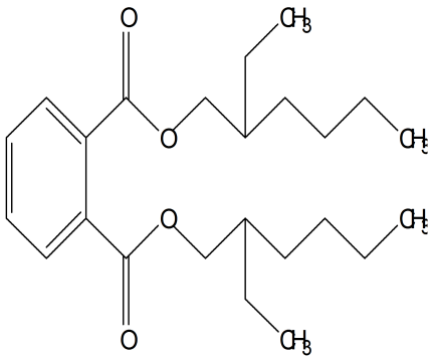


VIII

Futhermore, homoorientin (**IX**) and di(2ethylhexyl) phthalate (DEHP) (**X**) were isolated from the leaf of *Hymenocardia acida* (Sofidiya *et al* ., 2010a). Although the compound exists as an environmental contaminant, it is recently found to be produced by plants or microorganisms like bacteria or fungi (Ortiz and Sansinenea, 2018).

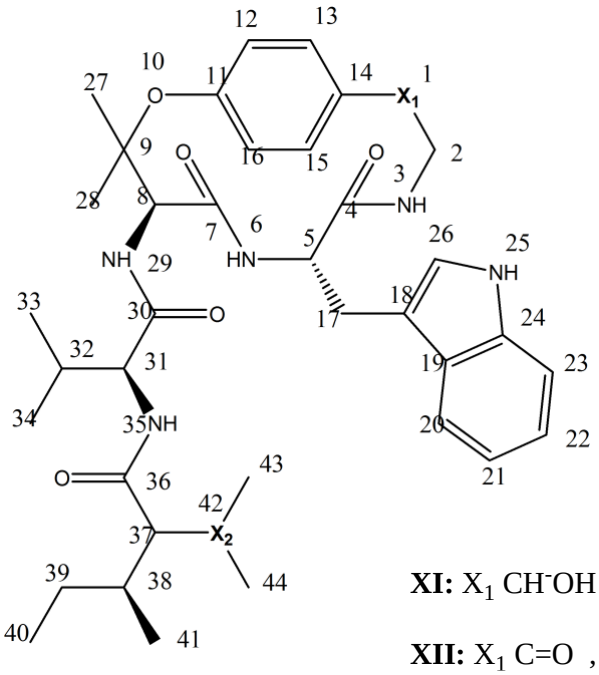


IX



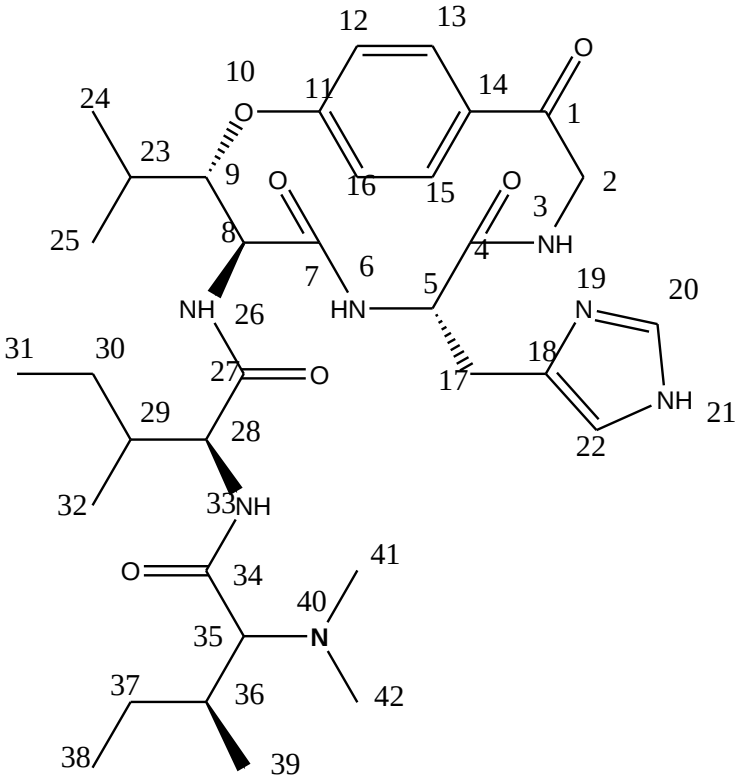
X

The root bark of *Hymenocardia acida* was found to contain four cyclopeptide alkaloids three of which were isolated for the first time from a natural source; hymenocardinol (**XI**) a derivative of hymenocardine with hydroxyl group, hymenocardine N-oxide (**XII**), hymenocardine-H (**XIII**), and hymenocardine (**VIII**) (Tuenter *et al*.,2016)



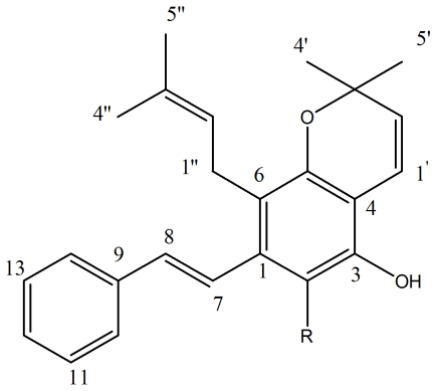
XI: X_1 $CH^{-}OH$, X_2=N

XII: X_1 C=O , $X_2=N^{+}$ $-O^{-}$



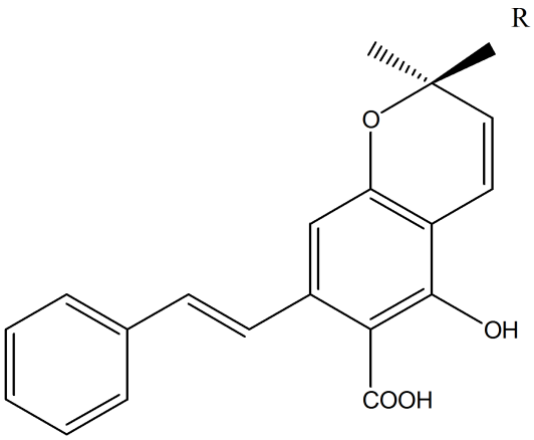
XIII

In addition, seven new stilbenoid compounds namely hymenocardichromene A (**XIV**), hymenocardichromene B (**XV**), hymenocardichromene C (**XVI**), hymenocardichromene D **(XVII**), hymenocardichromene E (**XVIII**), hymenocardichromene F (**XIX**), hymenocardichromanic acid (**XX**) were reported to be isolated from the active fractions of the leave extract during screening for antiproliferative activity of the plant (Starks *et al*.,2014).

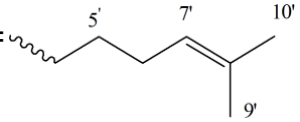


XIV: R=H

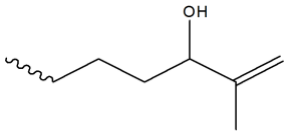
XV: R=COOH



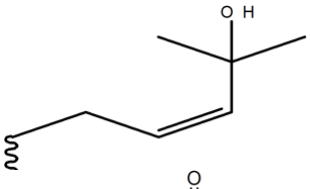
XVI: R=



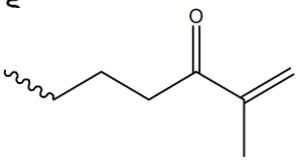
XVII: R=

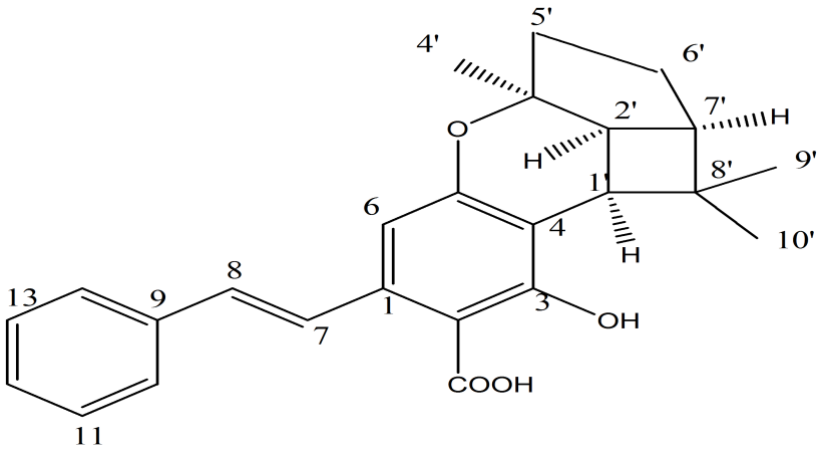


XVIII: R=



XIX: R=





XX

BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES

Anti-sickling activity has been reported from leaf and stem bark (Iyadi *et al*., 2003; Ibrahim *et al*., 2007). In another study, anthocyanins were reported to be responsible for the antisickling activity of *Hymenocardia acida* (Mpiana *et al*., 2009).

In a study conducted by Shimbe *et al*., (2016) Hexane, ethyl acetate and methanol extracts of *Hymenocardia acida* root exhibited a positive activity against *Staphylococcus aureus*, *Streptococcus pyrogens*, Methicillin-resistant *Escherichia coli*, *Klebsiella pneumoniae*, *Candida tropicalis*, and *Candida stellatoidea*. The methanol extracts of the stem bark and roots of *Hymenocardia acida* showed fungicidal effects on the fungus *Candida albicans* and bactericidal properties on *Staphylococcus aureus* and *Streptococcus pyogens* at a concentration of 1.0×103 mg/mL (Agbideye *et al*., 2020). Similarly, Starks *et al*., (2014) reported moderate activity of chromene and chromane stilbenoids against methicillin resistant *Staphylococcus aureus* at a concentration of 8 ųg/mL. Likewise, the aqueous and methanol extract of the leaf of *Hymenocardia acida* were reported to possess antibacterial activity (Sofidiya *et al*., 2009). Moreover, ethanol stem extract of *Hymenocardia acida* was found to have antibacterial and antifungal activities against some selected organisms: *A. flavus* (fungus) followed by *B. subtilis* (gram +ve rod bacteria), *S. mutans* (gram +ve), *S. auricularis* (gram +ve), *S. aureus* (gram +ve), *C. albicans* (fungus), *S. pyogenes*(gram +ve) and *M. gypseum* (fungus) respectively this provides evidence for the traditional use of the plant as chewing stick (Oshomoh and Idu, 2012). In a similar study, ethanol leaf extract of *Hymenocardia acida* was reported to have significant effect against some opportunistic respiratory pathogens and moderate activity against *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. However, the extract didn't inhibit growth of *Candida albicans* and *Klebsiella pnuemoniae* (Obidike *et al*., 2011). Also, the anti-amoebic effect of *Hymenocardia acida* was reported by Tona *et al*., (1998). Sar *et al*., (2014) reported that *Hymenocardia acida* had a positive effect against allergic airway inflammation. The methanol leaf and stem bark exract of *Hymenocardia acida* was reported to have significant antidiarrheal activity (Bafor *et al*., 2018; Usman *et al*., 2021). Abu *et al*., (2009) reported the *in vitro* potential of aqueous ethanol extract of *Hymenocardia acida* in the treatment of African trypanosomiasis. In a study conducted by (Freiburghaus *et al*., 1996; Hoet *et al*., 2004) methylene chloride and petroleum ether extracts of *Hymenocardia acida* leaf and root bark, respectively were believed to have strong *in vitro* antitrypanosomal activity. However, the antitrypanosomal study carried out by Yusuf *et al*., (2012) revealed that both methylene chloride and petroleum ether extracts of *Hymenocardia acida* leaf and root bark do not possess strong *in vitro* antitripanosomal activity. Antiplasmodial activity of the plant has also been reported (Vonthron-Senecheau 2003; Mahmout *et al*., 2008; Mwangu-Kabi *et al*., 2020)

Additionally, ethanol extract of *Hymenocardia acida* stem bark caused cessation of oestrus cycle at the diestrus phase in female albino rats (Abu and Uchendu 2011). Similarly, strong anti-implantation and antifertility activities were observed when ethanol extracts of the plant stem bark was administered to female albino rats during pregnancy (Abu and Uchendu, 2010). Moreover, sperm immobilization properties of aqueous ethanol extract of stem bark of the plant was evaluated by Abu *et al*., (2011) and the result showed that the extract has an effect on the motility of rat spermatozoa.

Furthermore a research conducted by Ukwe (1997) showed that the aqueous extract of stem bark of *Hymenocardia acida* exhibited antiulcer effects in laboratory animals.

It has been reported that the aqueous and methanol leaf extracts of *Hymenocardia acida* Tul. Exerts its pharmacological activity by interaction with antioxidant enzymes, reactive oxygen species and extra cellular calcium which may likely be the reason why the plant possesses various pharmacological activities (Ogbunugafor *et al*., 2010). Sofidiya *et al*., (2009) reported that methanol extracts of *Hymenocardia acida* exhibited antioxidant activity which was attributed to its phenolic compounds. The significant antioxidant activity of this plant might be the reason why the plant

possesses anti-cancer activity. In a study conducted by Muanza *et al*., (2008), the methanol extract of the root bark exhibited moderate cytotoxic activity against 60 human cell lines. Cytotoxicity of extracts from the leaf of *Hymenocardia acida* has been reported by Vonthron-Senecheau (2003). In addition, leaf extract of *Hymenocardia acida* showed activity against NCI-H460 lung cancer cells (Starks *et al*., 2014).

In a research conducted by (Ezeigbo and Asuzu 2012), the methanol leaf extract of *Hymenocardia acida* demonstrated significant hypoglycemic activity in alloxan diabetic rats and reduced serum lipid levels associated with diabetes mellitus. Similarly, methanol and chloroform extracts of *Hymenocardia acida* were found to ameliorate insulin resistance in skeletal muscle cells (Ezeigbo *et al*., 2016).

Saponin rich fraction of *Hymenocardia acida* exhibited significant analgesic activity (Olotu *et al*., 2011). Furthermore, the aqueous leaf extract of *Hymenocardia acida* was reported to possess significant anti-inflammatory and anti-nociceptive activity (Sofidiya *et al*., 2010bs). Also, Sackeyfio (1988) reported that *Hymenocardia acida* extract possessed anti-inflammatory activity in rat.

Wada *et al*., (2017) reported that ethanol leaf extract of *Hymenocardia acida* protected 50% of mice against seizures; it increased the mean onset of seizures induced by-aminopyridine and protected 33.3% of mice against pentylenetetrazole induced convulsion. Similarly methanol leaf extract of the plant demonstrated anticonvulsant activity which is believed to be due to the presence of bioactive compounds (Haruna *et al*., 2017)

Hymenocardia acida can also find application in the management of hypertension as the methanol extracts of root bark of the plant was reported to possess vaso-relaxant and hypotensive activity (Nsaudi *et al*., 2013).

TOXICITY STUDIES

The acute toxicity studies of methanol leaf and root bark extract of *Hymenocardia acida* showed no mortality at a dose of 2000mg/kg (Ezeigbo and Asuzu, 2012; usman *et al*., 2021). In a similar study conducted by Haruna *et al*., 2017, the oral median lethal dose (LD_{50}) of *Hymenocardia acida* in mice was estimated to be above 5000 mg/kg body weight. This shows that *Hymenocardia acida* is not toxic after. In addition, the sub chronic and chronic toxicity study of aqueous ethanol extract of *Hymenocardia acida* stem bark indicated that the plant is relatively safe (Abu and Uchendu, 2010). Moreover, the ethanol extract of root bark of *Hymenocardia acida* has been reported to be safe and has beneficial nutritional constituents (Olotu *et al*., 2017). In addition, aqueous leaf extract of the plant demonstrated potentials in ameliorating deleterious effects of aluminium chloride intoxication (Yakubu *et al*., 2016) and in a similar study, the ethanol leaf extract of *Hymenocardia acida* has been reported to possess mild ameliorative effect against aluminium chloride-induced toxicity (Yakubu *et al*., 2017).

CONCLUSION AND RECOMMENDATION

This review has highlighted various ethnomedicinal uses, phytochemical constituents and pharmacological activities of *Hymenocardia acida*. Promising pharmacological activities of this plant may be attributed to its various phytochemical constituents. Therefore *Hymenocardia acida* should be standardized and used as herbal supplement in the treatment of various ailments.

CONFLICT OF INTEREST

The authors declare no conflict of Interest

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