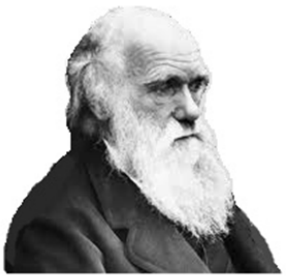
Available online at www.worldnewsnaturalsciences.com



World News of Natural Sciences

An International Scientific Journal

WNOFNS 37 (2021) 41-57 EISSN 2543-5426

Zanthoxylum rhetsa (Roxb.) DC.: A Systemic Review of its Ethnomedicinal Properties, Phytochemistry and Pharmacology

Tochukwu Oluwatosin Maduka* and **Chiyere B. C Ikpa**

Department of Chemistry, Imo State University, Owerri, PMB 2000, Imo State, Nigeria

*E-mail address: tochukwumaduka.edu@gmail.com

ABSTRACT

Zanthoxylum rhetsa also known as Indian prickly ash belongs to the family of aromatic deciduous trees and shrubs, Rutaceae that grows in tropical and subtropical regions of the world. The local use of the plant in different part of the world cannot be over emphasized as it has been both as food, medicine and for pest control. In folk medicine, various parts of *Zanthoxylum rhetsa* are used for the treatment of dental caries, dizzyness and bloating, malaria, urinary diseases, rheumatism, diuretic, stomach ache and diarrhea. Secondary metabolites have been isolated from the roots, stem barks, and fruits. The plant contains Alkaloids, phenolics and terpenoids as the main constituents of the specie. The presence of those compounds gives base for the several biological activities of the plant such as antibacterial, anti-inflammatory, antinociceptive and antidiarrhea, antioxidant, cytotoxic, thrombolytic Activity and photoprotective properties. This review comprehensive study focused on knowledge regarding several ethnomedical uses of the plant, phytochemical constituents and biological activities of the plant.

***Keywords*:** *Zanthoxylum rhetsa*, Rutaceae, Phytochemistry, biological activities

1. INTRODUCTION

Plants have developed chemical defenses over millions of years against environmental threats such as UV radiation, reactive oxygen species, microbial attacks and adverse weather conditions etc. these chemicals have been classified as various secondary metabolites in plants. These metabolites have been utilized as herbal drugs due to their therapeutic activities.

(Received 20 March 2021; Accepted 19 April 2021; Date of Publication 27 April 2021)

The quality, efficacy and safety of the herbal drugs can be ensured by finding reliable characteristics, one of which would be determination of all the phytochemical present in the plant. This would ensure the reliability of plant pharmacology and repeatability of their clinical research. Understanding the bioactivity and determining the authenticity and reliability of chemical constituent of herbal drugs and formulation is vital to this cause. The current scenario unveils the importance of studying plant as potential source of drugs throughout the world.

The plant of emphasis in the research belongs to family Rutaceae, Zanthoxylum rhetsa (Roxb.) DC. *Zanthoxylum rhetsa* Christened Indian prickly ash by de Condole (1824), is a specie of flowering plant in the family Rutaceae, a shrub or tree that sometimes grows to a height of 26 m (85 ft). The plant is sometimes deciduous and has stems with thick, cone-shaped spines on the older stems. The leaves are 140-230 mm long and pinnate, with nine to twenty three egg-shaped to elliptical leaflets.

The flowers are arranged on the ends of branch lets, sometimes also in leaf axils, in panicles up to 150 mm long. The herb is well distributed in tropical and subtropical regions in Africa and other part of the world (Waterman, PG, 1986, "*Zanthoxylum rhetsa*" 2020). The use of z.rhetsa is reflected in different commercial areas. For example: Z.rhetsa plays important roles in construction process, perfumery and food industry as well as in traditional medicine. The timber of this species has been used (Dalziel, 1937; Oliver-Bever, 1982) in house and boat-building, decorative paneling joinery, construction of talking drums and in the paper and pulp industry.

The roots, bark and leaves are used in various medicinal preparations for example (Olatunji, 1983) paste made from the hard spines of Z. rhetsa is used as a pain relief and to increase lactation in nursing mothers (Lalitharani, 2013). The bark has been reported to be a remedy for stomach and chest pains, and also to treat snake bite. The fruits and seeds of *Z. rhetsa* are used to treat toothache, dizzyness and bloating, malaria, urinary diseases and rheumatism. The leaf decoction is used to treat intestinal worm infections and as insecticide. The most popular domestic use of the root in Nigeria is as chewing stick to clean the mouth. Due to the warm, pungent and benumbing effect when chewed, the aromatic warm taste with profuse salivation is believed to be beneficial to the elderly and those with sore teeth and dental caries (Adesina, 2005).

The specie has also been reported to be routinely used as food in some Asian countries, for example; the shoots are consumed as food by indigenous people of northeast India, and the Northern Thai people use the fruit as a spice, and an appetizer especially in pork salad and curry (Wongkattiya, 2018). The plant bark extract has also been used in the cosmetic industry as an ingredient in formulations of natural sunscreen (Santhanam et al, 2019). The Zanthoxylum genus is well known to contain phytochemicals which are responsible for its medicinal/therapeutic properties, particularly, Characteristic secondary metabolites of *Zanthoxylum* species include lignoids, alkaloids, amides, flavonoids, terpenes, sterols and coumarins (Patiño, 2008).

Alkaloids are abundant in the trunk, root and bark, and are typically of the isoquinoline and quinolone types. Lignoids are also abundant in the genus. Previous phytochemical investigations on *Z. rhetsa* have shown the presence of a variety of compounds including monolignols, coumarins, alkaloids and lignans.

These compounds are a few of the isolated compounds from the plant species. The plant has been reported to exhibit antimalarial, antimicrobial, anticancer, antidiarrheal, antioxidant and antiviral activities and many more therapeutic activities.

2. NOMENCLATURE

Table 1. Scientific Classification of the plant

Kingdom:	**Plantae**
Clade:	Tracheophytes
Clade:	Angiosperms
Clade:	Eudicots
Clade:	Rosids
Order:	Sapindales
Family:	Rutaceae
Genus:	*Zanthoxylum* L.
Species:	*Zanthoxylum rhetsa* (Roxb.) DC.

(A)

(B)

(C)

(D)

Figure 1(A-D). *Zanthoxylum rhetsa* (Roxb.) DC.: **(A)** prickles, **(B)** stem barks, **(C)** leaves and fruits, **(D)** tree length.

3. ETHNOMEDICAL AND TRADITIONAL USES

Traditional healers have used different species of the *Zanthoxylum* for treatment of a wide range of disorders, including urinary and venereal diseases, rheumatism and lumbago. The bark decoction is used to treat chest pain and chewed bark applied as antidote for snake bites. The eastern Nigerians use the roots as chewing stick to treat dental caries.

The *Kanikkars* tribe the apply the paste prepared by rubbing the hard spines on a rock along with water on the breast to give relief from pain and increase lactation in nursing mothers (Suresh Lalitharani, 2010). In the folk medicine of Naga tribes in India, it is used as a deworming remedy. Stem bark and root bark of *Z. rhetsa* are used to treat malaria, rheumatism, loss of stomach tone; fruit could be used in the treatment of diarrhea and rheumatism. (Nguyen Van Hieu, 2020).

In India traditional medicine, the bark has been used to treat cardiac, respiratory diseases, tooth infection, stomach infection and rheumatism.

The fruits are used as spice and the essential oil extracted from the fruits is known as "Mullilam oil" which is used as anti-inflammatory, antiseptic, anticholera, diarrhea, hypo-cholesterolemic, mosquito repellent and soothing agent for dental caries. In the Philippines, the powdered bark mixed with oil is a best formula to treat stomach ache.

3. 1. Vernacular Names

It is commonly known as "Malvapoou" in *Kanikkar* tribals of Agasthiarmalai Biosphere Reserve, Western Ghats, Tamil Nadu. Local name in Bangladeshi is Bazna, Bazinali. The tree is locally known as 'batangberduri' (Malay) or 'tirphal' (Indian) also commonly known as mullilam in some part of India.

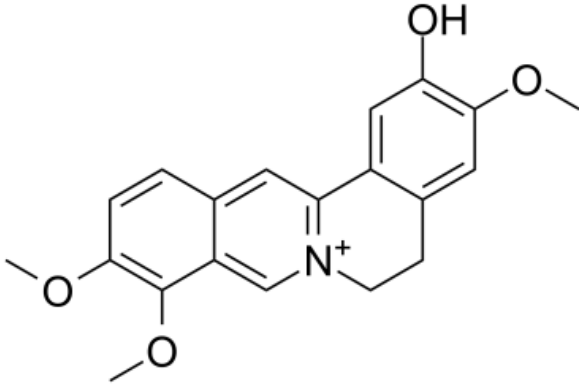
3. 2. Phytochemistry

The large pan-tropical genus Zanthoxylum is very well known (Mester, 1983; Simanek, 1985) for its diverse chemistry, particularly of alkaloids, aromatic and aliphatic amides, sterols and polyphenols. These secondary metabolites are well distributed in the Zanthoxylum species investigated to date. In this section, the isolated compounds are presented.

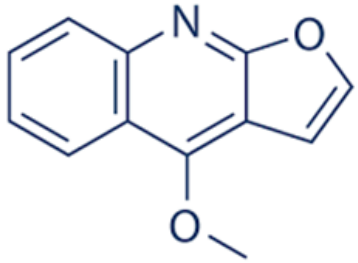
3. 3. Alkaloids

Alkaloids are abundant in the stem and root bark, and are typically of the isoquinoline and quinolone types. From the stem bark of the plant Santhanam (2016) isolated a Berberine alkaloid Columbamine and Quinolone alkaloid 8-methoxy-N-methylflindersine, Furoquinoline alkaloids dictamnine and skimmianine were isolated by Rahman and his colleagues (2008), other alkaloids isolated from the stem bark by Rahman were *Rutaecarpine*, canthin-6-one and evodiamine.

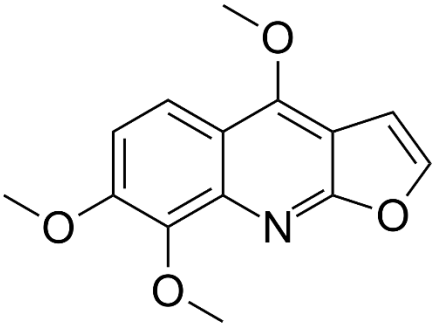
Alkaloids were also isolated from the roots of the plant, they include quinoline alkaloids Zanthodioline and 8-methoxy-N-methylflindersine (also isolated in the bark) isolated by Zohora et al (2019), and Ahsan et al, (2014) isolated five alkaloids Chelerybulgarine, Simulanoquinoline, 2-episimulanoquinoline and 2,11-didemethoxyvepridimerine B and Rhetsidimerine.



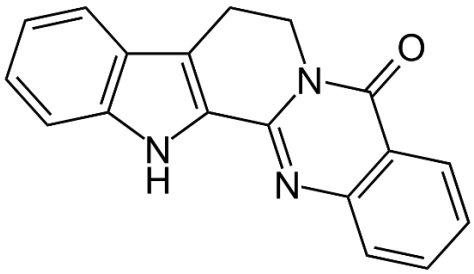
Columbamine



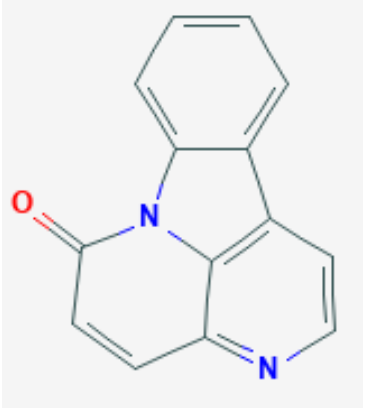
Dictamnine



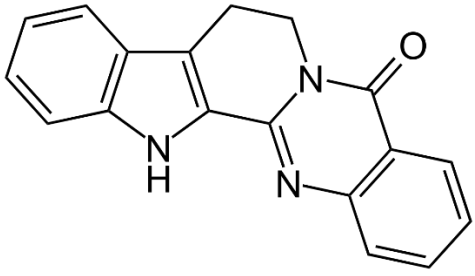
Skimmianine



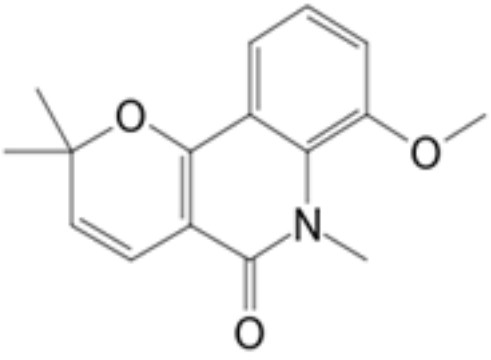
Rutaecarpine



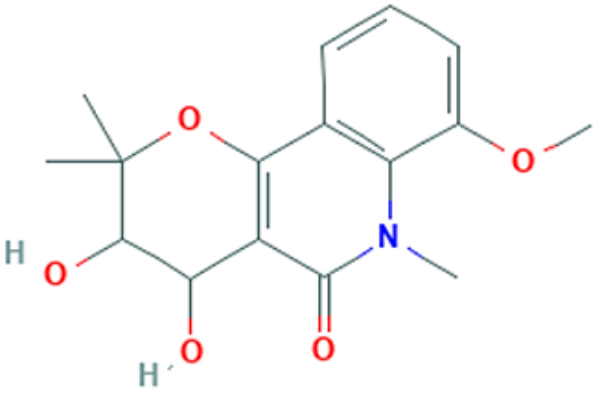
Canthin-6-one



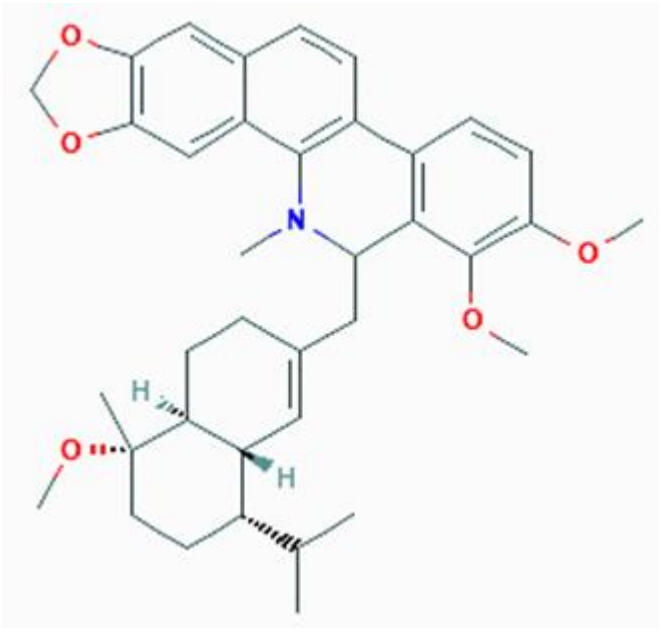
Evodiamine



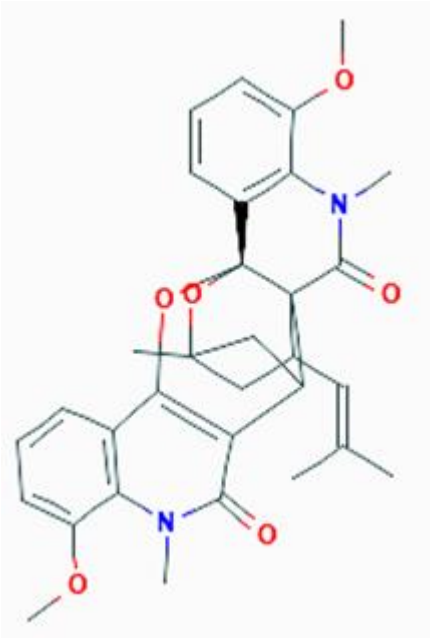
8-methoxy-N-methylflindersine



Zanthodioline

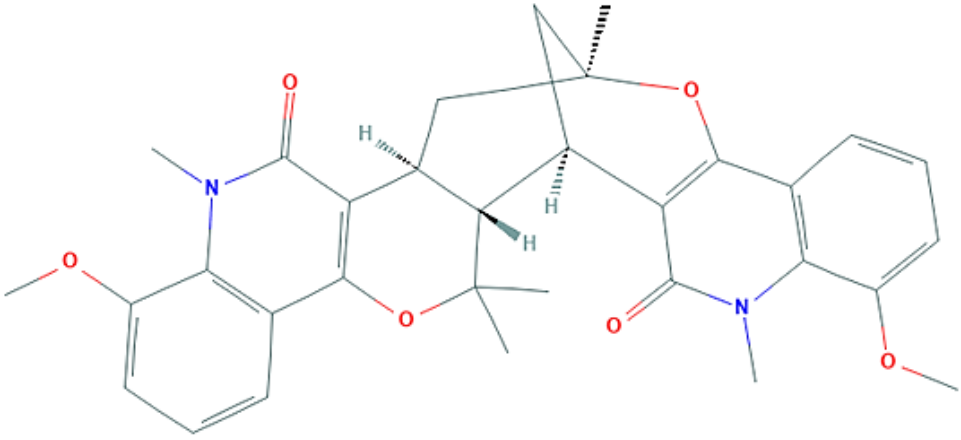


....



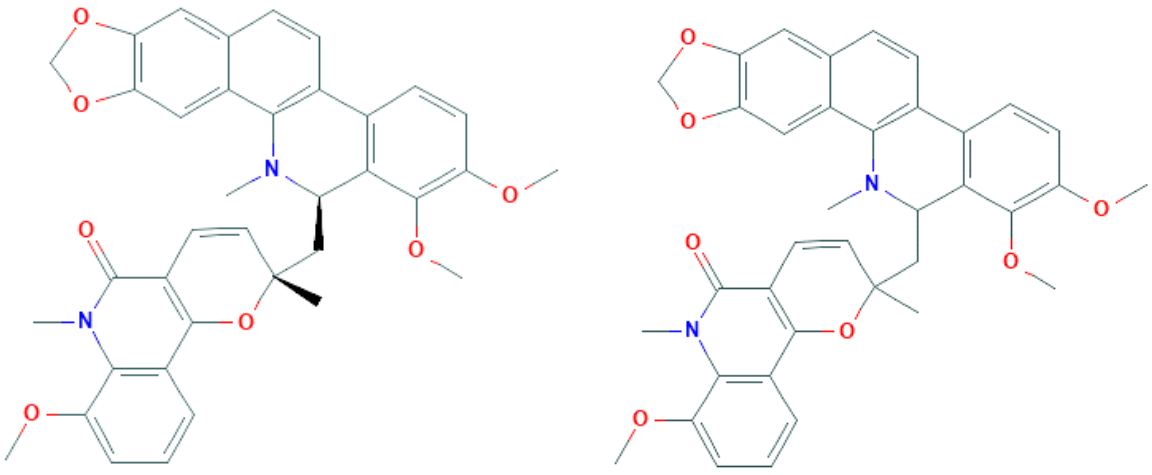
Chelerybulgarine

Rhetsidimerine



..

2,11-Didemethoxyvepridimerine B

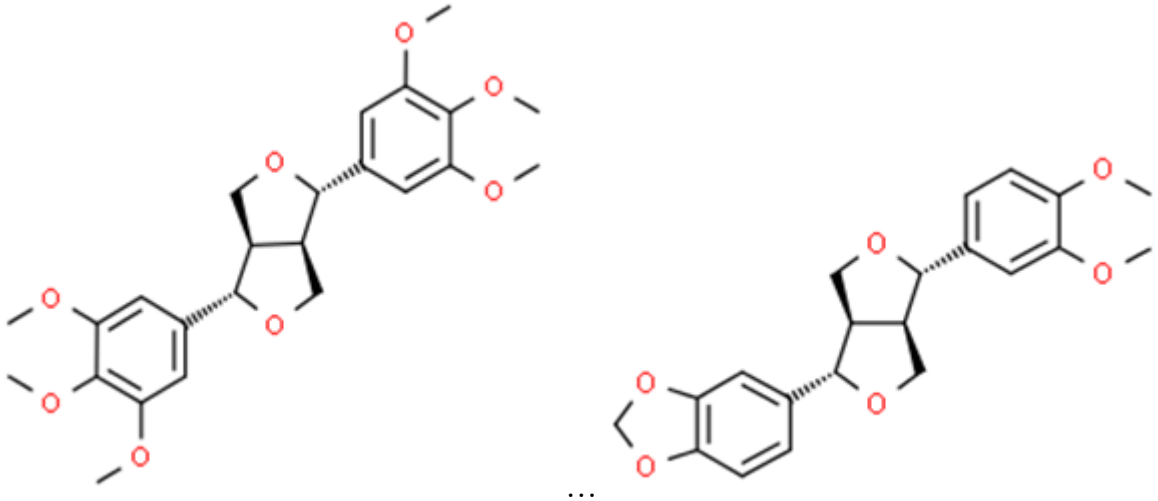


2-episimulanoquinoline Simulanoquinoline

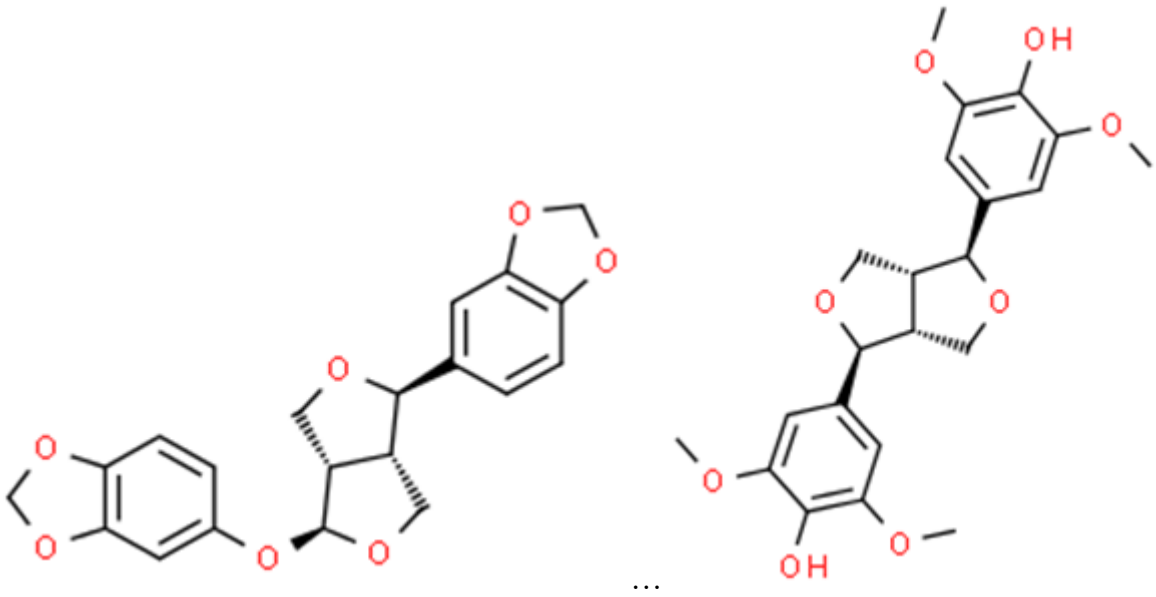
Figure 2. Showing the structure of alkaloids isolated from the stem bark and roots of *Zanthoxylum rhetsa*

3. 4. Phenolic compounds

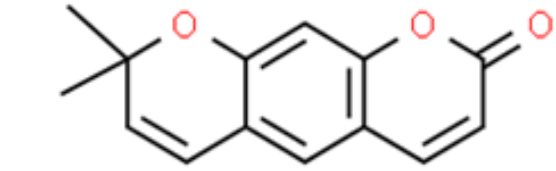
Phenolic compounds are a group of small molecules characterized by their structures having at least one phenol unit. Based on their chemical structures, phenolic compounds can be divided into different subgroups, such as phenolic acids, flavonoids, tannins, coumarins, lignans, quinones, stilbens, and curcuminoid. They possess antioxidant activity, their antioxidant capacities are related to these hydroxyl groups and phenolic rings. All phenolic compounds in this literature have been isolated from the stem bark of the plant, the phenolic compounds found to have been isolated are from the Lignans and Coumarins subgroup.



Yangambin Kobusin



Sesamin … Syringaresinol



Xanthyletin

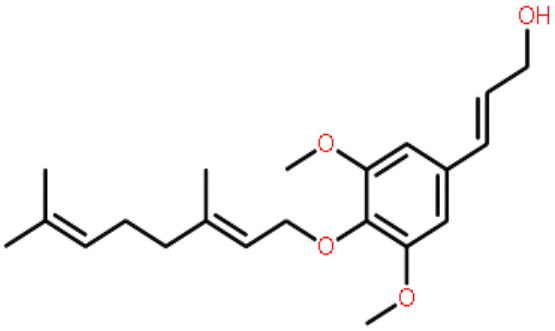
Figure 3. Showing the structure of the phenolic compounds isolated from parts of the plant terpenoids

The lignans isolated are yangambin and kobusin isolated by Santhanam (2016), Sesamin isolated by Ahsan et al (2000) and Rahman et al (2008) isolated Syringaresinol. Ahsan et al (2000) further isolated Xanthyletin a Coumarin from the stem bark of the plant.

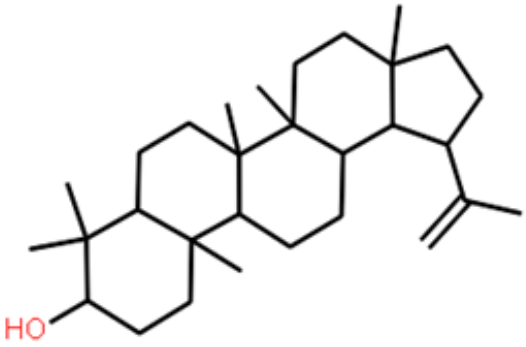
The terpenoids, also known as isoprenoids, are a large and diverse class of naturally occurring organic chemicals derived from the 5-carbon compound isoprene, and the isoprene polymers called terpenes. Certain terpenes were widely used in natural folk medicine. Terpenoids have been isolated in the fruits and bark of of *Zanthoxylum rhetsa*.

A triterpenoid lupeol (Santhanam et al; 2016) and 3, 5-Dimethoxy-4-geranyloxycinnamyl alcohol have been isolated in the stem bark of the plant and Mathur reported the isolation of Mullilam-diol an Odidodiol from the fruits of the plant.

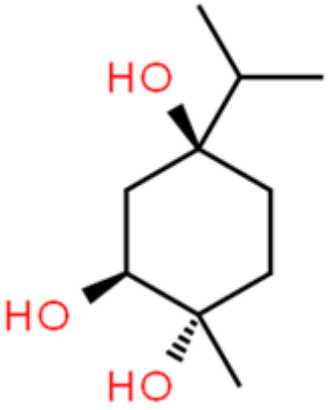
These compounds have been reported to possess pharmacological properties for example, Lupeol, selectively induced substantial head and neck squamous cell carcinoma (HNSCC) cell death (Lee TK et al., 2007).



3, 5-Dimethoxy-4-geranyloxycinnamyl alcohol



Lupeol



Mullilam-diol

Figure 4. Showing isolated terpenoids

Table 2. Compounds isolated from different parts of *Zanthoxylum rhetsa*

Plant part	Phytochemical	Compound	Molecular formula	Reference
bark	alkaloids	**berberine alkaloid**: columbamine (s)	$C_{20}H_{20}NO_4^+$	Santhanam (2016)[S] Rahman (2008)[R]
		quinolone alkaloid: (8-methoxy-N-methylflindersine)	$C_{16}H_{17}NO_3$	
		furoquinoline alkaloids: dictamnine (R)	$C_{12}H_9NO_2$	
		skimmianine (R)	$C_{14}H_{13}NO_4$	

		other alkaloids include: rutaecarpine (R) canthin-6-one (R) evodiamine (R)	 $C_{18}H_{13}N_3O$ $C_{14}H_8N_2O$ $C_{19}H_{17}N_3O$	
	phenolics	**lignan:** yangambin (s) kobusin (s) sesamin (A) syringaresinol (R)	 $C_{24}H_{30}O_8$ $C_{21}H_{22}O_6$ $C_{20}H_{18}O_6$ $C_{20}H_{18}O_6$	 Santhanam (2016)[S] Ahsan (2000)[A] Rahman (2008)[R]
		coumarin: xanthyletin (A)	 $C_{14}H_{12}O_3$	Ahsan (2000)[A]
	terpenoids	lupeol (s) 3,5-dimethoxy-4-geranyloxycinnamyl alcohol	$C_{30}H_{50}O$ $C_{21}H_{30}O_4$	Santhanam (2016)[S]
fruit	terpenoids	Mullilam-diol	$C_{10}H_{18}O_3$	Mathur (1967) [M]
roots	alkaloids	chelerybulgarine (A) simulanoquinoline (A) 2-episimulanoquinoline (A) 2,11-didemethoxyvepridimerine B(A) rhetsidimerine (A) **quinoline alkaloid:** zanthodioline (Z) (8-methoxy-N-methylflindersine) (Z)	$C_{37}H_{46}NO_5$ $C_{37}H_{34}N_2O_7$ $C_{37}H_{34}N_2O_7$ $C_{32}H_{34}N_2O_6$ $C_{32}H_{34}N_2O_6$ $C_{16}H_{19}NO_5$ $C_{16}H_{17}NO_3$	Ahsan (2014)[A] Zohora (2019)[Z]

3. 5. Pharmacology

It is interesting to note that scientific studies including selected biological investigations, based on ethno medical information have led to the discovery of new bioactive compounds some of which are potential leads for the pharmaceutical sector. Some of the biological activities of *Z.rhetsa* are discussed in this part of the literature.

3. 6. Antibacterial activity

Compounds isolated from the stem bark has been tested against a panel of bacteria (both Gram positive and Gram negative) and fungi by Rahman et al, Among the compounds tested, the lignans exhibited more potent antibacterial activities compared to the alkaloids (Rahman et al, 2008). Zohora et al employed the agar disc diffusion method for the determination of antimicrobial activities. The methanol crude root extracts of Z. rhetsa and its Carbon Tetra Chloride, Chloroform, aqueous soluble fractions and 8-methoxy-n methylflindersine exhibited significant antibacterial activity against microbial growth which indicated that these extracts

contain chemical substances having antibacterial property. The antibacterial activity of compounds isolated from the roots and stem barks of *Zanthoxylum rhetsa*was evaluated. The result presented by Tantapakul et al (2012) after testing for the antibacterial activity of Dihydrochelerythrine extracted from Z.rhetsa, showed that Dihydrochelerythrine exhibited strong activity against methicillin-resistant *Staphylococcus aureus* SK1 and moderate activity against *Escherichia coli* TISTR 780 with MIC values of 8 and 16 g/mL, respectively.

3. 7. Anti-inflammatory activity

Parthiban et al (2017), carried out *in vitro* study of anti-inflammatory activity of stem of the plant *Z. rhetsa* (Roxb.) by protein denaturation and HRBC method. *The* stem extract showed significant anti- inflammatory activity. The anti-inflammatory activity of essential oil was also tested by Nguyen Van Hieu et al (2020), they measured the production of NO in lipopolysaccharide (LSP)-activated RAW 264.7 macrophage cells. The essential oil of *Z. rhetsa* (ZR) showed significant inhibitory effect of NO production with the IC50 value of 16.42 ng/mL. They concluded that *Z. rhetsa* possesses excellent anti-inflammatory activity and thus have great potential in treatment of inflammation.

3. 8. Antioxidant activities

A great number of medicinal plants contain chemical compounds that exhibit antioxidant properties. Antioxidant activities has been studied in vitro by free Radical scavenging activity. The Radical scavenging activity of the oil samples from *Z. rhetsa* seeds have been tested with DPPH radical according to a method developed in-house by Theeramunkong et al, 2018. In the antioxidant activity test the extracted oil (at concentration 1200µg/ml) showed 78.5 % and 75.5% activity comparable to that of α - tocopherol. The free radical scavenging effect of different parts like seed, seed coat and the entire fruit extracts were assayed *in vitro* by 1, 1-diphenyl-2-picrylhydrazyl (DPPH), the results showed a concentration dependent increase in the scavenging effect, The free radical scavenging activity of the extracts was compared with the synthetic antioxidants like BHT and PG. it showed strong Antioxidant activity in comparison with the standard antioxidant. The antioxidant activity of the petroleum ether (PE), carbon tetrachloride (CTC), chloroform (CF) and aqueous (AQ) soluble fractions of crude methanolic *Z rhetsa* root bark with two isolated quinolone alkaloids, 8-methoxy-n-methylflindersine and zanthodioline was also assessed by Zohora et al, (2019) by using DPPH assay. AQ fraction exhibited strongest antioxidant, activity among four fractions. The CTC and CF soluble fractions exhibited significant antioxidant.

3. 9. Antinociceptive and antidiarrheal activity

The methanolic extract of *Z. rhetsa* stem bark was tested for Analgesic activity by acetic acid induced writhing and antidiarrheal activity by castor oil induced diarrhea in mice. The extract was given by oral route to Mice at doses of 250 and 500 mg/kg, significantly reduction in the abdominal contraction induced by acetic acid and the diarrheal episodes induced by castor oil in mice was noticed (Rahman, 2002). The observed anti-diarrheal activity of the plant seems to confirm the local use in pain and diarrhea related ailments. The antidiarrheal activity of the essential oil of the plant was assessed against castor oil induced diarrhea by Naik et al, 2015. They reported that the antidiarrheal activity of the oil might be associated with the spasmolytic activity of the active constituents of the oil which reduce peristaltic movement.

3. 10. Cytotoxicity and anticancer activity

Santhanam and his colleauges investigated the chloroform fraction and kobusin extracted from the bark and reported it exhibit cytotoxic effect against B16-F10 melanoma cells. The selective cytotoxicity of the extract and isolated compounds was attributed to the metabolic defects in the cancerous cells or the peculiar reaction of the compounds against the melanoma cells (Santhanam, 2016). The cytotoxicity of the petroleum ether extract of *Z. rhesta* stem bark has also been reported by ahsan, 2000. Santhanam et al, 2016 different solvent fractions of Z. rhetsa bark the solvent fractions and purified compounds were tested for their cytotoxic potential against human dermal fibroblasts (HDF) and mouse melanoma (B16-F10) cells, using the MTT assay. All the solvent fractions and purified compounds were found to be non-cytotoxic to HDF cells. However, the chloroform fraction and kobusin exhibited cytotoxic effect against B16-F10 melanoma cells. Synthesis of silver nanoparticles (AgNPs) from *Zanthoxylum rhetsa* (Roxb.) DC seed coat extract was reported by Nayaka et al; 2020. Its Cytotoxicity assay on A549 cell line was used for MTT assay, the MTT assay revealed that the synthesized AgNPs have good anticancer activity against A549 Lung cancer cell line. Antileukemic potential of leaf extract of Z. rhetsa along with probable mechanism of cytotoxicity.

3. 11. Thrombolytic Activity

Thrombolysis is the breakdown (lysis) of blood clots by pharmacological means, and commonly called clot busting. An in vitro thrombolytic model was used to evaluate the clot lysis effect of different extracts of root bark of Z. rhetsa along with streptokinase as a positive control and distilled water as a negative control. The fractions of the root bark of Z. rhetsa showed an adequate amount of thrombolytic activity except the pet-ether soluble fractions and the pure compounds. The result confirms adequate thrombolytic activity of Z. rhetsa roots (Fatema-Tuz-Zohora et al, 2019).

3. 12. Photoprotective properties

Sunburn, premature skin aging, skin cancers and suppression of the immune system are linked to exposure of the skin to UV light. The use of plant extracts as active ingredient in sunscreen formulations is in the nascent stage. Santhanam and his colleagues has studied extensively the photo protective properties of the bark extract the plant. In 2013, Ramesh Kumar Santhanam et al (2013) had a first report on the photo protective properties of the different solvent extract the plant bark based on the sunscreen protection factor (SPF value) and UV absorption spectrum of various solvent fractions of the plant. The ethyl acetate fraction had the highest SPF value (13.36±0.12) followed by butanol (8.6±0.08), at a test concentration of 100µg/ml. their results indicated that the bark extract of *Z. rhetsa* could be utilized as a natural active ingredient in broad spectrum sunscreens and anti-ageing cosmetic preparations. A further report done in 2019 by santhanam et al (2019) used the ethyl acetate fraction of Z rhetsa bark as an active ingredient in two sunscreen cream formulations (F1 and F2). The UV protection properties of the formulated creams were evaluated by assessment of SPF values (F1: 3.60 ± 0.28, F2: 6.90 ± 0.57), UVA effectiveness (moderate for both test formulations) and critical wavelengths (F1: 365.4, F2: 360.3). Both formulations showed pseudo plastic behavior and were stable at all conditions except for samples kept at 40 °C. Altogether, these results suggested that the ethyl acetate fraction of Z. rhetsa bark has great potential to reduce exposure

to harmful UVA/UVB radiations. Subsequently, in another report, the ethyl acetate fraction and hesperidin were tested for their effects against UVB-induced cytotoxicity and expressions of inflammatory cytokines (IL-6, IL-1β, and TNF-α), NF-κB, and MMPs (MMP1, 3, and 9) in human dermal fibroblasts (HDF). The fraction and hesperidin significantly inhibited the expressions of NF-κB, MMP 1, MMP 3, and MMP 9 in HDF cells treated with UVB. Results obtained suggested that the fraction have the potential to be used as active ingredients in sunscreen and anti-photo aging formulations.

4. CONCLUSION

The present review describes the botanical description, traditional uses, ethno medical uses phytochemistry and pharmacology of *Z. rhetsa.* Available scientific literature shows that diverse secondary metabolites have been isolated from the stem bark, root and fruit of the plant which include but not limited to alkaloids, terpenoids, phenolics. Information from reports show that many of these phytoconstituents exhibit pharmacological activities. Thus, validating the local claims of *Z. rhetsa* as an important resource for therapeutic agents. Consequently, this literature review may offer support to researchers who desire to make further investigations on the pharmacological properties of the plant.

References

[1] Adesina SK (2005) The Nigerian zanthoxylum; chemical and biological values. *Afr. J. Trad. CAM* 2 (3): 282-301

[2] Ahsan M, Haque MR, Hossain B, Islam SN, Gray AI , Hasan CM, (2014) Cytotoxic dimeric quinolone–terpene alkaloids from the root bark of Zanthoxylum rhetsa. *Phytochemistry* 103: 8-12

[3] Ahsan M, Zaman TA, Hasan CM, Ito C, Islam SKN (2000) Constituents and cytotoxicity of Zanthoxylum rhesta stem bark. *Fitoterapia* 71; 697-700

[4] Candolle D, Pyramus A (1824). Prodromus Systematis Naturalis Regni Vegetabilis. Paris: Sumptibus Sociorum Treuttel et Würtz. p. 728. Retrieved 19 August 2020.

[5] Dalziel JM (1937) (reprinted 1955). The useful plants of West Tropical Africa. 1937 xii + 612 pp. London : Crown Agents for the Colonies

[6] Kumar GR, Chandrashekar BS, Lukose O, Ravindra M, Ravikumar K (2019) Evaluation of in-vitro antioxidant property and total phenolic content of Zanthoxylum rhetsa fruit extracts. *Journal of Pharmacognosy and Phytochemistry* 8(3): 1139-1144.

[7] Lalitharani S, Mohan VR, (2010). GC-MS analysis of ethanolic extract of Zanthoxylum rhetsa Roxb. DC spines. *J. Herbal. Med. Toxi.* 4: 191-192

[8] Mathur RK, Ramaswamy SK, Rao AS, Bhattacharyya SC. Terpenoids. 108. Isolation of an oxidodiol from Zanthoxylum rhetsa. *Tetrahedron* 1967 May; 23(5): 2495-8. doi: 10.1016/0040-4020(67)80086-3. PMID: 6044203

[9] Mester I. (1983) Structural Diversity and Distribution of Alkaloids in the Rutales, in, "Chemistry and Chemical Taxonomy of the Rutales: (P.G. Waterman and M.F. Grundon Eds.) Academic Press London, and references cited, pg. 31-96.

[10] Nayaka S, Chakraborty B, Pallavi SS, Bhat MP, Shashiraj KN, Ghasti B (2020) Synthesis of biogenic silver nanoparticles using Zanthoxylum rhetsa (Roxb.) DC seed coat extract as reducing agent and in-vitro assessment of anticancer effect on A549 lung cancer cell line. *International Journal of Pharmaceutical Research* 12: 3, 306-314

[11] Nguyen VH, Nguyen VH, Kieu TH, Dong TH, Dang MT, Pham TH, Duong KL, Nguyen TT, Nguyen HT (2020) Inhibitory effect on nitric oxide production of essential oil from Zanthoxylum rhetsa (Roxb.) dc. *Fruit Journal of Pharmacognosy and Phytochemistry* 9(5): 67-70

[12] Olatunji OA (1983). The Biology of Zanthoxylum Linn (Rutaceae) in Nigeria, in "Antiinfective agents of Higher Plants origin" (Essien, Adebanjo, Adewunmi, Odebiyi Eds.), Proceedings of the Fifth International Symposium on Medicinal Plants pp. 56-59.

[13] Parthiban S, Kumar GK, Boopathi T, Sangeetha G, Kokila MT and Devan VS (2017) In vitro anti-inflammatory activity of stem of Zanthoxylum rhetsa (Roxb.) Dc. *World Journal of Pharmaceutical Research* Volume 6, Issue 3, 591-600

[14] Patiño LOJ, Prieto RJA, Cuca SLE. (2012) Zanthoxylum Genus as Potential Source of Bioactive Compounds. In: Rasooli I., Editor. *Bioactive Compounds in Phytomedicine.* InTech 2012; pp 185-218

[15] Rahman, M. M., Gray, A. I., Khondkar, P., & Islam, M. A. (2008). Antimicrobial activities of alkaloids and lignans from zanthoxylum budrunga. *Natural Product Communications*, 3*(*1), 45-47

[16] Santhanam RK, Ahmad S, Abas F, Ismail IS, Rukayadi Y, Akhtar MT and Shaari K (2016) Bioactive Constituents of Zanthoxylum rhetsa Bark and Its Cytotoxic Potential against B16-F10 Melanoma Cancer and Normal Human Dermal Fibroblast (HDF) Cell Lines. *Molecules* 2016, 21, 652; doi: 10.3390/molecules21060652

[17] Santhanam RK, Ahmad S, Abas F, Ismail IS, Rukayadi Y, Shaari K (2013) Photoprotective properties of Zanthoxylum rhetsa: An in vitro analysis. *J. Chem. Pharm. Res.* 5(12): 1512-1520

[18] Santhanam RK, Fakurazi S, Ahmad S, Abas F, Ismail IS, Rukayadi Y, Akhtar MT, Shaari K (2018) Inhibition of UVB-induced pro-inflammatory cytokines and MMP expression by Zanthoxylum rhetsa bark extract and its active constituent hesperidin. *Phytotherapy Research* 1-9. DOI: 10.1002/ptr.6092

[19] Santhanama RK, Akhtara MT, Ahmad S, Abasa F, Ismaila IS, Rukayadia Y, Shaaria K (2017) Utilization of the ethyl acetate fraction of Zanthoxylum rhetsa bark extract as an active ingredient in natural sunscreen formulations. *Industrial Crops and Products* 96: 165-17. http://dx.doi.org/10.1016/j.indcrop.2016.11.058

[20] Simanek V. (1985). Benzophenanthridine alkaloids in "The Alkaloids, Chemistry and Pharmacology" (Arnold Brossi, Ed.) Academic Press, London Vol. 26: 186-240.

[21] Tantapakul C, Phakhodee W, Ritthiwigrom T, Yossathera K, Deachathai K, and Laphookhieo S (2012) Antibacterial Compounds from Zanthoxylum rhetsa. *Arch Pharm Res* Vol 35, No 7, 1139-1142. DOI 10.1007/s12272-012-0703-9

[22] Terence K Lee, Ronnie T P Poon, Jana Y Wo, Stephanie Ma, Xin-Yuan Guan, Jeffrey N Myers, Peter Altevogt, Anthony P W Yuen (2007) Lupeol suppresses cisplatin-induced nuclear factor-kappaB activation in head and neck squamous cell carcinoma and inhibits local invasion and nodal metastasis in an orthotopic nude mouse model. *Cancer Res* 67 (18): 8800-9. doi: 10.1158/0008-5472.CAN-07-0801

[23] Theeramunkong S, Utsintong M (2018) Comparison between Volatile Oil from Fresh and Dried Fruits of Zanthoxylum rhetsa (Roxb.) DC. and Cytotoxicity Activity Evaluation. *Pharmacogn J.* 10(5): 827-832

[24] Theeramunkong S, Utsintong M. (2018) Comparison between Volatile Oil from Fresh and Dried Fruits of Zanthoxylum rhetsa (Roxb.) DC. and Cytotoxicity Activity Evaluation. *Pharmacog J* 10 (5): 827-32

[25] Tuz-Zohora F, Islam SN, Khan SA, Hasan CM and Ahsan M (2019) Antioxidant, Cytotoxic, Thrombolytic and Antimicrobial Activity of Zanthoxylum rhetsa Root Bark with Two Isolated Quinolone Alkaloids. *Pharmacology & Pharmacy*, 10, 137-145. https://doi.org/10.4236/pp.2019.103012

[26] Tuz-Zohora F, Islam SN, Khan SA, Hasan CM, Ahsan M (2019) Antioxidant, Cytotoxic, Thrombolytic and Antimicrobial Activity of Zanthoxylum rhetsa Root Bark with Two Isolated Quinolone Alkaloids. *Pharmacology & Pharmacy*, 10, 137-145. https://doi.org/10.4236/pp.2019.103012

[27] Waterman PG (1986). A Phytochemist in the African Rain Forest. *Phytochemistry* 25 (1): 3-17

[28] Wongkattiya N; Akekawatchai C; Sanguansermsri P; Fraser IH; Pratoomsoot, C, Sanguansermsri, D (2018) chemical compositions and biological properties of essential oil from Zanthoxylum rhetsa (Roxb.) dcandzanthoxylum limonella alston. *African Journal of Traditional, Complementary and Alternative Medicines*, Vol. 15, No. 2, pp. 12-18