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GENUS *HUNTERIA*- A ETHNOPHARMACOLOGICAL, CHEMICAL AND PHARMACOLOGICAL PERSPECTIVES

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ABSTRACT: *Hunteria* is a genus of plant in family Apocynaceae. It comprises of 12 species but more prevalent are *Hunteria umbellata* and *Hunteria zeylanica*. Taditionally *H. umbellata* have been used in the treatment of yaws and sexually transmitted infections, stomach ache, ulcers, diabetes mellitus and dysmenorrhoea. *H. zeylanica* is used to cure stomach-ache, wounds and cuts. *H. umbellata* has a relatively low oral toxicity profile but its prolonged use, particularly, at high doses should be with great caution. The phytochemical analysis of the *H. umbellata* plant extract revealed the presence of saponins, steroids, tannins, volatile oils, phenols and copious amount of alkaloids. *H. zeylanica* leaves and stem bark prominently contains alkaloids. Scientific researchers have shown that *H. umbellata* and *H. zeylanica* were active against various diseases such as bacterial infections, pain, fever, inflammation, diabetes, in obesity, hyperlipidemia, heart problems, in child birth and malaria. Aim of the current review is to explore potential species of Genus *Hunteria* for ethnopharmacology, toxicological studies, safety, phytochemical investigation and pharmacological properties.

INTRODUCTION: Genus *Hunteria:* *Hunteria* is a genus of plant in family Apocynaceae first described as a genus in 1824. It is native to Guinea-Bissau, Sierra Leone, Liberia, Ivory Coast, Ghana, Benin, Nigeria, Cameroon, Gabon and Democratic Republic of Congo Africa and to South and Southeast Asia. [1] The genus hunteria includes following species [1] along with their distribution.

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Hunteria ballayi Hua - Central African Republic, Republic of Congo, Cameroon, Gabon, *Hunteria camerunensis* K. Schum. ex Hallier f. - Republic of Congo, Cameroon, Gabon, *Hunteria congolana* Pichon - Republic of Congo, Zaïre, Kenya, *Hunteria densiflora* Pichon – Zaïre, *Hunteria ghanensis* J.B. Hall & Leeuwenb. - Ivory Coast, Ghana, *Hunteria hexaloba* (Pichon) Omino – Gabon, *Hunteria macrosiphon* Omino - Republic of Congo, Gabon, *Hunteria myriantha* Omino – Zaïre, *Hunteria oxyantha* Omino - Republic of Congo, Zaïre, Gabon, *Hunteria simii* (Stapf) H. Huber - Guinea, Ivory Coast, Liberia, Sierra Leone, *Hunteria umbellata* (K.Schum) Hallier f. - W + C Africa from Senegal to Zaïre, *Hunteria zeylanica* (Retz.) Gardner ex Thwaites - Somalia, Kenya, Tanzania, Mozambique, S China, India, Sri Lanka,

Andaman & Nicobar Islands, Indochina, W Malaysia, Sumatra.

Ethnopharmacology:

Ethnomedical uses of *Hunteria umbellata* include treatment of yaws and sexually transmitted infections, stomach ache and ulcers, diabetes mellitus and dysmenorrhoea. South-west Nigeria, traditional birth attendants/midwives employ the fresh leaves and pulp of fresh fruits of *Hunteria umbellata* in the induction and/or augmentation of labour in gravid uterus at term. [2] Hot and cold decoctions made from the plant seeds have also been reported to be highly valued in the local treatment of obesity, hypertension, pain and swellings, anaemia and as immune booster.[3-5] Plant was reported to be used for bacterial infection.[6] A leaf decoction of *H. zeylanica* is drunk to cure stomach-ache.[7] The leaves of *H. zeylanica* are used as a healing poultice on wounds and cuts.[8, 9]

Toxicological studies:

A study was conducted to investigate the *in-vivo* sub-acute toxicity of the aqueous fruit pulp extract of *Hunteria umbellata (H. umbellata)*. Sub-acute toxicity was evaluated after administering daily oral doses of 200, 400 and 800 mg/kg of *H. umbellata* extract, for 28 days to the rats. Anthropometric, biochemical, hematological and histopathological parameters were assessed using standard procedures.

There were significant reductions ($p<0.01$) in the pattern of weight gain in 200 and 400 mg/kg *H. umbellata* treated rats but no significant differences in the organ weight index between control and treated animals. Hematological and biochemical analysis showed no marked differences in any of the parameters examined in either the control or treated groups but there was significant ($p<0.05$) thrombocytosis.

Pathologically, neither gross abnormalities nor histopathological changes were observed. *H. umbellata* led to activation of the reticulo endothelial tissue of the spleen as evidenced by proliferation of the sinus histocytes and activation of the lymphoid aggregates in the lungs, indicating activation of the local immune system of the lungs. *H. umbellata* fruit pulp is relatively nontoxic in animals but there is increased tendency to cause thrombocytosis on prolonged use.[10] The statistical analysis on the determination of acute toxicity of *Hunteria umbellata* was carried out in mice. Data on the acute toxicity studies of the seed extract of *Hunteria umbellata* administered via the intraperitoneal route was analyzed using the two-parameter Weibull model.

The results show that *Hunteria umbellate*(HU*)* may be slightly toxic when administered intraperitoneally. The acute oral and intraperitoneal toxicity studies of HU were determined in Swiss albino mice while its 90-day oral toxicity and toxicity reversibility profile on anthropometric, biochemical, haematological and histopathological parameters were also assessed using standard procedures. Results showed that the LD_{50} values for the acute oral and intraperitoneal toxicity studies for HU were estimated to be 1000 mg/kg and 459.3 mg/kg, respectively. Visible signs of immediate and delayed toxicities including starry hair coat, respiratory distress, and dyskinesia were observed. Overall, results of this study showed that *Hunteria umbellata* has a relatively low oral toxicity profile but its prolonged use, particularly, at high doses should be with great caution. [11]

Phytochemical reports:

The phytochemical analysis of the *Hunteria umbellata* plant extract revealed the presence of saponin, saponin glycosides, steroid, tannins, volatile oils, phenols and copious amount of alkaloids. [2] Stem bark of *Hunteria umbellata* extract showed presence of alkaloids, saponin, flavonoids, reducing sugars and cardiac glycoside whereas leaf extract of *Hunteria umbellata* showed the presence of tannins, volatile oil, reducing sugars, alkaloids, saponin and cardiac glycoside.[12] A new bisindole alkaloid, erinidine, isolated from the water seed extract of *Hunteria umbellata* (K. Schum.) Hallier f. (Apocynaceae).[13]

Twenty alkaloids were isolated from the leaves and stem bark of *Hunteria zeylanica*, collected in Kenya. They were: 3-*epi*-dihydrocorymine 3-acetate, norisocorymine, corymine, 3-*epi*-dihydrocorymine 17-acetate, picralinal, picrinine, 3- *epi* - dihydrocorymine, isositsirikine, lanceomigine, geissoschizol, gentianine, kopsinine,

eburnamine, norpleiomutine, pleiocarpamine, tubotaiwine, pleiomutinine, 19′-*epi*-pleiomutinine, yohimbol and 10-hydroxy-16-*epi*-affinine.[14] Investigation of the leaves and stems of *Hunteria zeylanica* resulted in the isolation of one new indole alkaloid, 11-hydroxyrhazimanine (1), and nine known analogs. Decarbomethoxy dihydrogambirtannin (2), dihydroantirhine (3), and 3-oxomehranine (4) were isolated from Hunteria genus for the first time.[15] Two new indole alkaloids, bisnicalaterine D (**1**), consisting of an eburnane and a corynanthe type of skeletons, and nicalaterine A (**2**) were isolated from the bark of *Hunteria zeylanica*.[16]

Pharmacological reports:

Oxytocic effect:

The aqueous extract obtained by maceration technique by Falodun A *et al*. was subjected to pharmacological testing *in-vitro* on a piece of isolated rat uterus previously pretreated with stilbesterol, suspended in De Jalon at 37 degrees C and aerated with 95% Oxygen and 5% CO(2). The oxytocic activity of the aqueous pulp extract of the pulp of fruit of *Hunteria umbellata* was compared with uterine stimulant like oxytocin. The extract affected the contractility of the uterus significantly ($P<0.05$) in a dose dependent manner. The effect of 10mg/ml extract was blocked by 0.1 ml of 0.1mg/ml atropine. The extract also potentiated the response shown by various doses of oxytocin. The investigation revealed that *Hunteria umbellata* has oxytocic effect thus justifying the use by the traditional birth attendants.[2]

Analgesic Effects:

A study was carried out by Adeyemi OO *et al*. to evaluate the aqueous seed extract of *Hunteria umbellata* at the dose of 50-200mg/kg for analgesic activity, and determine its possible mechanism(s) of action. *H. umbellata* (HU) were investigated in different experimental models of analgesia using the tail flick, tail immersion, acetic acid-induced writhing tests and formalin-induced algesia. Oral pre-treatment with 50-200 mg/kg of HU caused significant and dose related analgesic effect in the treated rats in all the experimental models used. This analgesia was mediated via central and peripheral mechanisms. Overall, the results showed that HU possesses analgesic effect which lends support to its folkloric use in the local management of pain.[17]

Antibacterial effects:

In-vitro microbiological technique was employed using the minimum inhibitory concentration (MIC) assay by Josephs GC *et al*. The antibacterial activity of the extracts was evaluated using nutrient agar final concentrations of 15, 20, 25, 50, 75, 100 and 150mg/ml. Ciprofloxacin was used as the reference drug for comparison using final nutrient agar concentrations of 0.3, 0.4, 0.5, 1.0 and 1.5µg/ml.

The stem bark extract of *Hunteria umbellata* inhibited the growth of *Staphylococcus aureus* and *Escherichia coli* at the concentrations of 50, 75, 100 and 150 mg/ml, with 50mg/ml as the minimum inhibitory concentration. While the leaves extract had a minimum inhibitory concentration of 150mg/ml against *Staphylococcus aureus* and *Escherichia coli*. Ciprofloxacin inhibited the growth of both bacteria at concentrations of 0.5, 1.0 and 1.5µg/ml, with a minimum inhibitory concentration of 0.5µg/ml. In conclusion, the results indicate that the methanol extracts of the stem bark and leaves of *Hunteria umbellata* possess antibacterial activity against gram - positive and gram – negative bacterial isolates. This activity may be attributed to the reported phytochemical constituents in the plant with known antibacterial actions. This authenticates its ethnomedicine use in the treatment of bacterial infections.[12]

Hypoglycaemic effects:

A study was carried out by Adejuwon AA *et al*. to evaluate antihyperglycemic profile of erinidine isolated from *Hunteria umbellata* seed. Antihyperglycemic potentials tested in *in vitro* models such as dipeptidylpeptidase (IV), glycogen phosphorylase, HIT-T15 cell insulin secretion, glucose uptake activity, aldose reductase assays and α-glucosidase inhibition assay testings. In addition, 50 mg/kg of erinidine and that of other fractions were evaluated in *in vivo* models of normal and chemically-induced hyperglycemic rats. The *in vitro* study showed the antihyperglycemic action of erinidine to be weakly mediated via α-glucosidase inhibition mechanism

as the results for other *in vitro* tests such as dipeptidylpeptidase (IV), glycogen phosphorylase, HIT-T15 cell insulin secretion, glucose uptake activity and aldose reductase assays were all negative. However, the *in vivo* results showed 50 mg/kg erinidine given *per os* to normal and alloxan-induced hyperglycemic rats to significantly ($p<0.05$, $p<0.001$) attenuate an increase in their post-absorptive blood glucose concentrations after 3 g/kg glucose loading in the rats, suggesting its antihyperglycemic mechanism to be via α-glucosidase inhibition.

This result, although, further corroborated the *in vitro* findings but also suggests that erinidine needs to be biotransformed *in vivo* for its inhibitory activity on intestinal glucose absorption to become evident. Thus, the present study suggests erinidine to be the possible antihyperglycemic agent in *Hunteria umbellata* seed extract mediating its antihyperglycemic action via intestinal glucose uptake inhibition.[18]

A study was designed by Adeneye AA *et al*. for evaluating the peripheral glucose utilization and anti-oxidative mechanisms of 50 mg/kg, 100 mg/kg and 200 mg/kg of HU(*Hunteria umbellata*) in alloxan-induced diabetic rats in Groups IV-VI rats as well as in the control groups (Groups I-III). Experimental type 1 DM (Diabetes mellitus) was induced in male Wistar rats through intraperitoneal injection of 150 mg/kg of alloxan monohydrate in cold 0.9% normal saline after which the diabetic rats were orally treated with 50-200 mg/kg of HU for 14 days.

Effects of HU on the rat body weight, percentage body weight changes and fasting blood glucose (FBG) were determined on days 1 and 15 of the experiment. Also, on day 15 of the experiment, HU effect on serum insulin, liver enzyme markers, proteins, albumin, triglyceride, total cholesterol and lactate dehydrogenase as well as on hepatic tissue oxidative stress markers, liver glycogen and glucose-6-phosphatase were determined after sacrificing the rats under diethyl ether anesthesia. Results showed that oral treatments with 50-200 mg/kg of HU caused significant ($p<0.0001$) improvements in the weight loss caused by alloxan-induced diabetes, while causing significant ($p<0.05$, $p<0.001$ and $p<0.0001$) dose-related reductions in the FBG levels despite causing non-significant ($p>0.05$) alterations in the serum INS levels in the treated rats. Also, repeated oral treatment with HU caused significant ($p<0.0001$) reversal in the decrease and increase in the hepatic glycogen levels and glucose-6-phosphatase activity, respectively, caused by alloxan-induced diabetes.

Similar significant ($p<0.0001$) and complete reversal effects were recorded in the serum hepatic enzyme markers, total protein, albumin, triglyceride, total cholesterol and lactate dehydrogenase as well as on hepatic tissue oxidative stress markers such as superoxidase dismutase (SOD), catalase (CAT), malonialdehyde (MDA) and reduced glutathione (GSH) of HU-treated rats when compared to that of untreated alloxan-induced diabetic rats. In conclusion, results of this study showed HU treatment to significantly ameliorate the hyperglycemia and oxidative stress in alloxan-induced diabetic rats which was mediated via increased hepatic glycogen deposit, decreased hepatic glucose-6-phosphatase activity and improvement in antioxidant/free radicals scavenging activities.[19]

Weight Losing, Antihyperlipidemic and Cardioprotective Effects:

Adejuwon AA and Peter AC carried out a study on weight losing, antihyperlipidemic and cardioprotective effects of alkaloid fraction of *H. umbellata.* Adult female Wistar rats (weight range: 120-150 g) were randomly divided into 4 and 5 treatment groups in the normal and triton-induced hyperlipidemic models, respectively and were daily treated for 14 d before they were humanely sacrificed under inhaled diethyl ether anesthesia.

About 5 mL of whole blood was obtained by cardiac puncture from each treated rat, from which serum for lipids assay was subsequently separated. Tissue samples of livers of treated rats were harvested and processed for histopathological analysis. Repeated daily oral treatments of normal rats with 25 and 50 mg/kg/day of alkaloid fraction of *H. umbellata* resulted in significant ($P<0.05$ and $P<0.001$) and dose-dependent weight loss, and decreases in the serum triglyceride, total

cholesterol and low density lipoprotein cholesterol, while significantly (P<0.001) increased the serum levels of high density lipoprotein cholesterol fraction. Similarly, oral pre-treatments with 25 and 50 mg/kg/day of alkaloid fraction of *H. umbellata* for 14 d before induction of hyperlipidemia with triton WR-1339 significantly (P<0.01, P<0.001) and dose-dependently attenuated increases in the average body weights, serum levels of triglyceride, total cholesterol and low density lipoprotein cholesterol while also significantly (P<0.01, P<0.001) and dose-dependently attenuated significant (P<0.001) decrease in the serum high-density lipoprotein cholesterol levels when compared to the untreated control values.

However, the results obtained for 50 mg/kg of alkaloid fraction of *H. umbellata* in both normal and triton WR-1339-induced hyperlipidemic rats were comparable to that recorded for 20 mg/kg of simvastatin. Similarly, oral pretreatments with 25 and 50 mg/kg/day of alkaloid fraction of *H. umbellata* significantly improved the histological lesions of fatty hepatic degeneration induced by triton WR-1339 treatment. Overall, results of this study showed that repeated oral treatments with 25 and 50 mg/kg/day of alkaloid fraction of *H. umbellata* elicited weight losing, anti hyperlipidemic and cardioprotective effects in triton WR-1339 induced hyperlipidemic rats that were mediated via *de novo* cholesterol biosynthesis inhibition.[20]

Vasorelaxant Activity:

Two new bisindole alkaloids, bisnicalaterines B and C (**1** and **2**) consisting of an eburnane and a corynanthe type of skeletons, were isolated from the bark of *Hunteria zeylanica*. Hirasawa Y et al. determined their absolute structures by combination of NMR, CD, and computational methods, and each of them was shown to be in an atropisomeric relationship. Bisnicalaterines B and C (**1** and **2**) showed potent vasorelaxant activity on isolated rat aorta.[21]

Anti-inflammatory and Antioxidant effects:

The anti-inflammatory effect of the aqueous fruit pulp extract of *Hunteria umbellata* was evaluated using the carrageenan and dextran-induced rat paw edema, xylene-induced ear edema and formalin-induced arthritis inflammation tests by Igbe I *et al*. Oral administration of the extract produced significant ($p < 0.05$) antiedematogenic effect with a dose of 500 mg/kg throughout the period of the experiment in the dextran induced paw edema and at the 3 h in the carrageenan model. The extract (250 and 500 mg/kg) exhibited a dose-related and significant ($p < 0.01$) inhibition of xylene induced ear edema and the effect was similar to that produced by dexamethasone (1 mg/kg).

In the chronic inflammation (formalin induced arthritis) the extract did not show any significant anti-inflammatory activity. Oral acute toxicity assays did not show any mortality at 15 g/kg of the plant extract. The results indicate that the aqueous extract of *H. umbellata* possesses acute inflammatory activity which may be mediated by either inhibition or by blocking the release of prostaglandins and histamine, thus supporting the usage of the plant in traditional medicine treatment of inflammation.[22]

The acute anti-inflammatory activity of 50 mg/ kg of each of the seed fractions was evaluated by Adeneye AA *et al*. in carrageenan and formalin-induced oedematous Wistar rats. The fraction's antioxidant activities were evaluated using 1,1-Diphenyl-2-picrylhydrazyl (DPPH) free radical, superoxide anions and nitric oxide scavenging methods, in addition, to determining the phenolic contents of the fractions using standard procedures. Results showed that *Hunteria umbellata* (HU), HU_b(butanol) and HU_{Af}(Alkaloid fraction) significantly ($p<0.05$ and $p<0.001$) inhibited carrageenan and formalin-induced inflammation in the rats.

Similarly, HU_b and HU_{Af} at 0.2-0.8 mg mL^{-1} exhibited significant ($p<0.05$ and $p<0.001$) DPPH free radical, superoxide anion and nitric oxide scavenging activities with the most significant effect recorded for HU_{Af}. Their proanthocyanidin contents were estimated to be 38.90±1.67 and 53.67±1.12 mg g^{-1} of dry extract, respectively while their total flavonoid contents were estimated to be 0.50±0.03 and 11.78±1.47 mg g^{-1} of dry extract, respectively. Also, their total phenolic contents were estimated to be 39.68±2.56 and 97.12±3.32 mg g^{-1} of dry extract. The anti-

inflammatory activity of HU and its butanol fraction is attributed to its alkaloid content which was partly mediated via its anti-oxidant mechanism.[23]

The effects of crude alkaloids extracted from the stem bark of *Hunteria zeylanica* GARD. (*H. zeylanica*) on acute inflammatory responses such as carrageenin-induced paw edema in rats and croton oil and arachidonic acid-induced ear edema in mice were investigated by Reanmongkol W *et al*. Oral administration of *H. zeylanica* alkaloid extract (200-400 mg/kg) significantly suppressed the paw swelling induced by carrageenin. In the croton oil-induced ear edema, topically applied *H. zeylanica* alkaloid extract, at doses of 200 and 400 mg/ml, also significantly reduced ear edema. Moreover, the extract (50-200 mg/kg, p.o.) reduced in a dose-dependent manner the ear swelling induced by topically applied arachidonic acid (2 mg/ear). These results suggest that the inhibitory effects of *H. zeylanica* alkaloid extract on acute edema formation are partly due to inhibition of 5-lipoxygenase and cyclooxygenase activity.[24]

Antiplasmodial effects:

A series of bisnicalaterines and nicalaterine A isolated from bark *H. zeylanica* of showed potent antiplasmodial activity against *Plasmodium falciparum* 3D7[16] when investigated by Nugroho AE *et al*.

Cytotoxic effect:

A new bisindole alkaloid, bisnicalaterine A (**1**), consisting of two vobasine-type skeletons, and 3-epivobasinol (**2**) and 3-*O*-methylepivobasinol (**3**), with vobasine-type skeletons, were isolated from the leaves of *Hunteria zeylanica*, and their structures were elucidated on the basis of spectroscopic data and chemical correlation by Nugroho AE *et al*. Bisnicalaterine A showed moderate cytotoxicity against various human cancer cell lines[16].

CONCLUSION: This review paper covers the traditional uses and benefits of components present in different species of Genus *Hunteria* as an alternative medicine for many diseases. The pharmacological effects exhibited by this Genus have been elaborated in depth with citations from studies that have been conducted using species of this Genus of plant.

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CONFLICT OF INTEREST: We declare that we have no conflict of interest.

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