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Traditional Uses, Phytochemistry and Biological Activities of *Entada Africana* Guill and Perr: A Comprehensive Review

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ABSTRACT

All around the world *Entada africana* is used traditionally/folk to treat several diseases, as a source of gum, insecticides, food and in some carpentry works. Several studies explored pharmacological and ethno botanical aspects of this plant and isolate various phytochemicals which are responsible for its anti-inflammatory, analgesic, antibacterial, antioxidant, antiviral, anti-angiogenic, cytotoxic properties. Sugars, triterpenes, flavonoids and saponins are mainly responsible for the abovementioned pharmacological activities. However, some more research is required to identify other phytochemical constituents which can be used to cure other ailments.

Keywords: *Entada africana*, Phytochemical constituents, Pharmacology, Traditional uses.

INTRODUCTION

Entada africana guill and *perr* known as "*Tawatsa*" and "*Ogurobe*" [1] is a small tree distributed in tropical and subtropical regions [2] and used as local remedy for various ailments. Various studies explored its ethno botanical uses i.e. against malaria fever [3], treat suppurating wounds and applied as a hemostatic agent. The plant possess anti hepatotoxic, anti-proliferative, anti leishmanial, antioxidant, antimicrobial, and antiulcer properties [4-7]. The available information on this species was collected from scientific databases such as pubmed, scifinder, science direct, scopus, web of science, and google scholar. The search terms used for this review included *Entada africana*, phytochemical composition, essential oils, medicinal uses, pharmacology and toxicity, no limitations were set for languages.

Habitat and distribution

It mostly grows in savannah areas of high rainfall i.e. Nigeria and on ground water sites especially on lower slopes or banks of swamps. It is very sensitive to bush fire. Its trees are found in Sudan zone, southern Sahel, in Burkina Faso, Senegal, Cameroon, Uganda, Republic of Congo, Nigeria and Zaire [8, 9].

Botanical description

The genus *Entada adans* belonging to *Fabaceae* family contains about 30 species of lianas and scandent shrubs or subshrubs [2]. The *E. africana* popularly known as Legumes, is the third largest order of seed-plants containing about 600 genera with 12000 species [10]. It is a

small tree up to 4-10 m; bark brown-grey to black, very rough, transversely stripped, scaly; leaves 3-9 pairs, bioinnate, alternate, 8-24 pairs of leaflets, stalk glabrous, 15-45 cm long; rachis 25-30 cm long; pinnae 2-9 pairs; leaflets 8-24 pairs, 2-3 × 0.5-1.5 cm, elongated elliptic and rounded apex and occasionally minutely notched, base asymmetrical, lower edge more rounded than the upper; flowers creamy-white or reddish yellow, about 6 mm long; slightly scented and densely clustered in a spike-like racemes, 5-15 cm long; fruit is a pod, flat, fragile, slightly curved seeds, thick wavy margins, reddish-brown on the outside, contains about 10-15 broad elliptic flat seeds [11-18].

CHEMICAL CONSTITUENTS

Various phytochemicals which are isolated from the different parts of *E. africana* plant is described in Table 1.

Plant part and extract	Phytochemicals
Stem bark extracts of n-hexane, ethyl acetate (EtOAc) and methanol (MeOH)	Steroids/triterpenes, cardiac glycosides, tannins, flavonoids, steroids/triterpenes, carbohydrates, saponins and cardiac glycosides [12].
Leaf and stem bark extract	Glycosides, saponins, tannins, flavonoids, coumarins, triterpenes and sterols [13].
Stem bark acetone and MeOH extracts	Polyphenol and flavonoids [14].
Stem bark fractions (methylene chloride (F_0), methylene chloride-MeOH (95/5: v/v) (F_5), methylene chloride-MeOH (90/10: v/v) (F_{10}), methylene chloride-MeOH (75/25: v/v) (F_{25}) and MeOH (F_{100})	Sterols, terpenes, polyphenols, flavonoids, sugars and saponins [15].
n-hexane, methylenechloride-MeOH mixture and distilled water extracts	Steroids/triterpenes, reducing sugars, flavonoids, polyphenols, tannins and leucoanthocyanins [16].
Seeds	Saponins and tannins [17].
Stem bark, ethanol extract, diethyl ether fraction, chloroform fraction, methanol soluble and insoluble	Alkaloids, amino acids, anthraquinones, cardiac glycosides, saponins, tannins, steroids, triterpenes; flavonoids and saponins [18].

Table 1: Various phytochemicals isolated from of *E. Africana*.

DISCUSSION

Pharmacological activities

Analgesic activity: The ethanolic leaf extracts (200 and 800 mg/kg) of *E. africana* showed significant inhibition (58.62% and 65.51%) of writhing on acetic acid-induced abdominal mice (200, 400, and 800 mg/kg b.w. po, respectively) [19].

Anti-angiogenic activity: The root extracts (n-hexane, chloroform, chloroform/methanol and methanol) of *E. africana* was evaluated in zebrafish embryos model and chick chorioallantoic membrane (CAM) for anti-angiogenic activity. Among all extract, chloroform/methanol extract potently inhibited vessel formation (60%) as compared with control zebra fish embryos where 2-methoxyestradiol (2-ME) and 17-bestradiol (30 mg/ml) used as standard showed 52% inhibited vessel formation. Fractions 9 and 10 among different fraction of chloroform/methanol showed potential anti-angiogenic activity (40% and 30% of inhibition on vessel formation at 50 mg/ml). In CAM assay, fractions 9 and 10, apigenin, robinetin and Retinoic Acid (RA), the inhibition percentages were 65%, 40%, 33%, 27% and 75%, respectively [20].

Anti-endometrial activity: The aqueous root extracts (127.5, 255, and 510 mg/kg) of *E. africana* evaluated in rats by using microgynon 30 as the reference substance significantly decreases the dysmenorrhea and endometrial implant volume. The extract increased the catalase activity, MDA level, antral follicles, reduced luteinized unruptured follicle number and induced animals to be in the estrus phase. It was concluded that *E. africana* prevented the progress of endometriosis, reduced dysmenorrhea, promoted ovarian follicle growth, prevented anovulation, and stimulated the special period of rat sexual desire [21].

Anti-inflammatory activity: The anti-inflammatory activity of fractions (EaChl (CH_2Cl_2), Ea_5 (CH_2Cl_2/MeOH5%), Ea_{10} (CH_2Cl_2/MeOH 10%), Ea_{25} (CH_2Cl_2/MeOH 25%), and EaMet (MeOH)) of the stem bark extract was evaluated by using lipopolysaccharide (LPS)-induced inflammation in RAW 264.7 macrophages model. The Ea_5 fraction was found to be the most potent in inhibiting NO production (IC_{50}-18.36 µ g/ml) and showed the highest inhibition percentage (89.068%) in comparison with baicalin (63.34%), an external standard at 50 µ g/ml. Ea_5 and baicalin significantly inhibited the expression of TNF α, IL_6 and IL_1 β mRNA, attenuated mRNA expression of inducible NO synthase in a concentration-dependent manner, stimulated the expression of anti-inflammatory cytokines (IL10 and IL13), and showed a 30% inhibition of the activity of p38 MAPK kinase [22].

The ethanolic leaf extract (200, 400 and 800 mg/kg) was studied for its anti-inflammatory activities in egg albumin-induced hind paw edema. The extract (200 mg/kg b.w.) significantly inhibited of paw edema (120–150 min), comparable to that produced by diclofenac (10 mg/kg) [19].

The bark fraction Ea_5 (CH_2Cl_2/MEOH 5%) and isolated compound, baicalin on NO production and the expression of pro-inflammatory cytokines mRNA by microglia in response to LPS was evaluated. The Ea_5 (0.05 to 50 µ g/ml) and baicalin (5 µ g/ml) inhibited LPS-induced NO production in a dose dependent manner. Ea_5 was most prominent in NO inhibition (87.07%), in compared to baicalin (70.85%). Ea_5 strongly suppressed the expression of TNF α, IL-1 β, IL-6 and iNOS in microglia and inhibited the activity of p38MAPK Kinase (up to 30%). It was suggested that *E. africana* might be contain promising compounds useful for the treatment of diseases cause by over-activation of microglia such as Alzheimer disease and other neurological diseases [23].

Anti-leishmanial activity: The anti-leishmanial activity of dichloromethane, methanol and water extract of *E. africana* root (17.5 and 35 µ g/ml) was studied against extracellular and intracellular forms of Leishmania major. The water extract exhibited a marked activity with 15.5% survival (promastigote form) and 5% survival in amastigote form at 35 µ g/ml concentration [24].

Anti-malarial activity: The methanolic extract of *E. africana* was showed potential anti-malarial activity (IC_{50}>100 µ g/ml) against Plasmodium falciparum where chloroquine phosphate (IC_{50}-0.15 µ g/ml) used as standard [P20]. Also, the ethanolic leaf extract showed moderate anti plasmodial activity ($10 \leq IC_{50} \leq 50$ µ g/ml) against chloroquine-sensitive (HB_3, IC_{50}-26.36 µ g/ml) and chloroquine-resistant (FcM29, IC_{50}-28.86 µ g/ml) of P. falciparum strains [19].

Anti-microbial activity: The anti-microbial activity of methanolic leaf extracts of *E. africana* was evaluated *against Bacillus cereus, Escherichia coli, Klebsiella pneumoniae, Mycobacterium fortuitum, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhimurium, Staphylococcus aureus, S. pyogenes and Candida albicans* by broth dilution method. Among all, the extract showed antibacterial activity only against B. cereus (MIC-125 µg/ml) [21].

The methanolic extract of *E. africana* showed significant antimicrobial activity against *E. coli, Shigella flexneri, Salmonella enteritidis Salmonella paratyphi, Staphylococcus aureus, Fusarium oxysporum, Rhizopus nigricans* (>2.50 mg/ml), *Proteus mirabilis, Serratia marcescens, Klebsiella pneumoniae* (1.80 mg/ml) and *Mucor rouxi* (1.20 mg/ml) by broth micro dilution method [5].

Similarly, the dichloromethane/methanol (1:1) extract of *E. africana* bark was evaluated against *E. coli, Enterobacter aerogenes, K. pneumoniae* and *Providencia stuartii* by micro broth dilution method. It was found that the extract showed activity only against *E. coli* with MIC 64 µg/ml [25].

Anti-oxidant activity: The anti-oxidant activity of methanolic extract was evaluated using DPPH radical scavenging with ascorbic acid as standard. The extract and ascorbic acid showed prominent activity (IC_{50}-0.47 µ g/ml and 4.79 µ g/ml) [5].

In another study, the Crude Extracts (CEs) and five fractions i.e. methylene chloride, methylene chloride/methanol (95/5; v/v), methylene chloride/methanol (90/10; v/v), methylene chloride/methanol (75/25; v/v), methanol (100%) were evaluated by DPPH, hydroxyl (OH °) radical, reducing ability and lipid peroxidation assay. It was found that methanol (100%) efficiently scavenged the DPPH free radical (EC_{50}/IC_{50}-41.062 µ g/ml), also inhibited lipid peroxidation and methylene chloride/methanol (90/10; v/v), methylene chloride/methanol (75/25; v/v) fraction and methanol (100 %) fraction were considered to be most active in reducing power [15].

Anti-proliferative activity: The anti-cancer activity of isolated compounds, ester saponins (1-9) from the roots of *E. africana* were evaluated against the J774.A1, HEK-293, and WEHI-164 cell lines. The compound 3 showed the highest cytotoxic activity with IC_{50}-0.031-0.25 µ M. Compounds 4, 7, and 8 showed moderate activity (IC_{50}-0.56-3.9 µ M), while compounds 5, 6, and 9 displayed activity against J774.A1 cells (IC_{50}-1.2-3.1 µ M) but no activity against the other cell lines [26].

In another study, the inhibitory effect of ethanol leaf extract was evaluated on THP-1 cell. It was found that the extract was non cytotoxic at the concentration tested (100 µ g/ml) [19].

Cytoprotective activity: The Crude Extracts (CEs) and five fractions of *E. africana* were evaluated against H_2O_2-induced oxidative stress in HC-04 cells. The cytoprotective activity of methylene chloride/methanol (75/25; v/v) fraction was comparable to quercetin (3.40 µ g/ml), inhibiting LDH leakage with IC_{50}-3.8 µ g/ml. It was concluded that methylene chloride/methanol (75/25; v/v) fraction of *E. africana* promoted the nuclear translocation of Nrf2 in a human hepatocyte cell line [15].

Anti-ulcer activity: The anti-ulcer activity of *E. africana* ethanol leaf extract (200, 400 and 800 mg extract/kg b.w) was evaluated on ethanol and indomethacin induced gastric ulceration. The extract (800 and 400 mg/kg) exhibited 54.55% prevention of ulceration in ethanol induced gastric ulceration and 57.14% prevention of indomethacin induce ulceration [7].

Anti-tussive activity: The antitussive activity of the water extract of *E. africana* root (250, 500 and 1000 mg/kg, p.o.) was evaluated against citric acid-induced cough in guinea-pigs. It was observed that the extract (1000 mg/kg) significantly reduced (65% inhibition) bronchoconstriction induced by histamine (99.25% and 34.00% for control and extract). Furthermore, the extract (1000 mg/kg) provoked a broncho dilatation response when administered under basal conditions [27].

Anti-viral activity: The anti-viral activity of methylene chloride–methanol (MCM) stem bark crude extract and different MCM fractions (EaF_0, EaF_5, EaF_{10}, EaF_{25}, and EaF_{100}) of *E. africana* were evaluated against hepatitis B virus. It was found that the MCM fraction (EaF_{10}) exhibited the strongest anti-HCV properties (IC_{50}-0.453 mg/ml) and no reduction of cell viability at antiviral concentrations. This fraction also significantly induced the expression of heme oxygenase-1 (HO-1) (5.36-fold), and 2'-5'oligoadenylate synthetase-3 (OAS-3) by 4.46-fold after 6 h and 2.31-fold after 24 h at the mRNA levels [28].

Enzyme inhibitory activity: The bark extract of *E. africana* showed 94% inhibition of mushroom tyrosinase [29].

Haemolytic activity: The haemolytic activity of methanolic extract of *E. africana* was evaluated on human A^+ red blood cells. However, the extract did not show haemolytic activity [5].

Hepato-(protective/curative) activity: The hepato protective effect of the crude extract of *E. africana* (45 g) and their fractions EaFc (methylene chloride/methanol 100:0, v/v), EaF_5 (methylene chloride/methanol 95:5, v/v), EaF_{10} (methylene chloride/methanol 90:10, v/v), EaF_{25} (methylene chloride/methanol 75:25, v/v) and EaFm (methylene chloride/methanol 0:100, v/v) were investigated against paracetamol-induced toxicity in primary cultures of rat hepatocytes. The methylene chloride/methanol fractions (90:10 v/v) were found to be the most hepato-protective (EC_{50}-13.47 µ g/ml) compared to silymarin (13.71 µ g/ml) [15].

Immunomodulatory activity: The water extract, and acidic fractions (Ea50 °C and Ea100 °C) from *E. africana* root was evaluated for complement fixing activity. The neutral fractions were least active with ICH_{50} 370 and 390 µ g/ml, respectively, for the fractions Ea_{50} and Ea_{100}. Furthermore, the least acidic fraction of the 100 ° C extracts was the most active, with ICH_{50} 75 µ g/ml. All fractions lost activity when subjected to weak acid hydrolysis [3].

Toxicological study: The toxicity of different extracts (dichloromethane, methanol and water extract) of *E. africana* root (17.5 and 35 µ g/ml) was evaluated against unparasitized RAW 264.7 mouse macrophages. The extract showed slight toxicity with 79.9 and 82.3% survival of macrophages [P13]. The acute toxicity of methanolic extract of *E. africana* showed toxicity with LD_{50} 950 mg/kg against male Swiss albino mice [5].

Medicinal uses: *E. africana* is used to treat various diseases i.e. cataract, cough, as an antidote in food-poisoning, treating dysentery and diarrheas, treatment of hepatitis, malaria, to reduce fever, against bronchitis, treating rheumatism, in treating sore, skin-eruptions, skin-infections, wound dressing [3], treat diabetes, dysentery and diarrheas, reduced hypertension [30], stop headache [31], expel intestinal worms [32], against constipation [33], oedema site, neuralgic malaria [34], whooping cough and cough, treating dysentery and diarrheas, reduce fever, stomach worms [35], wound dressing [36], abdominal pain, female infertility [21], throat complaints [7], treat infectious diseases, including sexually transmitted diseases [37].

CONCLUSION

In this mini review we have briefly summarized the traditional uses, ethno botanical description, ethno pharmacological properties and phytochemical constituents that have been isolated from *E. africana* and their subspecies. Further research should be conducted to explore new potential therapeutic agents and their ethno pharmacological properties of *E. africana* for the treatment of life-threatening diseases.

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