

A Review on *Cnidoscolus aconitifolius*: Potential Therapeutic Plant

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ABSTRACT

The chemical analysis of *Cnidoscolus aconitifolius* (Euphorbiaceae) revealed that the plant contained alkaloids, flavonoids, saponins, tannins, glycosides, and trace elements. The pharmacological studies showed that *Cnidoscolus aconitifolius* possessed antidiabetic, antimicrobial, antioxidant, cytotoxic, antifertility, and anticancer properties. This review highlights the chemical constituents and pharmacological effects of *Cnidoscolus aconitifolius*.

(Keywords: *Cnidoscolus aconitifolius*, phytochemicals, therapeutic, chemical analysis, Chaya, tree spinach).

INTRODUCTION

Plants have been used by humans for the purpose of healing since ancient times. Some chemical components of these plants are responsible for their medicinal properties. The common chemicals are alkaloids, tannins, flavonoids, and phenolic compounds (Thirumurugan, 2010). Their concentrations and nature may vary in different plants which results in unique medicinal properties for a specific plant (Richard, et al., 2013; Amish, et al., 2017).

Recently, it has been reported that about 70% of the human population is dependent wholly or partially on plant-based medicine (Raven, et al.; 2006; Sakpa and Nwachi, 2014; Lennox and John, 2018). These plant based traditional medicine systems play essential roles in health care with about 80% of the world's population relying on them due to their availability and cheap sources (Owolabi, et al., 2007; Salahdeen and Yemitan, 2006; Anwana, et al., 2012) in which Nigeria is not left out.

Cnidoscolus aconitifolius has been used nutritionally and medicinally. It is commonly called Chaya or tree spinach. It is one of the most productive green vegetables eaten in south

western Nigeria where it is called Iyana Ipaja (Oyagbemi et al., 2008). It is also eaten by the inhabitants of south eastern Nigeria where it is called "Hospital too far" (Iwalewe, et al., 2005).

The aim of this review is to shed more light on the chemical constituents and some pharmacological effects of *Cnidoscolus aconitifolius* in order to support its use in the traditional system of medicine.

SYNONYMS

Cnidoscolus chayamansa McVaugh, *Cnidoscolus chaya* Lundell, *Cnidoscolus fragrans* (Kunth) Polh, *Cnidoscolus longipedunculatus* (Brandegee), Pax & K.Hoffm., *Cnidoscolus napifolius* (Desr.) Pohl, *Cnidoscolus palmatus* (Wild.) Pohl., *Cnidoscolus quinquelobatus* (Mill.) Leon, *Jatropha aconitifolia* Mill., *Jatropha napaeifolia* Desr. ex A.Juss., *Jatropha aconitifolia* var. *multipartite* Mull. Arg., *Jatropha fragras* Kunth, *Jatropha longipedunculata* Brandegee, *Jatropha napifolia* Desr., *Jatropha palmate* Wild., *Jatropha palmate* Sesse & Moc. Ex Cerv, *Jatropha papaya* Medik., *Jatropha quinequeloba* sesse, *Jatropha quinquelobata* Mill, *Jatropha urens* var. *inermis* Calvino, *Jatropha urens* var. *longipedunculata* Brandegee (The Plant List, 2012).

TAXONOMIC CLASSIFICATION

Kingdom: Plantae, Subkingdom: Tracheobionta, Superdivision: Spermatophyta, Division: Magnoliophyta, Class: Magnoliopsida, Subclass: Rosidae, Order: Euphorbiales, Family: Euphorbiaceae, Genus: *Cnidoscolus*, Species: *Cnidoscolus aconitifolius* (USDA, NRCS)

Description

Cnidoscolus aconitifolius is an ornament, evergreen, drought-deciduous shrub up to 6m in height with alternate palmate lobed leaves and milky sap and small flowers on dichotomously branched cyme. The leaves are large, 32cm x 30cm wide on succulent petiole (Ross-Ibarra and Molina, 2002; Fagbohun, et al., 2012; Omotoso, et al., 2014)

Distribution

Cnidoscolus aconitifolius originated as a domesticated leafy green vegetable in the Maya region of Guatemala, Belize, South–East Mexico during the pre-Cambrian period (Ross-Ibarra and Molina, 2002). The genus *Cnidoscolus* consists of 40-50 species found throughout Central America and the western Caribbean but has been introduced into other tropical and subtropical parts of the world such Nigeria (Donkoh, et al., 1990; Fagbohun, et al., 2012)

Traditional Uses

Traditionally, the leaves and shoot of *Cnidoscolus aconitifolius* were taken as laxative, diuretic, circulatory stimulants, to stimulate lactation and to harden fingernails and darken grey hair. It has also been recommended for diabetes, obesity, acne, kidney stone, eye problem, ability to cure alcoholism, insomnia, gout, scorpion stings, brain and vision improvement (Rowe,1994; Atauheme, et al., 1999; Fagbohun, et al., 2012).

PHYSIOCHEMICAL CHARACTERISTIC AND CHEMICAL CONSTITUENTS

Physiochemical Content

The dried leaves of the *Cnidoscolus aconitifolius* contain 47.03 ±1.02% of nitrogen free extract; 33.04± 3.14% of crude fibre; 7.03±0.23% of crude fat; 4.03±0.67% of crude protein, 6.10±1.10% moisture content and 3.04±0.32% ash content (Iwuji, et al., 2013). Also supported by Fagbohun, et al., (2012), Shittu, et al., (2014) and Adanlawo and Elekofehinti, (2012).

Chemical Compositions

The preliminary phytochemical reveals the presences of alkaloids, tannins, saponins, flavonoids, cardiac glycosides, oxalate, cyanogenic glycosides, phenol, and phlobatannin in the leaves of *Cnidoscolus aconitifolius* (Fagbohun, et al., 2012; Awoyinka, et al., 2007; Chukwu, et al., 2016, Obichi, et al., 2015).

Eleven flavonoid compounds-one C-glycosyl flavone and ten flavonol glycosides- were isolated and identified from leaf material of *Cnidoscolus aconitifolius*. The flavonol glycosides were the galactosides, glucosides, rhamnosides, and rhamnosylglucosides of quercetin and kaempferol, and two triglycosides of the latter flavonol (Kokterman, et al., 1984)

Chemical profile of methanolic leaf extract of *C. aconitifolius* was investigated by using ultraviolet-visible spectrophotometry (UV-VIS) (UV-2500PC spec.), Fourier transform infrared spectroscopy (FTIR) (Model-8400S spec.) and GC-MS (Model-QP2010 plus spec.). The UV-VIS profile revealed peaks corresponding to phenolic compounds and flavonoids or their derivatives. The FTIR spectrum confirmed the presence of alcohols, alkanes, alkenes, and alkyne.

The chemometric profile of the methanolic leaf extract of *C. aconitifolius* revealed 10 phytochemotypes ;Y-aminobutyric lactam (3.87%), DL-Proline-5-oxomethyl ester (5.80%), Tetradecyl-oxirane (1.18%), Methyl ester palmitic acid (2.23%), n-Hexadecanoic acid (11.8%), 9,12-Octadecadienoic acid (z,z)-methyl ester (3.37%), 9-Octadecanoic acid (Z) methyl ester(5.13%), 9-Octadecenoic acid (Z) (53.97%), n-Octadecanoic acid (6.844%) and 1,2,3-propanetriyl ester (E,E,E)-9-Octadecenoic acid (5.81%) (Omotoso, et al., 2014).

GC-MS analysis revealed the presence of 3,7,1,5-tetramethyl-2-hexadecen-1-ol, farnesyl bromide, β-sitosterol, squalene, β-amyrin, 1-heptatriacotanol, hexadecanoic acid, methyl ester, 2-pentadecanone, 6,10,14-trimethyl-, n-hexadecanoic acid, 9,12-octadecadienoyl chloride, (Z,Z, δ-tocopherol, Ergosta-5,22-dien-3-ol acetate, (3β,22E)-, 9,10-secocholesta-5,7,10(19)-triene-3,24,25-triol, (3β,5Z,7E)-acetamide, N-methyl-N-[4-(3-hydroxypyrrolidiny)-2-butynyl]-, 1-gala-l-ido-

octose, 10-methyl-E—11-tridecanoic acid, 2-(acetyloxy)-1-[(acetyloxy)methyl] ethyl ester, 11,14-Octadecadienoic acid, methyl ester, and cyclopentaneundecanoic acid methylester in the leaf extract (Osuoch, et al., 2020). Also, these six (6) compounds; dodecanoic acid-1, 2, 3-propanetriyl ester (51.18%), cyclotetradecane (15.59%), eicosanoic acid (18.47%); octadecanoic acid (1.21%), 4-nitrosophenyl-beta-phenyl propionate (4.38%), benzene acetic acid, phenyl malonic acid, and 3-oxo-4-phenylbutyronitrile (9.17%) were also obtained via GC-MS analysis (Ngozi and Ohaeri, 2014).

The phenolic profile of ethyl acetate fraction of *Cnidoscolus aconitifolius* as obtained from HPLC analysis revealed the following compounds: coumaric acid, amentoflavone, hesperidin, protocatechuic acid, kaempferol, dihydromyricetin, quercetin, and rutin. The most abundant compound is quercetin with 6.943 mg/g, while rutin is the least with 0.233 mg/g (Ajiboye, et al., 2018).

Cnidoscolus aconitifolius contain vitamins, some mineral and traced elements; sodium, manganese, magnesium, potassium, calcium, iron, phosphate, and zinc (Kuti and Kuti, 1999; Oyagbemi, et al., 2008; Obichi, et al., 2015; Aye 2012), and amino acids (Adanlawo and Elekofehinti, 2012)

PHARMACOLOGICAL EFFECTS

Antimicrobial Effect

Antimicrobial activities of methanolic extract of *Cnidoscolus aconitifolius* was studied by Fagbohun, et al. (2012), assayed using the concentrations of 500, 250, 125, 62.5, and 31.25mg/ml. The result of the antibacterial effects of the extract showed that *Klebsiella pneumonia* had a zone of inhibition that varied from 1.0mm (125mg/ml) to 4.5mm (500mg/ml), *Pseudomonas aeruginosa* with a zone of inhibition of 1.5mm (125mg/ml) to 5.0mm (500mg/ml), similarly, *Escherichia coli* had a zone of inhibition of 1.0mm (125mg/ml) to 3.5mm (500mg/ml). *Staphylococcus aureus* had a zone of inhibition of 1.0mm (62.5mg/ml) to 6.5mm (500mg/ml). Although, all test bacteria were resistant to the extract at lower concentrations of 31.25mg/ml and 62.5mg/ml except *S. aureus*.

The effect of methanolic extract of *C. aconitifolius* on radial mycelial growth of the test fungi after varied hours of incubation showed that *Aspergillus tamari* had a percentage inhibition that ranged from 22% (31.25mg/ml) to 100% (500mg/ml) at 24hrs, similarly it had a percentage inhibition of 12% (31.25mg/ml) to 76% (500mg/ml) at 72hrs. *A. niger* had a percentage inhibition of 9% at 31.25mg/ml to 91% at 500mg/ml after 24hrs, but it completely inhibited the growth at 31.25mg/ml and 72% at 500mg/ml after 72hrs of incubation (Fagbohun, et al., 2012).

Also Ekeleme, et al., (2013) revealed that the antibacterial activity of the *Cnidoscolus aconitifolius* leaves extract showed broad spectrum antibacterial activity at 200mg/ml, on *Staphylococcus aureus* (19.7±1.5mm), *Shigella species* (7.0±0.6mm), *Salmonella species* (5.0±0.1mm), and *Streptococcus pneumoniae* (17.1±0.2mm). The antimicrobial activity of the *Cnidoscolus aconitifolius* were evaluated on *Salmonella typhi* and *Staphylococcus aureus*. *S. typhi* showed some sensitivity to the ethanolic extract (1.5 ± 0.5 mm) unlike the dry and fresh water extracts but much more sensitive (P<0.05) to chloramphenicol (17 ± 0.1 mm). Though, fresh leaf water extract, dry leaf ethanolic extract and chloramphenicol showed 2.0 ± 0.5, 3.0 ± 0.1 and 11.5 ± 0.1 mm bioactivity, respectively (Awoyinka, et al., 2007).

Anti-Diabetic Effect

Chloroform fraction of hydromethanolic leaf extract of *Cnidoscolus aconitifolius* were evaluated in alloxan-induced diabetic Wistar rats. The chloroform fractions were found to cause decrease in blood glucose level in a dose dependent manner within dose range of 100-200mg/Kg. 100, 150 and 200mg/Kg of the extract lowered the diabetic blood glucose by 41.76, 71.11, and 73.46%, respectively. 150 and 200mg/Kg of the extract recorded dose- and time-dependent mortality. The percentage difference in blood glucose level caused by 100mg/Kg leaf extract was 39.00% compared with 77.48% caused by 0.5mg/Kg glibenclamide. Effective dose of the extract could prevent the rapid hypoglycaemic side effect in glibenclamide usage (Samuel, et al., 2014).

The effects of *Cnidoscolus aconitifolius* leaf extract and chlorpropamide on blood glucose

and insulin levels in the inbred type 2 diabetic mice was reported by Oladeinde, et al., (2006). After treatment with the extract, the glucose levels were measured at 0 and 2-hour intervals in experimental groups and controls.

Group I received no treatment and served as control; Group II was the reference and it received chlorpropamide; Groups I-III were moderately diabetic, 100-300 mg/dL blood glucose levels while Group IV were severely diabetic (> 300 mg/dL). Groups III and IV received *Cnidoscolus aconitifolius* leaf extract and served as test groups. There was no significant difference between the blood glucose levels at 0 and 2 hours for the control group, ($P > 0.23$) but there were statistically significant differences for Group II ($P < 0.0002$); Group III ($P < 0.002$) and Group IV ($P < 0.0001$).

For moderately diabetic mice, *Cnidoscolus aconitifolius* leaf extract and chlorpropamide decreased the glucose levels by 25.6% and 16.3%, respectively, while for the severely diabetic mice the extract decreased the blood glucose by 43.7%. It is suggested that *Cnidoscolus aconitifolius* leaf extract may possess an insulinogenic property that possibly stimulated dormant β -cells to secrete insulin (Oladeinde, et al., 2006).

The ethanol extract, fractions or glibenclamide demonstrated hypoglycemic/therapeutic actions by reducing serum glucose but increasing serum insulin and body weights of the diabetic rats after administration, unlike the diabetic control that had significant alteration of these parameters with respect to the normal control. Whereas the diabetic control had significant increase in pancreatic weights with no alteration in the heart weights, the ethanol extract, fractions or glibenclamide had no effect on these organs.

The ethanol extract, methanol fractions or glibenclamide showed better hypoglycemic actions than the n-hexane or chloroform fractions at the doses used and results obtained were corroborated by histology. Furthermore, the ethanol extract, n-hexane (at 250 mg/kg) and methanol fractions or glibenclamide improved glucose tolerance in glucose loaded normal rats. The methanol fraction (500 mg/kg) demonstrated anti-hypercholesterolemic, anti-hypertriglyceridemic and insulin modulatory properties in a manner akin to glibenclamide (Achi, et al., 2017).

The effect of *Cnidoscolus aconitifolius* leaf extract on the biochemical complication of Streptozotocin (STZ) induced-diabetes was scientifically verified.

Body weight changes, blood glucose and serum lipids were assessed as indicators of diabetes severity and complications. 60 mg/kg body weight of STZ was administered to male Wistar rats intraperitoneally once as a single dose. In a dose dependent manner (100 mg/kg and 200 mg/kg), the aqueous leaf extract were administered orally (by intubation) as single daily dose for a routine period of 21 days. Relative to the control, STZ treatment significantly increased ($p < 0.05$) blood glucose from 90.61 ± 5.9 mg/dL (Control) to 237.70 ± 18.7 mg/dL (STZ group alone).

Results further indicated that *Cnidoscolus aconitifolius* treated group significantly ($p < 0.05$) decreased blood glucose level in a dose dependent manner when compared with STZ induced diabetic group. Coupled with the loss in body weight and disturbed lipid homeostasis (serum total-cholesterol, LDL cholesterol, and TAG) in the diabetic group, *Cnidoscolus aconitifolius* significantly ($p < 0.05$) returned the changes in body weight and lipid profile close to control values. Serum lipids were significantly ($p < 0.05$) decreased except for serum HDL-cholesterol that was increased by the extract when compared with the STZ treated group. This support that in STZ-induced diabetic rats, aqueous leaf extract of *Cnidoscolus aconitifolius* may be effective for the treatment of insulin dependent diabetes mellitus (Mordi, 2012).

The *in vitro* antidiabetic was studied against α -amylase and α -glucosidase by ethyl acetate fraction of *Cnidoscolus aconitifolius* and acarbose (standard drug used). The result showed that as the concentration increased, there was a significant increase ($p < 0.05$) in both the fraction and acarbose inhibitory activity of α -amylase and α -glucosidase. The ethyl acetate fraction of *Cnidoscolus aconitifolius* had higher inhibitory activity against α -amylase and α -glucosidase with IC₅₀ of 13.85 and 18.98 μ g/mL when compared to the acarbose with IC₅₀ of 17.52 and 24.51 μ g/mL, respectively (Ajiboye, et al., 2018).

Antioxidant Activity

The free radical scavenging ability of *Cnidoscopus aconitifolius* was determined via metal ion chelating and ABTS radical scavenging assay. It was observed that as the concentration increased, the metal ion chelating radical scavenging activity of ethyl acetate fraction of *Cnidoscopus aconitifolius* also increased with IC₅₀ of 23.11 µg/mL. EDTA was used as a standard with IC₅₀ of 17.51 µg/mL. The same trend was also observed in ABTS radical scavenging activity of ethyl acetate fraction of *Cnidoscopus aconitifolius* with IC₅₀ of 14.14 µg/mL. Gallic acid was used as a standard with IC₅₀ of 19.50 µg/mL (Ajiboye, et al., 2018). It also inhibited DPPH free radicals, though the extract was found less potent (8.71% at 0.5 mg/ml) compared with the standard vitamin C (91.32% at 0.5 mg/ml) (Adeniran, et al., 2013).

Cytotoxicity and Anticancer Activity

The anticancer activity of the ethanolic leaf extracts of *Cnidoscopus chamayansa* were evaluated against HT-29 (colon carcinoma) cell lines using MTT assay method. The extract showed moderate cytotoxic activity against both the cancer and normal cell line (Kumarasamy, et al., 2014).

Ikpefan, et al., 2013 studied the cytotoxicity effect of the methanol extracts of the leaf, stem and root barks of the plant against tadpole of *Raniceps ranninus*. The effects were evaluated between the concentrations of 10-400 µg/ml over a period of 24hr. At 100µg/ml, the methanol extract of the leaf produced 76.67 ± 3.33 % mortality which increases to 100% at 400µg/ml, while the stem and root barks produced 38.67 ± 8.82 and 86.6 ± 3.33% mortalities respectively at a concentration of 400 µg/ml.

Antifertility

Cnidoscopus aconitifolius was evaluated on pituitary gonadal hormone axis in male Wistar rats. It was observed that the aqueous extract reduced significantly ($p \leq 0.01$) in testosterone level and elevated luteinizing hormone and Follicle stimulating hormone in the treated rats. The testosterone/estrogen ratio was also found elevated and the effects were duration of treatment dependent (Lucky and Festus, 2015).

Bone Marrow Histological Effect

Igho (2012) investigated the effect of alcoholic extract of *Cnidoscopus aconitifolius* on bone marrow biopsy in adult Wistar rats. The rats were acclimatized for two weeks, weighed and sorted into four groups (A - D) of three animals each with corresponding weights in the same group. Alcoholic extract of *Cnidoscopus aconitifolius* was administered orally to each animal in groups B – D at 200ml/kg, 300ml/kg and 500ml/kg, respectively. Group A was the control group and they fed with animal feed and water liberally. At the end of administration, animals were sacrificed and the bone marrow biopsy obtained from the xiphoid process of the sternum. This product was fixed in 10% formal saline and stained using hematoxylin and eosin. Results showed a marked dose dependent distortion of bone marrow histologic architecture.

CONCLUSION

Plants have been used by mankind in the form of medicine since their origin. Modern medicine showed several side effects at the cost of its fast relief. This medicine has several shortcomings as per as treatment toward diabetes, microbial infections etc. Hence, world is seeing with new hope toward herbal medicine. *Cnidoscopus aconitifolius* has proven to be a promising herb drug for diabetes, antimicrobial infection etc. Although its usage should be cautioned since its toxicity level has not been ascertained.

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