Pharmacology, Phytochemistry, and Toxicity Profiles of *Phytolacca dodecandra* L'Hér: A Scoping Review

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ABSTRACT

INTRODUCTION: *Phytolacca dodecandra* L'Hér. is a native plant of sub-Saharan Africa and Madagascar which is traditionally used for various ailments. Concerned with the scope of the available evidence, we designed a scoping review to critically analyze scientific evidence on *P dodecandra*'s pharmacology, toxicity, and phytochemistry to validate its ethnomedical use.

METHODS: We searched without language restriction in MEDLINE, Google Scholar, Scopus, Embase, and Web of Science through December 2019. Both published and unpublished articles were assessed for relevance and reviewed.

RESULTS: Of 600 articles retrieved through database search, a total of 48 articles were finally included. The butanol extract of berries was more potent molluscicidal than aqueous extract. The berries had also miracidial, anthelmintic, antifungal activity, and antibacterial effect against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa*, and *Salmonella* spp. The methanol extracts of roots had an antifungal *effect* against *Candida albicans, Cryptococcus neoformans, Microsporum gypseum*, and *Trichophyton mentagrophytes*. *Phytolacca dodecandra* was toxic to aquatic invertebrate and fish. The fishes were up to 4 times more sensitive than snails. Saponins were the main phytoconstituent isolated from berries. Terpenoid and phenolic were abundant in leaves and bark extracts.

CONCLUSIONS: Studies validated the traditional use of *P dodecandra* against snails, worms, and various bacterial and fungal infections. Limited phytochemical data call for future research to focus on isolation of compounds; test their toxicity and activity; and establish mechanism of action.

KEYWORDS: *Phytolacca dodecandra*, pharmacology, phytochemistry, toxicity, bioactivity, review

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Background

Medicinal plants have been used in the management of diseases since ancient times. In recent decades, we have witnessed the growing interest in herbal medicine used as complementary or alternative to conventional therapy across countries. Dissatisfaction with the outcomes of conventional therapies mainly increased side effects and the failure rate has been cited as important determinants for such increased use.[1]

Phytolacca dodecandra (L'Herit) is native to sub-Saharan Africa and Madagascar.[2] It is a member of the Phytolaccaceae family, and commonly known in Ethiopia as "endod." Other local names include soapberry, African soapberry (English), Phytolaque (French), and Fitolaca (Spanish), and in Tanzania it is called chihakahaka.[3] The plant is a sprawling woody climber with an average length of stems reaches 5 to 8 m. It grows very rapidly especially during the rainy season with erect, racemic, dioecious flowering stalks, and red berries.[4,5]

Phytolacca dodecandra have different medicinal and nonmedicinal uses. The dried powdered berries of *P dodecandra*, when placed in water, forms a foaming detergent solution.[2] For this reason, Ethiopia, Somali, and Uganda have traditionally been using the detergent solution for cleaning clothes for a century.[6] In East, central Africa, and Madagascar, extracts of berries, seeds, leaves, and roots have also been used traditionally as a purgative, anthelmintic, laxative, emetic, diuretic, and antidiarrheal for humans and purgative for animals.[2] The leaves sap and crushed roots and berries were applied to wounds for skin diseases such as ringworms, scabies, leprosy, boils, and vitiligo.[2,7] In DR Congo, an infusion of berries or roots is taken orally to treat rabies, malaria, sore throat, and respiratory problems. Boiled leaves are

also used to treat asthma and tuberculosis. In Tanzania, macerated root bark or leaves are used for the treatment of epilepsy. In southern Nigeria, the leaf decoction is used as a laxative in a newborn baby. In Rwanda, leaf sap is used to treat otitis media,[2] and the young leaves and shoot chewed to induce abortion.[8,9]

Since the first report of molluscicidal activity by Lemma,[6] the plant has received tremendous attention from researchers from various parts of the world for the control of helminthiasis and other ailments. This resulted in increased scientific evidence to confirm the various traditional claims of the plant. The voluminous amount of scientific studies calls for a structured summary of studies conducted on *P dodecandra* to inform the scientific community on the extent of the available evidence and identify research gaps for further studies. This could speed up rational utilization of the *P dodecandra* among the community. Therefore, we designed a scoping review to systematically summarize the available studies on pharmacological activity, toxicity, and phytochemical constituents of *P dodecandra.*

Methods

Study design

This is a scoping systematic review conducted using electronic database searches. The scoping review followed the Statement for Reporting Systematic Reviews and Meta-Analyses.[10]

Information sources and search strategy

The information was collected from electronic databases: MEDLINE, CINAHL, Scopus, Web of Science, Google, and Google scholar. To reduce selection bias, no limitation was applied to the language. Google was used to translate articles with a language other than English.

Keywords used for the search are as follows: [*phytolacca dodecandra*] OR [endod] OR [gobo berry] OR [african soap berry] OR [soap berry]

Study selection and data collection

TBB conducted the literature search. Eligibility assessment was performed independently by TBB, COA, and ELP based on predefined criteria. Disagreements between those 3 authors were resolved through discussion. A data extraction form was developed and pre-tested before being adopted for use. Seven authors, TBB, COA, and ELP extracted the data from included studies and HO, PEO, WA, CUT checked for correctness. The data collected included plant names, pharmacological activity tested with the model used, phytochemical constituents, toxicological study (urinalysis, hematology, and clinical chemistry) with a model used, plant part used, extraction method with extraction solvent used.

Inclusion and exclusion criteria

Data were extracted from the full text of published original research articles or unpublished dissertations, and conference papers. We included studies reporting in vitro, in vivo, and clinical trials of *P dodecandra* in any form, and crude extract, fractions, and isolated pure compounds from any part of the plant. Data from review articles either published or unpublished, and ethnobotanical studies and scientific studies beyond medicinal uses were assessed and excluded.

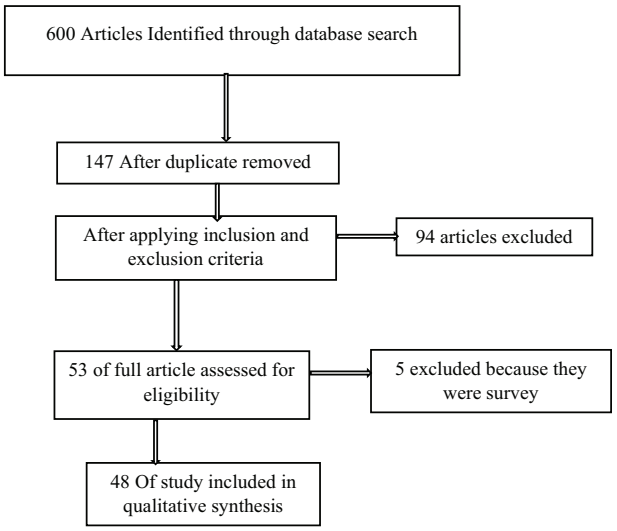

Figure 1. Flow of information through the different phases of a systematic review.

A total of 600 articles were retrieved through a database search. After the removal of duplication and assessed full-text articles based on inclusion and exclusion criteria, only 49 primary studies were finally included (Figure 1). Among the included studies, 39 were in vitro, whereas 10 were in vivo studies.

Pharmacological Activities

Molluscicidal activity

Phytolacca dodecandra is the most extensively studied plant molluscicide.[11,12] The molluscicidal effect of the plant was first discovered by Lemma in 1964.[6] In Ethiopia, at that time *P dodecandra* was widely used as a soap to clean clothes. The small berries were dried, powdered, and placed in water to form foaming detergents. It was noticed that in places along rivers where people washed clothes, there were more dead snails than adjacent areas.[5,13] Following this discovery, subsequent studies in Ethiopia and elsewhere have established that the plant is a potent molluscicide.[11,14-30]

The first laboratory aided test for its molluscicidal effect was conducted by Lemma in 1970.[5] Powdered ripe berries were added to different amounts of standard water to make the desired weight by volume expressed by parts per million. Ripe berries showed 100% mortality from 100 to 25 ppm and 25% mortality at 15 ppm after 24 hours.[5] Later the butanol extracts were tested against *Biomphalaria choanomphala, B pfeifferi*, and *Bulinus (Physopsis) nasutus* snails which revealed that exposure to 19 to 25 ppm for 6 hours or to 6 to 7 ppm for 24 hours resulted in 100% mortality.[16,24] Lemma[31] also reported 7- to

10-fold potency of butanol extract over aqueous extract. Similarly, a field study conducted in 2 streams of Chiweshe, Zimbabwe, showed a 100% molluscicidal effect at 0.02 mg/mL preparation of powdered berries after 24 hours of exposure.[29] Another comparative study[32] was conducted in Ethiopia which was aimed at developing an effective, cheap, and sustainable method of controlling schistosomiasis. Different formulations of *P dodecandra* were compared for potency, and then spray and drip-feeding methods were compared for simplicity and effectiveness in the field. Finally, the efficacy of *P dodecandra* powder soap was compared with *P dodecandra* spray method. The immediate and long-term effects of *P dodecandra* application on the snail population and schistosomal infection were determined. It was found that the spray method was more effective against *Biomphalaria pfeifferi* (100% mortality) than drip feeding method. Snail mortality ranged from 20% to 100% using *P dodecandra* soap.[32,33]

Madhina and Shiff[34] studied the miracidial effect of *P dodecandra* berries. The experiment compared infections resulting among *Bulinus globosus* exposed to *Schistosoma haematobium* miracidia in outdoor pond conditions with pond treated with *P dodecandra* and control. The study showed that there was a significant difference between *P dodecandra* and control (relative risk [RR] = 5.68 [2.04-15.9]).[34] Birrie et al[35] also found that aqueous extract of ground berries prevented snails from being infected by miracidia at a concentration of 4 ppm. The idea was proposed by Lemma[5] where 1000, 100, and 50 ppm were sufficient to kill both snail and all miracidia and cercariae within 10 minutes, 1 hour, and 2 hours, respectively.

Saponins from *P dodecandra* revealed hemolytic activity. Lemmatoxin and 3-*O*-(*O*-α-L-rhamnopyranosyl-[l, 2]-*O*-[β-D-galactopyranosyl-(1,3)]-β-D-glucopyranosyl) oleanolic acid saponins which showed a concentration causing 50% hemolysis (HC_{50}) of 5 and ppm, respectively.[36] The molluscicidal activity could be due to these potent hemolytic activities of saponins.

Anthelminthic effect

In Uganda, *P dodecandra* is being used for control of the helminthic disease.[8] The extract is prepared by taking 0.5 kg of mature leaves, boiled in 3 L of water to remain with 1.5 L and cooled. The extract of 1.5 L was given to adult cattle, 1 L to calves, and 100 mL to adult humans.[8,9] Nalule et al[9] conducted an in vivo experiment and found that *P dodecandra* was 57% effective as compared with a commercial anthelmintic drug(Albendazole). Another study was conducted on calves, using 3 types of worms: Fasciola, Strongyles, and Moniezia. It was found that there was no significant difference in eggs per grams of Moniezia parasite with Albendazole (7.5 mg/kg) and *P dodecandra* (14.24 mg/kg) but there was a significant difference with Fasciola and Strongyles. This suggests that Albendazole 10% is more effective than *P dodecandra* on Fasciola, Strongyles, and Moniezia species, whereas *P dodecandra* extracts have almost the same effect on all the 3 species of parasites studied.[37] In another study performed to evaluate the egg hatching inhibition effect of *P dodecandra* leaves of the hydro-alcoholic extract on *Haemonchus contortus*, the crude extracts of *P dodecandra* showed concentration-dependent inhibition activity and achieved 100% egg hatch inhibition at concentrations of 5 mg/mL after 48 hours of exposure.[38] A similar effect was reported in another in vitro study by Mohammed et al[39] which resulted in 99.4% inhibition of egg hatchability at a concentration of 2 mg/mL. The slight difference in potency was seen which could be attributed to extraction solvent and dose used. The mechanism and active compound from the plant have not been yet studied.

Antimicrobial effect

Phytolacca dodecandra has been traditionally used to treat infectious diseases.[40] The evaluation of the antibacterial effect of *P dodecandra* berries revealed an antibacterial effect against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa*, and *Salmonella* spp. and highly susceptible to reference strain than isolate. This could be due to exposure of an isolate to different drugs and could increase the chances of resistance.[41] Besides, 80% methanol extract of *P dodecandra* berries showed antibacterial activity against *Pseudomonas aeruginosa* standard strain of human pathogen but there was no activity against *S aureus* and *E coli*.[40,42] A polar solvent like 80% methanol extracts polar constituents like saponins which were less active against *S aureus* compared with Gram-negative bacteria like *P aeruginosa.* This could be due to the presence of pores in *P aeruginosa* which permits the entering of polar compounds.[43] Another study showed that leaf extract of dichloromethane had activity against *P aeruginosa* ATCC 27853 (MIC 12 mg/mL). Methanol and water extracts had also activity against *P aeruginosa* (MIC 1.4 mg/mL). Dichloromethane and ethyl acetate extracts of the roots of *P dodecandra* were also active against *P aeruginosa* ATCC 27853 with MIC of 2.5 and 3.5 mg/mL, respectively.[7] This consistent antibacterial effect is indicative of its antimicrobial effect especially if the compound could be isolated and screened.

Studies have established the antifungal activity of *P dodecandra*. The methanol extracts of the roots revealed antifungal activity against *Candida albicans, Cryptococcus neoformans*, and had higher activity against *Microsporum gypseum* clinical isolate and *Trichophyton mentagrophytes* clinical isolate (MIC of 3.4 mg/mL). The ethyl acetate extract of the roots also had mild antifungal activity. Besides, the aqueous extract of the leaves had moderate activity against *M gypseum* clinical isolate (MIC 110 mg/mL) and *T mentagrophytes* clinical isolate(3.4 mg/mL) and mild activity against *C albicans*. However, dichloromethane, hexane, methanol, and ethyl acetate leaves had no activity against fungal isolate tested.[7] The *n*-butanol and aqueous extract of berries also showed antifungal effect against *Histoplasma capsulatum* var. *farciminosum* with MIC of 0.39 to 0.78 mg/mL and 6.25 to 12.5 mg/mL, respectively.[44]

The aqueous extract was tested against 23 strains of dermatophytes and yeasts. The MIC against the dermatophytes tested ranged from 0.0195 to 0.156 mg/mL, whereas for all the yeasts the MIC was >0.5 mg/mL.[45] This conforms to the traditional use of the plants to treat skin disease. Further research is needed to isolate and test active compounds. Further study also needed to evaluate the mechanism on how the extract works so that the highly active product could be developed.

Antimalarial and antilarval effect of P dodecandra

The root and leaves of *P dodecandra* traditionally are used for the treatment of malaria in North-Western Ethiopia.[46,47] A study conducted on the leaf extract of *P dodecandra* against *Plasmodium berghei* demonstrated antimalarial activity in mice. The doses of 100, 200, and 400 mg/kg of the methanol extract of leaf demonstrated 18.67%, 50.93%, and 55.24% chemo suppression, respectively.[48]

Zeleke et al[49] reported 100% mortality of larvae of *Acropora arabensis* at a dose of 50 mg/L of the powder of *P dodecandra* in a laboratory and 96% mortality to the field population of *A arabensis*. The study was also conducted on the aqueous seed extract of *P dodecandra* from 5 to 50 mg/L. The 50 mg/L demonstrated 80% larvae mortality, unlike the powder which caused 100% death. This difference could be due to low extractive power of water and active substance could be left in the residue during extraction.[49,50] Studies have shown that potency can further be increased by aging berry powder in water. Getachew et al[50] evaluated the killing effect of the fresh and aged solutions against the fourth stage larvae of *A arabensis*. It was found that there was a slight improvement in the potency of aged over fresh preparations. Besides, the 80% ethanol and water extract was also tested against pupae *Anopheles gambiae* and showed a dose-dependent effect. The extracts of *P dodecandra* were potent for killing pubic lice and likely an alternative to synthetic insecticide. However, the active principle is not yet isolated and tested, and further research is needed to know the target and active substance responsible for its activity.

Photochemistry

Phytolacca dodecandra contains a dozen oleanolic acid glucosides.[23] Tura et al[41] reported that the aqueous extract of the fruit of *P dodecandra* contains saponins, tannins, and flavonoids (Table 1).

Toxicity

Aqueous extract of *P dodecandra* was tested for mammalian toxicity and ecotoxicity. It demonstrated that it inhibits alga growth with 94-hour exposure, EC_{50} of 68.49 mg/mL, toxic to aquatic invertebrate (*Daphnia magna*) with 48-hour exposure, LC_{50} of 19.8 mg/L, fish acute toxicity with 96-hour exposure, LC_{50} of 4.4 mg/L.[51] The butanol extract of *P dodecandra* was lethal to 50% of the fish and snails at concentrations of less than 3.0 ppm. The results also indicated that fish were approximately 2 to 4 times more sensitive to *P dodecandra* than snails.[52] Mammalian toxicity was also studied and acute oral toxicity yielded LD_{50} of 1740 mg/kg in males Sprague Dawley rats, 970 mg/kg in female, and 1340 mg/kg for combined sexes. However, in an another study on female Wister rats, there was no death observed up to a dose of 2048 mg/kg, but at a dose of 2048 mg/kg sign of toxicity such as reduced appetite, excessive urination, shivering, and sleepiness were observed.[53] The dermal irritation test conducted on a rabbit showed slight irritation to the skin. Acute dermal LD_{50} was also estimated as greater than 2 g/kg. The eye irritation test demonstrated significant irritation progressing to the opacity of the cornea by 24 hours post-dose.

Furthermore, repeated oral dose toxicity test on Sprague Dawley rats showed that *P dodeccandra* did not affect mortality, clinical signs, body weight, and food consumption throughout the dosing. There was no apparent dose-related change to urinalysis, hematology, or clinical chemistry values. There were no findings at gross necropsy and no microscopic lesions of the heart, spleen, kidneys, adrenal glands, or liver which could be attributed. The 28-day oral gavage testing indicated that daily treatment with *P dodeccandra* up to 500 mg/kg had no effects on the test animals; this dose represented a 28-day no observed adverse effect level.[54]

The mutagenic effect of *P dodecandra* berries was tested, only the butanol extract caused direct mutagenicity in TA98. After the addition of rat liver homogenate, again only the butanol extract was positive in TA98. The addition of gut flora extract as a metabolizing system generated a positive effect in both the methanol extract and the butanol extract. The water extract showed only a slight positive effect, which can most probably be ascribed to the presence of histidine in sample.[13] Lambert et al[54] also showed that aqueous extract of berries from *P dodecandra* was not mutagenic up to a concentration of 3 mg/plate.[14]

A study conducted by Mamo and Worku[55] demonstrated that the aqueous extract of *P dodecandra* had no significant effects on reproductive parameters studied such as the mean number of females giving birth, the mean number of days taken to give birth, the mean number of young born per group, and mean number of young surviving at 4 days post-parturition. However, the study conducted by Tachibana et al[56] showed mitogenic activity to human lymphocyte. Similarly, the aqueous extract of the leaves revealed an abortifacient effect. The extract at a dose of 500 mg/kg body weight was found 100% abortifacient.[53] The crude saponins and 2 purified saponins derived from *P dodecandra* were also found to have potent spermicidal activity. The most active was Lemmatoxin (ED_{50} of 10.7 μg/mL) and Lemma toxin-C (ED_{50} of 8.7 μg/mL).[57]

Phytolacca dodecandra was also evaluated for its toxicity in livestock. Eight calves fed fresh leaves or roots of the plant in

Table 1. Phytochemical constituent isolated from *P dodecandra*.

PLANT PARTS USE	SOLVENT USED	CLASS OF CHEMICAL COMPOUNDS	COMPOUNDS	REFERENCES
Berries	Aqueous	Saponins, tannins, flavonoids		Tadeg et al[40]
Leaves	Hexane, dichloromethane, ethyl acetate	Terpenoids and phenolics		Lemma[6]
Leaves	Methanol	Phenolics		Lemma[6]
Stem bark	hexane, dichloromethane and ethyl acetate	Terpenoids		Lemma[6]
Stem bark	dichloromethane, ethyl acetate, methanol	Phenolics		Lemma[6]
Root bark	Hexane, dichloromethane, ethyl acetate, methanol	Terpinoid and phenonics		Lemma[6]
Berries	Aqueous	Saponins	3-*O*-(2′,4′-di-*O*-[β-D-glucopyranosyl]-β-D-glucopyranosyl) 2-β-hydroxyoleanolic acid, 3-*O*-(*O*-alpha-L-rhamnopyranosyl-[1, 2]-*O*-[β-D-galactopyranosyl-[1, 3])-β-D-glucopyranosyl]2 β-hydroxyoleanolic acid, 3-*O*-(3′-*O*-[β-D-galactopyranosyl]-β-D-glucopyranosyl)2 β-hydroxyoleanolic acid.	Birrie et al[35]
Berries		Saponins	Aglycon contains: oleanolic acid, bayogenin and 2-hydroxyoleanolic acid	Getachew et al[50]
Berries	Methanol extract	Saponins	*O*-acetyl oleanolate (I) and methyl tri-*O*-acetyl bayogenin	Karunamoorthi et al[51]
Berries	Aqueous	Saponins	3-(2,4-di-*O*-[β-D-glucopyranosyl]-β-D-glucopranosyl)-olean-l2-ene-28-oic acid	Thiilborg et al[21] and Parkhurst et al[22]
Berries	*n*-butanol extract	Genins	Oleanolic acid, hederagenin, 2β-hydroxyoleanolic acid, and bayogenin	Stobaeus et al[52]
Root and leaves	*n*-butanol extract	Genins	Oleanolic acid, hederagenin, 2β-hydroxyoleanolic acid, and bayogenin, phytolaccagenin, phytolaccagenic acid,	Namulindwa et al[53]
Calli	*n*-butanol extract	Glycosides	Esculentoside, esculentoside L1.	Namulindwa et al[53]
Root	Methanol	Olean-12-ene-dicarboxylic acids	Phytolaccagenin, phytolaccagenic acid, and serjanic acid	Lambert et al[54]
		Genins	Dodecandral and dodecandralol	Lambert et al[54]

the daily ration died within 4 days and 10 sheep drenched daily with 15 or 30 g of the ground leaves died within 5 days. The toxic symptoms included salivation, muscular spasms, rapid, shallow respiration, coughing, and bloodstained diarrhea.[58]

Conclusions

Phytolacca dodecandra is extensively studied for the molluscicidal effect and widely implemented for the control of schistosome-transmitting snails. It also showed antihelminthic activity, antimicrobial activity, and antimalarial activity. Saponin is the main phytochemical constituent of the plant. *Phytolacca dodecandra* showed a toxic effect on aquatic invertebrate and fish. Mammalian toxicity was also studied and acute oral toxicity yielded LD_{50} of 1740 mg/kg in males Sprague Dawley rats. *Phytolacca dodecandra* was not mutagenic up to a concentration of 3 mg/plate and found to have potent spermicidal activity. Further research is needed to isolate and test compounds that are responsible for the activity and understand the mechanism of action.

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Author Contributions

TBB conceived the idea and wrote an initial draft of the manuscript. TBB, COA, ELP conducted the literature search and eligibility assessment. Data extraction was performed by TBB, COA, and ELP. HO, PEO, WA, and CUT checked again based on predefined format prepared. All authors reviewed the drafts for important intellectual content and read and approved the final manuscript.

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