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REVIEW

A Narrative Review of the Biological Activities of *Anredera cordifolia* (Ten). Steenis for Its Potential as a Natural Feed Additive for Livestock: Bridging Phytochemical Profile and in silico, in vitro, and in vivo Studies

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Abstract: Antibiotic growth promoters (AGPs) are commonly used as feed additives to enhance livestock productivity; however, their side effects, such as antimicrobial resistance in both animal and human bacterial pathogens, have arisen, thus leading to the discovery of safer alternatives. Plants added to the basal diet have been explored for their effectiveness in animal nutrition and health, particularly to replace AGPs. *Anredera cordifolia* (Ten). Steenis, which contains numerous secondary metabolites, is believed to contribute significantly to its biological activities. This review aims to identify the potential of *A. cordifolia* to be utilized as a natural feed additive for livestock and poultry, through exploration of its in silico, in vitro, and in vivo studies, as well as its application as a feed additive in various animal species. The Scopus and PubMed databases were used to initially search for articles published between 2015 and 2025, written in English. The resulting articles were further screened for their eligibility. The main biological properties of this plant studied in rodents were wound healing, anti-inflammatory, antioxidant, and antimicrobial, which, related to its application to goats, poultry, rabbits, and guinea pigs, confirmed antiprotozoal and anthelmintic properties, a reduction of methane production, and a decrease of cholesterol in egg yolk. The plant extract has no acute toxic effects or mortality in guinea pigs. Secondary metabolites contained in the leaves, such as flavonoids, have shown antioxidant and antimicrobial properties, while tannins can reduce methane and ammonia production in ruminants. Therefore, *A. cordifolia* leaves have the potential to be used as a feed additive, replacing AGP, to increase livestock productivity, with more benefits and fewer side effects.

Keywords: *Anredera cordifolia*, animal nutrition, antibiotic growth promoters, flavonoids, tannins

Introduction

The prohibition of using certain drugs, such as antibiotic growth promoters (AGPs) as feed additives, due to concerns about side effects such as antimicrobial resistance (AMR), is one of the factors that necessitate further research on plants. Indeed, curing various diseases with medicinal plants is as old as mankind itself. In general, "growth promoter" refers to products that boost the growth of an animal in the same unit amount of feed in a certain period.[1,2] AGPs refer to antibiotics such as macrolides, beta-lactams, sulfonamides, and tetracyclines, with a concentration ranging between 2.5 and 50 mg/kg, added to animal feed to accelerate growth rate, combat pathogen bacterial infection, and improve feed

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conversion efficiency in cows, sheep, and chickens.[3] Despite their multiple significant advantages, the use of AGPs may pose a challenge for farmers, and guidelines are critically necessary. In 2004, the WHO recommended assessing the risk and surveillance of AGPs used in livestock. Moreover, the pattern of AMR in both animal bacteria and human bacteria should also be reported.[4] The increase of AMR in animal feed has led to the complete ban on AGPs in animal feed by the European Union in 2006 and by the FDA in 2017. Intriguingly, therapeutic levels of AGPs may lead to mitochondrial toxicity, while subtherapeutic levels may improve mitochondrial function and defense mechanisms.[5] Therefore, guaranteeing the right dose is requisite. Regardless of the limited evidence on the association between AGPs and the trend of AMR in human bacterial pathogens, the idea of AGP-free animal production has encouraged consumers to demand safer dairy and poultry products.[3]

Plants, such as *Anredera cordifolia* (mignonette vine), *Azadirachta indica* (neem), *Bambusa arundinacea* (bamboo), *Curcuma longa* (turmeric), *Nigella sativa* (black cumin), *Vitex negundo* (chaste tree), and *Zingiber officinale* (ginger), have been utilized for improving animal growth performance.[2,6,7] Plant constituents, generally addressed as secondary metabolites, are commonly attributed to their role in treating various disorders through their mechanism as antioxidants and antibacterials, and are considered to have fewer adverse events compared to AGPs, thus driving their utility as natural feed additives for livestock.[7]

Anredera cordifolia (Ten). Steenis (family Basellaceae), synonym *Boussingaultia cordasta* Spreng., *Boussingaultia cordifolia* Ten., and *Boussingaultia gracilis* Miers, as described in the CABI Library (https://www.cabidigitallibrary.org/doi/full/10.1079/cabicompendium.112290), with the international common name of Madeira vine, mignonette vine, basell-potatoes, potato vine, lamb's tail, and Indonesian name binahong, is an evergreen, herbaceous climber with a twining growth form. This plant has fleshy oval or heart-shaped bright green leaves and thick potato-like aerial tubers that can easily break tree branches (https://www.cabidigitallibrary.org/doi/full/10.1079/cabicompendium.112290). *A. cordifolia* leaves do not have trichomes (epidermal hair structures to protect the plant against natural hazards), the stomata consist of guard cells (that control the opening and closing of the stomatal pore) on the upper side of the leaf and subsidiary cells on both the upper and lower sides to support the guard cells.[8] *A. cordifolia* is further classified into two subspecies, *A. cordifolia subsp. cordifolia* and *A. cordifolia subsp. gracilis*, which can be distinguished by the morphology of their vegetative organs and flowers, and pollen grain size.[9] The plant can be propagated vegetatively via its aerial bulbs, and the stems grow up to six meters in length. It is best cultivated in moist but well-drained soil under full to partial sun (https://www.nparks.gov.sg/florafaunaweb/flora/6/1/6143). It is native to South America and can be found in many tropical and subtropical countries (https://profiles.ala.org.au/opus/foa/profile/Anredera%20cordifolia). Because of its wild and invasive growth, *A. cordifolia* is described as a devastating weed that can destroy a rainforest. It is a declared noxious weed in Australia, New Zealand, South Africa, and Hawaii (https://www.cabidigitallibrary.org/doi/full/10.1079/cabicompendium.112290).

A. cordifolia leaves were reported to contain phytol at 35.68 g/100 g extract, carboxylic acids at a range of 28–25 g/100 g extract, flavonoids such as quercetin at 0.6 mg/100 g and vitexin at a range of 7.5–191.94 mg/100 mL of dry extract, with total flavonoids of 1.37 g/100 g extract, sterols, phenols with a total of 54.4 mg gallic acid equivalent (GAE)/100 g extract, terpenoids, tannins, and saponins at 28.14 ± 0.22 mg/g in the leaves, 3.65 ± 0.11 mg/g in the stems, and 43.15 ± 0.10 mg/g in the tubers. These secondary metabolites are thought to contribute importantly to its strong radical scavenging, antibacterial, and other biological activities.[10–18] The interest in *A. cordifolia* leaves, as a feed additive in livestock and poultry, marks a promising assembly of Indonesian ethnobotanical knowledge and scientific investigation. Its potential to improve the health and boost the productivity of livestock and poultry provides a strong justification to unlock further studies.[7]

Considering everything, this review aimed to identify the potential of *Anredera cordifolia* to be utilized as a natural feed additive for livestock by bridging phytochemical profile, in silico, in vitro, and in vivo biological activity studies, and its effects in animal nutrition and health. Indirectly, the use of this plant as a natural feed additive will relate to its contribution to the health of those who consume dairy and poultry products. To facilitate the review, an initial search within documents was carried out in the Scopus database using the keywords "Anredera cordifolia", with publication years limited to 2015 to 2025, subject areas limited to Pharmacology, Toxicology, and Pharmaceutics; and Agricultural and Biological Sciences; and Biochemistry, Genetics, and Molecular Biology, document type limited to article, keyword

limited to "Anredera cordifolia", "article", "plant extract", "nonhuman", and language limited to English, which resulted in a total of 96 papers. A second search in the PubMed database, using the same keywords, was conducted to enrich the review, filtered to the years 2015 and 2025, and limited to free full-text articles. The papers were screened and further filtered for their eligibility by three authors (KRGA, DR, and JL), and those which are not full-text articles, not open access, duplicate articles, not traceable, not original articles, not written in English, or not relevant to the topic of interest were excluded.

Phytochemical Profile

The phytochemical profile in *A. cordifolia* leaves collected from the Herbal Materia Medica Batu Laboratory, Batu, East Java, Indonesia (Google coordinate at S07°52.016' E112°31.199'), was analyzed using liquid chromatography-mass spectrometry (LC-MS). In this study, the leaves were extracted using 96% ethanol, and revealed the presence of six main phytochemicals, namely vitexin (flavonoids), saponin, betalain (pigments), bethanidine (alkaloids), terpenoids, and ursolic acid (carboxylic acids).[19] Another study reported that the leaves of *A. cordifolia*, obtained from the medicinal plant experimental garden, Research Center for Pharmaceutical Ingredients and Traditional Medicine, the National Research and Innovation Agency (BRIN), Lampung, Sumatra, Indonesia, when analyzed using ultra-high performance liquid chromatography tandem with high-resolution mass spectrometry (UHPLC-HRMS), demonstrated that 187 phytochemicals were identified in the 96% ethanol extract,153 phytochemicals in the 70% ethanol extract, and 105 phytochemicals in the 50% ethanol extract.[20]

In silico Biological Activity Studies

Unfortunately, only two open-access in silico study articles were identified in the Scopus database,[18,19] and one in the PubMed database.[21] Additional searches in the Google Scholar database yielded one article.[21] These articles reported wound healing,[19,20] antiviral and antibacterial properties,[21,22] of phytoconstituents in *A. cordifolia* leaves. The details of the studies are described in the following paragraphs.

Phytochemicals found in the leaves of *A. cordifolia*, namely, vitexin, saponin, betalain, bethanidine, terpenoids, and ursolic acid, were molecularly docked to the active site of matrix metalloproteinase-2 (MMP-2) enzyme or gelatinase A, a zinc-dependent enzyme that contributes to tissue regeneration, wound healing, and embryonic development. Of the six compounds, only saponin, ursolic acid, and vitexin could interact with the protein, and the complexes between the compounds and the enzyme were stable.[19] In another study, two carboxylic acids (trans-3-indole acrylic acid and gluconic acid), which were successfully isolated from the 70% ethanol extract of *A. cordifolia* leaves, could occupy the binding site of the MMP-1 and MMP-12 enzymes, with a comparable binding energy to that of the native ligand. The results were further validated by an in vitro approach using an NIH-3T3 fibroblast cell proliferation assay, and confirmed its wound healing properties.[20] Procyanidin and vitexin contained in *A. cordifolia* leaves strongly interact with an enzyme of a virus, suggesting their potential to be developed as an antiviral.[21] The antibacterial activity of three phytochemicals (linoleic acid, phytol, and hexadecanoic acid) contained in the leaf extract was studied towards the penicillin-binding protein 2 (PBP2) of *S. pneumoniae*, which revealed a potential to inhibit the growth of the bacteria by interacting with Trp374, Glu378, Thr526, Ser548, Gly549, Thr550, Phe570, Ser571, and Tyr595. Linoleic acid demonstrates the greatest potential, but lower compared to benzylpenicillin.[22]

In vitro Biological Activity Studies

We identified nine open-access in vitro study articles in the Scopus and PubMed databases,[23–32] describing antimicrobial as the most confirmed effects,[26,29,30] followed by radical-scavenging and/or antioxidant properties,[25,31] wound healing,[24] antidiabetic,[23] non-toxicity against normal cells,[26,27] cytotoxicity against cancer cells,[28] and anti-inflammatory effects.[32] An additional search in the Google Scholar database resulted in three articles, of which two were excluded because of duplication with those in the PubMed database, and one article was included that describes antimicrobial effects.[33] The details are described in the following paragraphs:

The 96% ethanol extract of *A. cordifolia* leaves collected at Yogyakarta, Indonesia, demonstrated high inhibitory activity against alpha-glucosidase and upregulated GLUT4 in adipocytes. These results were validated by the same

authors in alloxan-high fructose diet (HFD)-induced diabetic rats, which confirmed the antidiabetic activity of the ethanol extract of *A. cordifolia* leaves.[23] The leaves of *A. cordifolia* collected in Southern Brazil during the summer have shown genoprotective and phytogenomic effects in both normoglycemic and hyperglycemic conditions, elucidating the wound healing properties of this plant, which are likely associated with the abundant levels of phytol content.[24] An in vitro study revealed a strong radical scavenging activity, assessed via the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method, was observed in *A. cordifolia* leaves harvested in autumn compared to other seasons; however, no significant correlation was obtained between this activity and total polyphenol content.[25] Antibacterial activity of the 70% ethanol *A. cordifolia* leaf extract against *Streptococcus mutans* (ATCC 25175) was achieved with an average inhibition zone diameter of 14.513 mm at a concentration of 100%. Moreover, this study described no cytotoxic effects of the plant extract on normal BALB/3T3 fibroblast cells.[26] In vitro study of *A. cordifolia* towards 3T3 fibroblast cells was also reported in another study, thus confirming its safety towards normal cells.[27] However, the extract demonstrated selective cytotoxicity on HeLa cells, which was achieved by arresting the G1/S phase of the cell cycle and suppressing the Bcl-2 expression.[28]

The leaf extract in pharmaceutical preparations (gel and nanoparticles) was also reported in two studies. *A. cordifolia* leaf extract in gel formulations showed antibacterial activity against *Staphylococcus aureus*, with an inhibition zone diameter of 19.5 mm.[29] *A. cordifolia* leaf extract, prepared in nanoparticles using chitosan as the polymer and sodium tripolyphosphate as a crosslinker, was found to inhibit the growth of *Propionibacterium acnes*, a bacterium that is a major cause of acne.[30] The triterpenoid fraction of *A. cordifolia* leaf extract showed inhibition against *Staphylococcus epidermidis*.[33] Triterpenoids were described to possess the capacity to enter the cell membranes of bacteria, damaging the structure, permitting the leakage of important cellular components, inhibiting DNA synthesis, and leading to cell death.[34,35]

Moreover, the methanol stem fraction of *A. cordifolia* has shown antioxidant properties, as assayed using the cyclic voltammetry method.[31] Anti-inflammatory properties of *A. cordifolia* leaf extract, studied using the human red blood cell-membrane stabilization method, revealed an inhibition of hemolysis.[32] Intriguingly, a previous study disclosed that plants with strong antioxidant properties, such as *Orobanche orientalis, Cucumis melo, Albizzia julibrissin, Galium verum, Scutellaria tournefortii, Crocus caspius, Sambucus ebulus, Danae racemosa*, and *Artemisia absinthium*, showed inhibition towards erythrocyte hemolysis in mice.[36]

In vivo Biological Activity Studies

We identified 26 open-access in vivo study articles in the Scopus and PubMed databases,[37–62] describing anti-inflammatory and wound-healing effects as the most confirmed,[37–42] anti-obesity,[42–44] antidiabetic or hypoglycemic,[45–47] antihypertensive,[48–50] antioxidant,[51–53] and other biological activities.[54–56] The details are described in the following paragraphs:

A gel preparation consisting of 3% ethanol extract of *A. cordifolia* leaf, collected at Tigabinanga district, Karo regency, North Sumatra, Indonesia, could enhance alveolar bone healing by increasing the proliferation of fibroblasts, osteoblasts, and osteocytes in post-extraction sockets in Wistar rats. The wound healing effects were thought to be attributed to saponin content in the *A. cordifolia* leaf extract, which is associated with its antiseptic properties and its capacity to stimulate the expression of transforming growth factors.[37] Another study of an ointment made from the 5% leaf extract of *A. cordifolia* was effective in treating hot metal-induced topical burn in albino rats. These wound healing effects were believed to be contributed by the flavonoids, saponins, and tannins contained in the extract, which have antioxidant, anti-inflammatory, and antibacterial properties.[38] *A. cordifolia* extract, prepared by cold-extraction of the plant leaves obtained from Yogyakarta, Indonesia, using 96% ethanol, has shown anti-allergy properties by suppressing immunoglobulin E levels in the acute allergic rhinitis Wistar rat model, exposed to ovalbumin.[39] Moreover, treatment with *A. cordifolia* leaf extract from 10 days prepartum to 10 days postpartum could decrease offspring mortality and improve the leucocyte profile in the guinea pigs. These effects were expected due to the flavonoids, which possess antimicrobial and immunostimulant properties.[40] The effects of the cold cream containing *Garcinia mangostana, Anredera cordifolia*, and *Centella asiatica* extracts in the second-degree burn rat model were reported to reduce inflammatory cell infiltration and increase collagen levels, suggesting its anti-inflammatory and burn-healing properties.[41]

The anti-obesity and anti-inflammatory effects of ethanol leaf extract of *A. cordifolia* in rats were achieved by significantly reducing extracellular regulated kinase (ERK) levels and the number of macrophages in the adipose tissue of rats with high-fat diet-induced obesity.[42] The plant extract exerted anti-obesity properties in rats fed a high-fat diet by inhibiting adipogenesis and increasing phosphoinositide 3-kinase (PI3K) levels,[43] and decreasing peroxisome proliferator-activated receptor-gamma (PPAR-γ) transcription factor.[44] Antidiabetic or hypoglycemic effects of *A. cordifolia* extract in combination with *Muntingia calabura* and *Tinospora crispa* were studied in alloxan-induced diabetic Swiss-Webster mice. The combination of these extracts has shown a reduction in blood sugar levels after 14 days of oral administration.[45] Administration of *A. cordifolia* exhibited hypoglycemic properties by significantly reducing blood glucose levels in high-fat diet-induced diabetic rats, resembling those of glibenclamide, a known oral antidiabetic drug.[46] *A. cordifolia* leaf ethanol extract at a dose of 400 mg/kg markedly reduced blood glucose levels in hyperglycemic rats.[47] Antihypertensive activity of the ethanol extract of *A. cordifolia* leaves on angiotensin II–induced male Wistar rats revealed that at a dose of 50 and 100 mg/kg, it could decrease both systolic and diastolic blood pressure in the rats.[48] The antihypertensive effects of the ethanol extract of *A. cordifolia* were also studied in dexamethasone-induced hypertensive rats, resulting in a decrease in blood pressure, which is anticipated to be due to the vasodilation effect through the nitric oxide pathway.[49] Furthermore, a combination of *A. cordifolia* 50 mg/kg and *Sonchus arvensis* 50 mg/kg resulted in a reduction of systolic and diastolic blood pressure of epinephrine-induced male Wistar rats by inhibiting adrenergic receptors.[50] Antioxidant properties of *A. cordifolia* were reported in three articles.[50–52] These antioxidant properties were achieved by reducing the production of malondialdehyde (MDA) in glucose-induced cataract goat lenses,[51] in unilateral ureteral obstruction rat model,[52] and by reducing serum creatinine and urea in gentamicin-induced nephrotoxicity rats.[53] Other biological activities of *A. cordifolia*, such as antimicrobial activity against wild strain black-pigmented bacteria,[54] teratogenic,[55] and improving learning and memory without causing any noticeable side effects in a senescence-accelerated mouse-prone 8 (SAMP8) mouse model,[56] were also described.

Based on the review, the *A. cordifolia* plant, particularly the leaves, has demonstrated numerous biological properties; however, when bridging the results of the in silico (wound healing, antiviral, and antimicrobial),[19–22] in vitro (anti-proliferative, wound healing, anti-inflammatory, antimicrobial, antioxidant, and antidiabetic),[23–32] and in vivo (anti-inflammatory and wound healing, antioxidant, antiobesity, antidiabetic, and antihypertensive) studies.[37–56] However, while reviewing the papers, we encountered limitations, such as some studies only covered small sample sizes, there was a lack of long-term data, or other issues related to the reproducibility of the studies. Regardless of these limitations, we suggested that the main biological properties of this plant mainly point to wound healing, anti-inflammatory, antioxidant, and antimicrobial, and thus we further searched for its application for animal nutrition and health.

Applications of A. cordifolia for Animal Nutrition and Health

The applications of *A. cordifolia* for animal nutrition and health were reported in nine articles,[57–65] involving goats, chickens and hens, quails, rabbits, and guinea pigs.

Studies of the effects of dietary supplementation of the *A. cordifolia* leaf added to the basal meal of goats were as follows: A study was conducted in the milk of Saanen goats suffering from subclinical mastitis. Parameters measured were faecal endoparasites, bacterial counts, and serum albumin and globulin levels. The results revealed that *A. cordifolia* leaf given as a daily meal for 14 consecutive days has the potential to significantly ($p < 0.05$) lower the number of viable bacteria in the milk and gastrointestinal tract, and lower the number of oocytes and coccidial oocysts in the feces. The leaf extract also increased milk production and decreased subclinical mastitis. These effects were believed to be contributed by the antioxidant and antimicrobial properties of the constituents in the leaf. However, no differences were observed in serum albumin and globulin compared to goats treated with basal diets.[57] The leaves significantly reduced the quantity of Ostertagia sp. nematoda eggs in goats, with a reduction rate of 97.5%.[58] Moreover, Suryani et al (2024) reported that a complete randomized design with four replications of *A. cordifolia* (collected in the area of an oil palm plantation in Kumpeh, Muaro Jambi, Indonesia) in Etawa goats resulted in a reduction of protozoa by 30.2%, thus proposing its potential to enhance nutrient utilization, feed efficiency, and livestock performance in tropical areas.[59]

During the same year, the effects of *A. cordifolia* in combination with *Areca catechu* in young domestic chickens (*Gallus gallus domesticus*) infected with *Ascaridia galli* worms were also reported. The infected chickens were given

a meal that consisted of *A. cordifolia* and *A. catechu* for seven days, with combination doses as follows: group 1 was given 2 mg/kg of *A. catechu* seed and 1 mg/kg of *A. cordifolia* leaf extract; group 2 was given a combination of 5 mg/kg of *A. catechu* seed and 2.5 mg/kg of *A. cordifolia* leaf extract; and group 3 was not given any treatment. The study resulted in a significant reduction in the number of *A. galli* worm eggs per gram of feces in group 1 in a polynomial order-2 trendline, and *A. galli* worms were absent in 60% of chickens in group 1 and in 40% of chickens in group 2. In both parameters, the dose-response data follow a polynomial order-2 trendline ($y = 27.333x^2 - 90.333x + 79$ for the number of *A. galli* worms, and $y = 569.33x^2 - 1459.3x + 1030$ for the number of *A. galli* worm eggs, per gram of feces) with an R^2 value = 1. The immunohistochemistry in the intestine demonstrated that *A. cordifolia* improved healing processes in the intestine.[60] The anthelmintic effect is believed to be due to the presence of saponins, flavonoids, and tannins in the leaves, which could interfere with the worms' metabolism by binding the protein, resulting in a depletion of nutrient availability, starvation, and death.[59,61] The addition of 2–6% *A. cordifolia* leaf powder in the basal diet meal of 200 quails did not markedly alter egg production, egg characteristics, or egg protein content. However, reduced the cholesterol, triglyceride, and low-density lipoprotein (LDL) contents in yolk, and increased high-density lipoprotein (HDL) levels in yolk. The dose-response data for cholesterol ($y = -14.41x^2 + 100.25x - 119.09$), triglyceride ($y = -68.215x^2 + 510.79x - 140.11$), yolk LDL ($y = -0.92x^2 + 5.63x + 8.48$), and yolk HDL ($y = -7.46x^2 + 51.12x - 37.6$) follow a polynomial order-2 with an R^2 value = 1.[62] Another study by Murwani et al (2022) reported the supplementation of *Areca catechu* nut powder for 3 days in subsequential by *A. cordifolia* leaves powder for another 3 days, for three cycles with a total of 18 days. This study aimed to control the parasite larvae in ISA Brown layer hens. ISA stands for Institut de Sélection Animale; the synonym of ISA Brown hens is Hubbard Brown hens. The supplementation resulted in a reduction of *A. galli* worm numbers by 12.5% following a polynomial order-2 trendline dose-response relationship ($y = -0.5x^2 - 1.5x + 9$; $R^2 = 1$), and an improvement of intestinal histopathology, especially in the caecum, and serum albumin and transaminases, without affecting egg production. This study confirms the anthelmintic properties of *A. cordifolia* leaves.[63]

The effects of *A. cordifolia* leaf extract supplementation on the uterine involution process in rabbits,[64] and on the postpartum estrus cycle of guinea pigs (*Cavia cobaya*),[65] were also explored. It was announced in both studies that *A. cordifolia* supplemented in the diet could accelerate the time of postpartum estrus in both animals (rabbits and guinea pigs). It was pondered that these effects may be attributed to the protein in the leaf of *A. cordifolia*, which stimulates the production of nitric oxide (NO).[66] Endogenous NO has a pivotal role in numerous pathways involved in vasodilation, neurotransmission, inflammation, and apoptosis. It is enzymatically generated from the conversion of L-arginine (the enzyme's substrate) by a distinct family of nitric oxide synthase (NOS) enzymes, to produce L-citrulline (the main product) and NO (the side product).[67] Previous studies have shown that NO is released and mediated by different cells involved in anti-inflammation. The release of NO in the vascular endothelium can maintain vasodilator tone.[68] NO works together with reactive oxygen species (ROS), calcium ions, cyclic nucleotides, protein kinases/phosphatases, and signaling lipids. However, the mechanisms of NO production in plants are debatable and remain not fully answered.[69]

Until recently, we could not find safety limits for *A. cordifolia* consumption by livestock, because studies on the toxicity of this plant in animals are very few and focus on extracts. A study has confirmed that the plant extract has no acute toxic effects or mortality in guinea pigs at up to 90 mg/head;[70] however, more assays are required to determine a definitive lethal dose (LD_{50}) and specific safety guidelines for livestock.

Finally, in the following paragraphs, we describe the mechanism of the antioxidant and antibacterial properties of flavonoids and tannins, respectively.

Antioxidant and Antimicrobial Mechanism of Flavonoids and Tannins

Flavonoids are natural secondary metabolites with variable phenolic structures that are found in various parts of plants. Flavonoids are classified into different subgroups, namely flavones (eg, apigenin, luteolin, chrysin), flavonols (eg, quercetin, kaempferol, myricetin), flavanones (naringenin, hesperetin), flavanols or catechins, anthocyanins (cyanidin, delphinidin, pelargonidin), and chalcones (xanthoangelol, 4-hydroxyderricin, cardamonin), depending on the carbon of the C ring on which the B ring is bound, and the degree of unsaturation and oxidation of the C ring.[69] Flavonoids have been reported for their strong antioxidant properties. Antioxidants are compounds that prevent oxidation reactions by

acting as nucleophiles towards another molecule. Exogenous antioxidants, such as flavonoids, are a family of polyphenols that can alleviate oxidative stress by reacting with reactive oxygen species (ROS).[71]

Flavones such as apigenin, luteolin, and chrysin were reported for their antioxidant properties by attenuating tert-butyl hydroperoxide-induced oxidative stress via the activation of extracellular signal-regulated protein kinase 2 (ERK2)/nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant responsive element (ARE) signaling pathways in rat primary hepatocytes, as reported by Huang et al (2013).[72] Intriguingly, the three flavones were also described for their capacity in mitigating high mobility group protein1 (HMGB1)-induced neuroinflammation on BV2 microglia cells.[73] Apigenin, luteolin, and chrysin could reduce lipotoxicity-induced NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome activation and autophagy damage in macrophages by decreasing endoplasmic reticulum stress.[74]

Flavonols such as quercetin, kaempferol, and myricetin were reported for their antioxidant and antimicrobial properties by destroying the activity of pathogen bacteria and hindering the anchoring of surface protein, which reduces the adhesion of fibrinogen that promotes biofilm formation,[75] by increasing the bacterial cytoplasmic membrane permeability,[76,77] by inhibiting DNA gyrase and topoisomerase IV, and inhibiting the interaction of DNA binding helicase and deoxynucleotide triphosphates,[76] and other antibacterial mechanisms. Furthermore, the antioxidant activity of myricetin was described as having the strongest activity compared to quercetin and kaempferol.[78]

The effects of myricetin, naringin, catechin, rutin, quercetin, and kaempferol on the rumen microbial activity were studied by Oskoueian et al (2013). This study demonstrated that almost all the flavonoids markedly reduced the dry matter degradability, the methane production, the population of rumen microbes, and the total population of protozoa.[79] Moreover, phenolic acids and flavonoids in the form of Propolis extract, administered into the rumen via ruminal cannula twice a day, could reduce the *Entodinium* protozoa population, increase ruminal acetate concentration, and increase microbial protein synthesis in the rumen, as described by de Paula et al (2016).[80] Flavonoids were also reported for their anthelmintic activity on the larvae and adult worms of *Haemonchus contortus*.[81]

Plant secondary metabolites, such as saponins and tannins, were discussed in a review article to have shown an efficiency for ruminant reproduction, an improvement for milk and meat quality, a control for foam production, and methane (CH_4) production.[82] Tannins have been shown to alleviate nitrogen degradation in the rumen.[83] Another study reported the effects of tannins, in condensed form (not easily broken down in the body), on digestibility, milk production, blood parameters, methane emission, and energy and nitrogen balances in dairy goats. This study by Battelli et al (2024) revealed that condensed tannins reduced the production of methane from dairy goats, probably by decreasing feed digestibility.[84] Two hydrolysable tannins, namely ellagic acid and gallic acid, were reported by Manoni et al (2023) for their effects in significantly reducing the methane emissions and ammonia formation, and affecting the rumen degradability of the diet and the total short-chain fatty acid (SCFA) production.[85] The capacity to decrease ammonia formation may be linked to the reaction between tannins and proteins, by subtracting nitrogen from rumen degradation and increasing its retention.[83] Further, a very recent study by Carrazco et al (2025) on the effects of a commercial feed additive composed of quebracho, chestnut tannins, and saponins on lactating dairy cows resulted in a decrease in the enteric production of methane, carbon dioxide (CO_2), and nitrous oxide, and, unexpectedly, a slight increase in ammonia production.[86] Dietary tannins were also delineated for their capacity to alter protozoan composition and rumen microbial community, thus decreasing methane production.[87]

Conclusion

In summary, regardless of the numerous reported biological activities of *Anredera cordifolia* (Ten). Steenis (family Basellaceae), we confirmed that there is an association between the phytochemical profile, the in silico, in vitro, and in vivo biological activity studies of the leaf extracts, and the applications of *A. cordifolia* leaves as a feed additive blended into the basal diet meal in different types of animals. Therefore, we arrive at a suggestion that the main biological properties of this plant possibly point to antioxidant (by alleviating oxidative stress), antimicrobial (including antibacterial, antiviral, antifungal, and antiprotozoal), wound healing, and anti-inflammatory. The application of this plant to goats, poultry, rabbits, and guinea pigs confirmed antiprotozoal and anthelmintic properties, a reduction of methane and ammonia production, and a decrease of cholesterol in egg yolk, which dose-response follows a polynomial order-2 trendline. These effects are believed to be attributed to secondary metabolites contained in the leaves, such as flavonoids,

which have been known for their role in antioxidant and antimicrobial properties, and tannins, which possess the capacity to reduce the methane and ammonia formation in ruminants by altering protozoan composition. *Anredera cordifolia* leaves may have the potential to be utilized as a feed additive, replacing the antibiotic growth promoters (AGPs), to increase livestock productivity. This plant is easily propagated vegetatively via its aerial bulbs, best cultivated in moist but well-drained soil under full to partial sun, and is an invasive growth; thus, it is believed to have more benefits with less cost and fewer side effects for the enhancement of the productivity of both poultry and dairy animals. However, further investigations, such as the optimal dosage and administration of *A. cordifolia* leaves in livestock and poultry feeds, are needed to ensure safety and further unveil its full benefits.

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Disclosure

The authors report no conflicts of interest in this work.

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