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Review article

Amaranthus retroflexus: a dual-edged plant with promising therapeutic potential and toxicological concerns: a review

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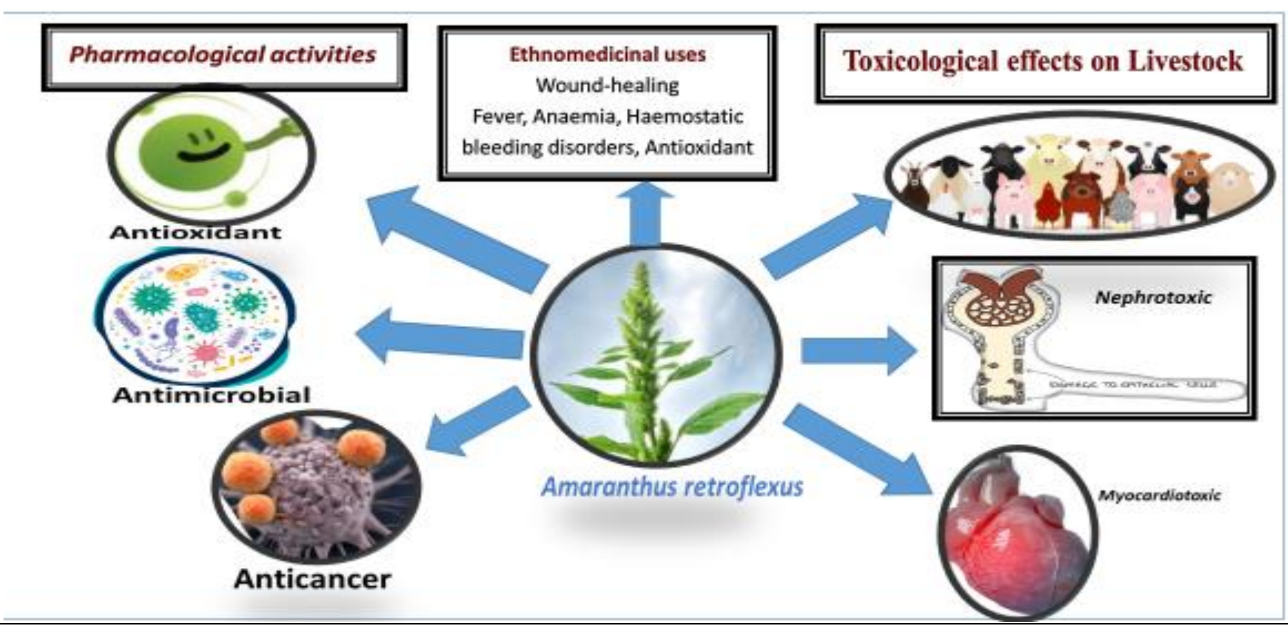
ABSTRACT

Amaranthus retroflexus, a member of the Amaranthaceae family often regarded as an agricultural weed, has emerged as a plant of pharmacological interest. Its rich phytochemical composition, including polyphenols, flavonoids, sesquiterpenes, and glucosides, underpins its potent antioxidant, antimicrobial, and anticancer activities. Notable compounds such as rutin and Amarantholidols exhibit strong antioxidant properties, suggesting potential roles in combating oxidative stress. The plant has shown antimicrobial efficacy against various pathogens and preliminary anticancer effects through cytotoxicity on cancer cell lines. However, *A. retroflexus* is highly toxic to livestock, with nephrotoxic, myocardiotoxic, and oxalate-related effects causing acute renal failure and significant mortality in animals. This duality of medicinal potential and toxicological risk highlights the need for cautious exploration. Comprehensive research is necessary to elucidate its mechanisms of action, minimize risks, and harness its therapeutic value. With proper management and targeted studies, *A. retroflexus* could be transformed from a toxic weed into a valuable source of natural medicine.



Keywords: *Amaranthus retroflexus,* Antioxidant, Anticancer, Antimicrobial, Bioactive compounds.

INTRODUCTION

Amaranthus retroflexus (**Figure 1),** commonly known as redroot pigweed, is a globally distributed plant belonging to the Amaranthaceae family. Native to the tropical regions of the Americas, it has adapted to diverse climates and is now naturalized on multiple continents, thriving particularly in agricultural and disturbed soils. Although often regarded as a weed due to its invasive nature and potential to reduce crop yields, redroot pigweed also offers notable nutritional and medicinal benefits [1,2]. This herbaceous annual, part of a family comprising over 165 genera and approximately 2,040 species, can grow up to 3 meters tall. It is characterized by broad, lance-shaped leaves (10–15 cm long) and dense flower clusters containing both male and female flowers, enabling robust growth and efficient reproduction. Historically, indigenous communities across the Americas, Asia, and Europe have utilized its leaves and seeds as a food source. Modern scientific research has uncovered the plant's rich phytochemical profile, revealing significant potential health benefits. However, toxicity concerns persist, particularly for livestock, with reports of nephrotoxic effects following ingestion. While redroot pigweed holds promise as a medicinal and nutritional resource, its dual nature as a beneficial plant and an invasive species underscores the need for careful management and further investigation [3-6].

Figure 1: *Amaranthus retroflexus*

Taxonomy

Amaranthus retroflexus L., commonly known as redroot pigweed, belongs to the family Amaranthaceae. It is classified as follows [7]:

Kingdom: Plantae, Clade: Angiosperms, Clade: Eudicots,

Order: Caryophyllales, Family: Amaranthaceae, Genus: *Amaranthus*

Species: *A. retroflexus*

Morphology

A. retroflexus is a fast-growing, annual herbaceous weed that thrives in a wide range of environmental conditions. It is a C4 plant, known for its efficient photosynthetic pathway, particularly under high light intensities and elevated temperatures. The plant typically grows to heights of 50–150 cm, with a sturdy, erect stem that may exhibit slight reddish coloration.

The leaves are simple, alternate, and ovate to lanceolate in shape, with a pointed tip and slightly wavy margins. The surface of the leaves is green, and the veins are prominent. The plant produces small, greenish flowers that are densely packed into terminal and axillary spikes. These flowers are monoecious, with separate male and female flowers on the same plant.

The seeds are small, black, and shiny, enclosed within a utricle fruit. The prolific seed production of *A. retroflexus*, combined with its robust root system, contributes significantly to its invasiveness and ability to colonize a wide range of habitats, including agricultural fields, roadsides, and waste areas.This species exhibits a high degree of morphological plasticity, allowing it to adapt effectively to varying environmental conditions. Such adaptability enhances its competitive ability, making it a persistent and challenging weed in many regions [8].

Ethnomedicinal and Nutritional Uses of *Amaranthus retroflexus*

Historically, *A. retroflexus* has been extensively used in traditional medicine to treat various ailments. Across cultures, it is valued for its antioxidant, haemostatic, and wound-healing properties. Ethnomedicinally, it has been applied to address conditions such as fever, anaemia, and bleeding disorders. The leaves and seeds, known for their haemostatic activity, are commonly used to manage heavy menstrual bleeding, haemorrhoidal issues, diarrhoea, and intestinal colic [9,10]. In northern Iran, for instance, the *A. retroflexus* soups were prepared, demonstrating its dual role as both a medicinal and nutritional resource. Additionally, *A. retroflexus* has allergenic potential, with its pollen being a recognized trigger for IgE-mediated respiratory allergies. This is particularly problematic in arid and semi-arid regions, such as Iran, Kuwait, and Saudi Arabia, where high concentrations of airborne pollen can cause seasonal allergy outbreaks. Nutritionally, *A. retroflexus* has served as a food source for indigenous populations across the Americas, Asia, and Europe. Its leaves and seeds are rich in essential minerals like calcium and iron, as well as ascorbic acid (vitamin C) and vitamin A precursor. Even today, young leaves are prepared as leafy greens or added to soups in various regions, appreciated as an affordable, nutrient-dense food that requires minimal cultivation, making it accessible to low-income communities [10].

The medicinal efficacy of *A. retroflexus* is largely attributed to its array of polyphenolic compounds, flavonoids, and other secondary metabolites that contribute to its antioxidant, anti-inflammatory, and antimicrobial activities. Flavonoids such as rutin, along with saponins, alkaloids, carbohydrates, tannins, and organic acids, add to the plant's pharmacological profile. Notably, the leaves contain higher concentrations of these beneficial compounds compared to the seeds. Further studies reveal a range of bioactive compounds in *A. retroflexus*, including glucosides and glycosides, which also exhibit antioxidant properties. These antioxidants are crucial for scavenging free radicals in the body, potentially reducing oxidative stress and lowering the risk of chronic diseases. The presence of these phytochemicals has spurred research interest in *A. retroflexus* for its antioxidant, antibacterial, anti-inflammatory, and hepatoprotective properties [11-13]. In addition to its pharmacological components, *A. retroflexus* contains valuable nutrients and minerals like zinc, iron, copper, sodium, potassium, and manganese, essential for immune response, cellular signaling, and antioxidant defense. Studies using advanced techniques like atomic absorption spectrophotometry have highlighted these nutrients, as well as the plant's protein, fiber, and fatty acid profiles, reinforcing its value as a nutritious food source. Furthermore, analyses employing UHPLC-UV-MS have examined the polyphenolic content, noting its potent antioxidant properties and potential to prevent oxidative stress-related conditions such as cardiovascular diseases and certain cancers [14, 15].

However, despite its medicinal and nutritional benefits, *A. retroflexus* poses toxicological risks, particularly in livestock. Veterinary studies document cases of nephrotoxicity in animals such as cattle, sheep, pigs, and horses after ingestion. Symptoms often include acute renal failure, perirenal edema, and significant kidney damage due to unknown compounds in the plant that can lead to degeneration of kidney tubules, fibrosis, and tubular proteinosis. Severe cases can result in extensive kidney damage and even death in affected animals. This toxicity underscores the importance of cautious use in animal feed and emphasizes the need for responsible application in therapeutic contexts [16].

A. retroflexus is a versatile plant, recognized for its nutritional value, medicinal properties, and potential toxic risks. Its widespread availability, historical significance as a food source, and the rich profile of bioactive compounds position it as a promising candidate for further research. However, its allergenic nature and toxic effects in animals require careful evaluation, particularly when considering its application in both dietary and therapeutic settings [17].

Secondary Metabolites

In *A. retroflexus*, a diverse range of bioactive sesquiterpenes, sesquiterpene glucosides, and prenylpropanoids with notable antioxidant properties have been identified. Among the isolated sesquiterpenes, four compounds specifically have been characterized: Amarantholidols A, Amarantholidols B, Amarantholidols C, and Amarantholidols D. These sesquiterpenes contribute significantly to the plant's medicinal profile, particularly its antioxidant capacity [18]. In addition to these sesquiterpenes, several sesquiterpene glucosides have been isolated from *A. retroflexus*, enhancing its pharmacological diversity. These include Amarantholidoside I, Amarantholidoside II, Amarantholidoside III, Amarantholidoside IV, Amarantholidoside V, Amarantholidoside VI, and Amarantholidoside VII [19]. These glucosides contribute to the plant's antioxidant and other bioactive properties, showcasing its potential as a natural therapeutic agent. Additionally, a range of prenylpropanoids has been identified within *A. retroflexus*, with their chemical structures fully characterized. These include compounds like Ferulic acid, Umbelliferone, Apigenin, Boropinic acid, 4-Geranyloxyferulic acid, 7-Isopentenyloxycoumarin, Auraptene, and Umbelliprenin [20-22]. These phenylated compounds are well-regarded for their antioxidant activities and play a role in neutralizing free radicals, thus offering protective benefits against oxidative stress. The phytochemical richness of *A. retroflexus*, demonstrated through its array of sesquiterpenes, glucosides, and prenylpropanoids, highlights its potential as a valuable source of natural antioxidants with applications in both traditional and modern medicinal contexts.

Pharmacological Properties

Anti-cancer activity

A. retroflexus, shows promising anticancer potential due to its cytotoxic activity, which may offer therapeutic implications. Bioassays have been conducted to explore its cytotoxic effects, especially against renal cell lines, where the plant's extracts reduced cell viability in a dose-dependent manner. When exposed to higher concentrations, such as 100 ppm, bovine kidney cells displayed significant cytotoxicity, with a reduction in cell viability by approximately 49% after 24 hours, while even lower doses like 0.1 ppm caused a 35% reduction. This suggests a potent cytotoxic response associated with *A. retroflexus* compounds, potentially applicable in cancer research focusing on renal cell carcinomas and related malignancies. The cytotoxic effects of *A.retroflexus* may be attributed to its diverse phytochemical profile, including terpenes, alkaloids, and saponins, which are known to interact with cell viability pathways, possibly targeting mitochondrial functions essential for cancer cell metabolism. The MTT assay, a standard method for evaluating mitochondrial integrity and cellular metabolic activity, further confirmed the plant's ability to compromise cell survival, highlighting its promise in targeting rapidly dividing cancer cells. Furthermore, the brine shrimp lethality test indicated that while *A. retroflexus* is generally not toxic at higher ppm values to non-specific cells, its toxicity becomes more pronounced in renal cell cultures. This selective toxicity is significant, as it implies the plant's extracts may possess specific bioactivity against certain cancer cell types, underscoring the need for more targeted studies on its anticancer properties. Future research could explore isolation of active compounds, investigate underlying mechanisms, and conduct in vivo evaluations to assess its potential as an anticancer agent, particularly for cancers of the kidney and other organ systems where selective cytotoxicity could be therapeutically advantageous [23].

Antioxidant Activity

Methnolic extract of *A. retroflexus* leaf was subjected to study the antioxidant activity, which is rich in bioactive phytochemicals such as ascorbic acid, polyphenolic compounds, and flavonoids. These constituents have demonstrated significant antioxidant abilities, which contribute to the plant's overall antioxidant potential. Several assays were conducted to evaluate the methanolic extract and individual phytochemicals for their capacity to neutralize reactive oxygen species (ROS) and mitigate oxidative stress. The DPPH radical scavenging assay and hydrogen peroxide (H_2O_2) scavenging test were among the key methods used, as they are standard techniques for assessing antioxidant efficacy. Additionally, the plant's potential to inhibit lipid peroxidation was examined using the thiobarbituric acid reactive substances (TBARS) assay, which underscores its capacity to protect cellular membranes from oxidative damage. The phosphomolybdenum complex formation assay further validated the strong antioxidant properties of these compounds. The results showed a robust, dose-dependent antioxidant response from the methanolic extract, attributed largely to the presence of ascorbic acid, polyphenols, and flavonoids. These phytochemicals exhibited antioxidant activities comparable to the reference standard α-tocopherol, positioning *A. retroflexus* as a promising natural source of antioxidants. This makes it a potential alternative to synthetic antioxidants such as BHA, BHT, and TBHQ, which have raised concerns about possible toxicity and carcinogenicity. The findings suggest that *A. retroflexus* could serve as a safer, naturally derived antioxidant option [18, 24].

Antimicrobial Potential

The antimicrobial potential of *A. retroflexus* L. has garnered attention due to its efficacy against various bacterial and fungal strains. The 30-residue antimicrobial peptide Ar-AMP, isolated from the seeds, demonstrated strong antifungal activity. This peptide effectively inhibited the growth of fungal pathogens such as *Fusarium culmorum*, *Helminthosporium sativum*, *Alternaria consortiale*, and *Botrytis cinerea*. Additionally, Ar-AMP caused morphological changes in *Rhizoctonia solani* at micromolar concentrations, showcasing its potent antifungal properties.In separate studies, aqueous, ethanol, and chloroform extracts of *A. retroflexus* demonstrated antimicrobial activity against Gram-positive bacteria, including *Staphylococcus aureus* and *Sarcina lutea,* as well as the fungal pathogen *Candida albicans.* Notably, the chloroform extract from dry seeds demonstrated broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria, as well as significant antifungal activity. These findings suggest that *A. retroflexus* has promising antimicrobial properties, making it a potential natural source for combating drug-resistant pathogens. However, no synergistic effects were observed when combining the chloroform extract with standard antibiotics, indicating that its antimicrobial actions are likely independent [25].

Toxicological Effects on Livestock

A. retroflexus (redroot pigweed) is highly toxic to livestock, including pigs, cattle, sheep, and goats, with occasional effects in horses. The plant's toxicity arises from oxalates, nitrates, and unidentified nephrotoxic and myocardiotoxic compounds. Soluble oxalates bind calcium in the bloodstream, forming insoluble calcium oxalate, which damages kidney tubules and leads to oxalate nephrosis and renal failure. Nitrates, while present, rarely induce sudden death but can contribute to methemoglobinemia in ruminants. Unknown nephrotoxic agents further exacerbate kidney damage, while cardiac toxins may result in secondary heart failure.

Clinical signs typically appear 5–10 days after ingestion and include weakness, trembling, incoordination, knuckling of the fetlocks, hind limb paralysis, and recumbency. In pigs, mortality rates in symptomatic cases can reach 75–80%. Gross pathological findings include swollen, pale kidneys with perirenal edema and fluid accumulation in body cavities (ascites and hydrothorax). Microscopically, kidney lesions show tubular necrosis, glomerular atrophy, and interstitial fibrosis in chronic cases. Elevated serum urea nitrogen, creatinine, and potassium are biochemical hallmarks, with hyperkalemia contributing to cardiovascular failure. Most poisonings occur in late summer or fall, particularly during droughts when forage is scarce. Symptoms develop rapidly, and death can follow within 1–2 days of onset. Chronic cases may also exhibit edema and ulceration of the digestive tract. Immediate removal of animals from affected areas is crucial, as toxic effects may persist for up to 10 days after exposure. The absence of a specific antidote underscores the importance of preventive management to mitigate risks associated with *A. retroflexus* [26}.

CONCLUSION

Amaranthus retroflexus offers a dual profile of significant therapeutic potential and notable toxicological risks. Its bioactive compounds, such as rutin and Amarantholidols, highlight its antioxidant, antimicrobial, and anticancer properties, making it a promising candidate for natural drug development. However, its toxicity to livestock due to nephrotoxic, myocardiotoxic, and oxalate-related effects underscores the need for caution in its use. Comprehensive research is essential to unravel its pharmacological mechanisms, mitigate toxic risks, and explore its clinical applications. With careful management and targeted studies, A. retroflexus could transition from a toxic weed to a valuable medicinal resource.

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