

Pharmacological Actions and Phytoconstituents of *Amaranthus spinosus* Linn: A Review

Guria Tanmoy¹, Mondal Arijit², Singha Tanushree¹, Singh Jagadish³, *Maity Tapan Kumar¹

¹Department of Pharmaceutical Technology, Jadavpur University, Kolkata-700 032, India

²Drug Development Diagnostics & Biotechnology Division, Indian Institute of Chemical Biology, Kolkata-700 032, India.

³Guru Ghasidas Vishwavidyalaya, Bilaspur (C.G.), 495009, India.

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ABSTRACT

This work presents a brief overview of the morphological, phytochemical and pharmacological properties of *Amaranthus spinosus* Linn. The available information on the ethnopharmacological uses in traditional medicine, phytochemistry, pharmacology and clinical practice of *Amaranthus spinosus* were collected via a library and electronic search (PubMed, ScienceDirect, Google Scholar and Spingerlink). Phytochemical investigation of this plant has resulted in the identification of more than 20 active chemical constituents, among which betalains, hydroxycinnamates, saponins, steroids and flavonoids are the predominant ones. The plant has desirable effects like cooling, digestible, alexiteric, laxative, diuretic, stomachic, antipyretic, improves the appetite, useful in kapha and biliousness, blood disease, burning sensation, hallucination, leprosy, bronchitis, rat bite, piles and leucorrhoea. This article enumerates an overview of phytochemical and pharmacological aspects that is useful to researchers for further exploration necessary for the development of this potential herb.

Keywords: Traditional medicine; Phytoconstituents; Pharmacological activity; Toxicity

INTRODUCTION

Herbalism has a long tradition of use outside of conventional medicine. It is becoming more mainstream as improvements in the analysis and quality control along with advances in clinical research which showed the value of herbal medicine in treating and preventing the disease¹. Therefore, nowadays research has been focused on scientific evaluation of traditional drugs of plant origin. *Amaranthus spinosus* Linn, is one such plant that has been frequently used in traditional system of medicine. *A. spinosus* Linn. (Family: Amaranthaceae) is commonly known as “Kate Wali Chaulai (Kanatabhajii)” in Hindi, used as vegetable and cultivated throughout India, Sri Lanka and many tropical countries². The juice of *A. spinosus* is used by tribes in Kerala, India to prevent swelling around stomach while the leaves are boiled without salt and consumed for 2-3 days to cure jaundice³. The plant is consumed as a vegetable for its high concentration of antioxidant components^{4, 5, 6, 7} and high nutritive values due to presence of fiber, proteins and high concentration of essential amino acids, especially lysine⁸. The root is used as an expectorant; lessens the menstrual flow, useful in leucorrhoea and leprosy. The seed is used as a poultice for broken bones. In the last decade, many active secondary metabolites have been isolated and screened for various *in-vivo* and *in-vitro* pharmacological activities, which suggested its uses in promoting and maintaining health.

To provide further support and evidence for the ethnopharmacological use of this plant, a systematic review on the modern Phytochemistry and pharmacological properties was performed.

Botanical Description: An erect glabrous herb of 30-60 cm in height; stems are hard, often reddish in color, with many grooved branches and with sharp divaricate spines, often exceeding 1.3 cm long in the leaf-axils. Leaves are 3.2-7.5 of 1.3- 3.8 cm, ovate or lanceolate. Petioles are 2-6.3 cm in length. Flowers very numerous, sessile, in dense axillary. Clusters and in terminal and axillary dense and interrupted spikes; bracteoles linear, bristle-pointed, usually longer than the sepals. Perianth of male flowers 2.5-3 mm, long; sepals 5, ovate, acute, bristle-pointed. Perianth of female flowers scarcely 1.5 mm long, sepals 5. Capsules were 1.5 mm long, ovoid, thickened at the top, circumscissile about the middle, membranous, rugose; styles, divaricate, pubescent^{9, 10}.

Amaranthus spinosus is widely distributed throughout the tropics and warm temperate regions of Asia from Japan to Indonesia to India, Bangladesh, the Pacific islands and Australia as a weed in cultivated as well as fallow lands¹¹. This plant is widely distributed in roadsides, waste places and fields in Southeastern North America, also found in Cambodia, Philippines and Maldives as a valued food plant.

Pharmacological Activities

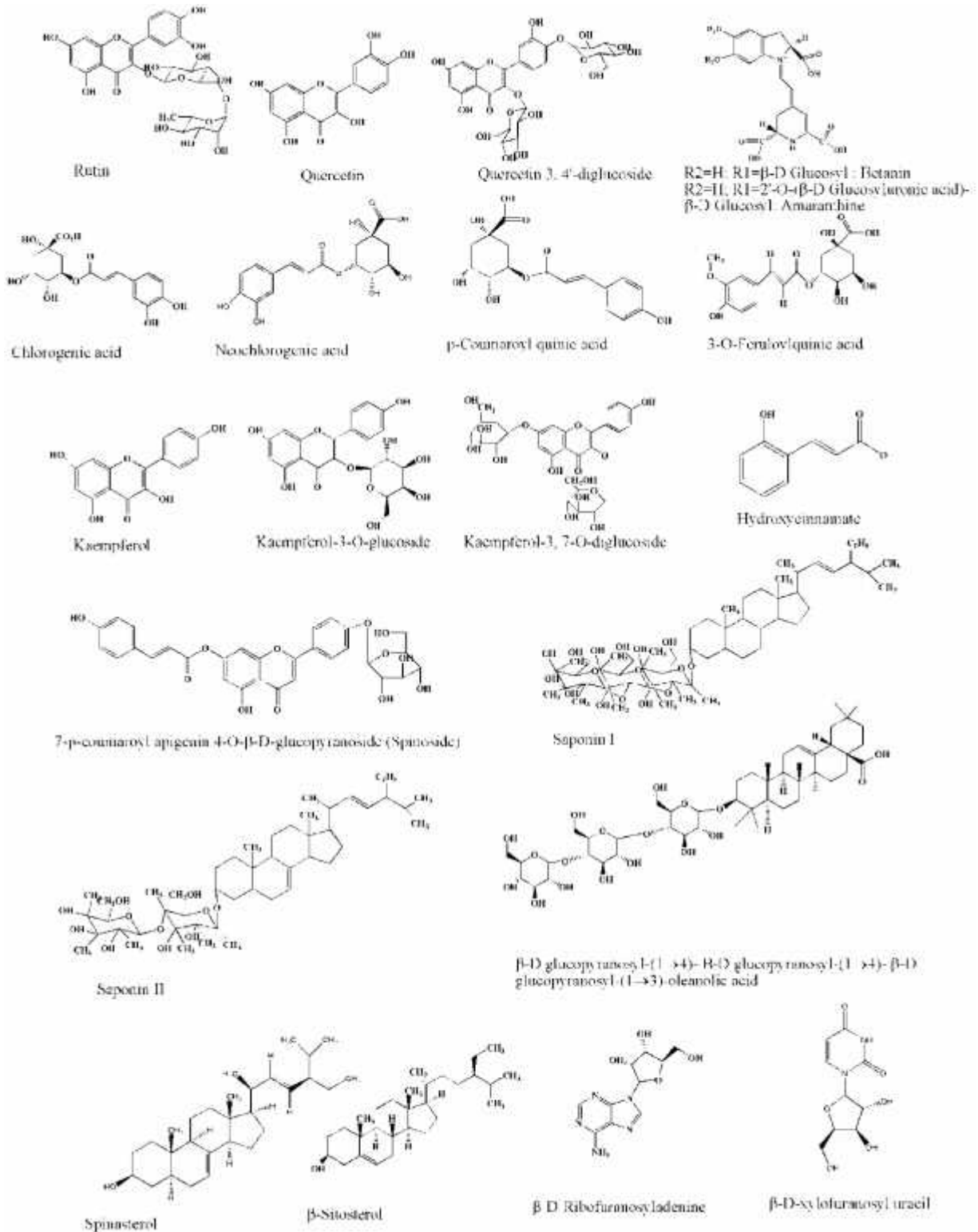


Fig. 1: The chemical structure of some active compounds from *Amaranthus spinosus*.

Hepatoprotective and Antioxidant Activity: Ethanolic extract of whole plant of *Amaranthus spinosus* showed hepatoprotective and antioxidant activity against carbon tetrachloride (CCl₄) induced hepatic damage in rats. This study suggested that possible hepatoprotective activity may be due to antioxidant defense factors and the presence of flavonoids and phenolic compounds in it^{12, 13}. The extract showed hepatoprotective activity against d-

galactosamine/ lipopolysaccharide (d-GalN/LPS) -induced liver injury in rats¹⁴. Kumar *et al*¹⁵ showed the potentiality of the methanol extract of whole plant of *A. spinosus* Linn, (MEAS) against paracetamol-induced liver damage in Wistar rats. They predicted that the presence of amino acids, flavonoids and phenolic compounds in the MEAS responsible for its market hepatoprotective and antioxidant activities.

Table 1: Pharmacological activities of *Amaranthus spinosus* Linn.

Pharmacological activities	Parts use	Extract	Reference
Hepatoprotective Activity			
against carbon tetrachloride (CCl ₄) induced hepatic damage in rats.	whole plant	ethanolic extract	[12, 13]
against d-galactosamine/ lipopolysaccharide (d-GalN/LPS) -induced liver injury in rats.	whole plant	ethanolic extract	[14]
against paracetamol-induced liver damage in Wistar rat	whole Plant	ethanol extract	[15]
Antioxident activity			
(a) non-enzymatic haemoglycosylation assay	whole Plant	petroleum ether, chloroform, methanol, and water extract	[16, 17]
(b) DPPH assay	leaves	methanolic extract	
	leaves	chloroform, n-hexane and ethyl acetate extract	[17]
	leaves		[20]
Antigenic and allergenic activity	pollen		[18]
Anti diabetic activity			
Alpha amylase enzyme inhibition by CNPG3 (2-chloro-4-nitrophenol a-D-maltotrioxide)	leaves	methanol extract	[21]
Streptozotocin-induced diabetic rats			
Alloxan-induced diabetic rats	stems	methanol extract	[22]
	stems	methanol extract	[23]
Anti-inflammatory activity			
carrageenan induced paw oedema	leaves	ethanol extract	[24]
	whole plant		
	leaves	methanol extract	[26]
acetic acid induced	whole plant	petroleum ether and ethanolic extract	[25]
		methanol extract	[27]
peripheral analgesic activity	leaves		[28]
Anthelmintic activity			
Indian earthworms (<i>Pheritima Posthuma</i> & <i>Tubifex tubifex</i>)	whole plant	aqueous extracts	[27, 29]
Anti-malarial activity			
<i>Plasmodium Berghei</i>	stem	aqueous extracts	[30]
Heamatologic activity	leaf	ethanol extract	[31]
	whole plant	methanolic extract	[32]
	except root		
Immunomodulatory activity			
Stimulatory effect on spleen cells from female mice.	leaves	water extract	[34]
Dexamethasone (DEX)-induced apoptosis in murine primary splenocytes.	leaves	water extract	[35]
cell-mediated immune response (CMIR)		pet. ether, aqueous, alcoholic extract	
	leaves		[36]
Gastrointestinal activity			
charcoal meal method	leaves	aqueous extract	[37]
		aqueous-methanolic extract	
Laxative activity	whole plant		[38]
Anti-diarrheal and anti-ulcer activity			
charcoal meal	whole plant	ethanol extract	[39]
Antitumor activity			
Brine shrimp lethality bioassay	leaves	methanol extract	[20]
EAC bearing mice	leaves	ethanol extract	[40]

Table 1: Pharmacological activities of *Amaranthus spinosus* Linn.

Pharmacological activities	Parts use	Extract	Reference
Antitumor activity			
Brine shrimp lethality bioassay	leaves	methanol extract	[20]
EAC bearing mice	leaves	ethanol extract	[40]
Antibacterial activity	leaves	chloroform , n-hexane and ethyl acetate extracts	[20]
	roots	ethanol and aqueous extracts	
	leaves	hexane, ethyl acetate, dichloromethane and methanol extracts	[41]
Diuretic activity	whole plant	aqueous extract	[42]
Other activities			
biochemical role	whole plant except root	methanolic extract	[43]
			[44]

The antioxidant activity of *A. spinosus* was evaluated by non-enzymatic haemoglycosylation assay. The result reported that secondary metabolites rutin and quercetin showed the inhibition of haemoglycosylation as maximum 42% and 52%, respectively^{16, 17}. The antioxidant activity of *A. spinosus* was studied in roadside plants which was postulated to be continuously exposed to the high levels of pollutants such as nitrogen oxides and sulfur dioxides from automobile emission. *A. spinosus* possess a very good free radical scavenging system for combating air pollution through analysis of the enzymes (i.e superoxide dismutase, catalase, ascorbate peroxidase, glutathione reductase and phenolic peroxidase) activities¹⁸. Amaranthaceae plants contain betalain pigments which show antioxidant activities by the DPPH assay^{19, 20}. Their EC₅₀ values range from 3.4- 8.4 μ M. The antioxidant activity of *A. spinosus* extract may be due to its bottling content.

Anti diabetic activity: The alpha amylase and the antioxidant potential of methanol extract of *A. spinosus* (MEAS) was established by *in vitro* alpha amylase enzyme inhibition by CNPG3 (2-chloro-4-nitrophenol a-D-maltotrioxide) and *in vivo* antioxidant potential of malondialdehyde (MDA), glutathione (GSH), catalase (CAT) and total thiols (TT) in alloxan-induced diabetic rats. This study provided evidence that the methanolic extract of *A. spinosus* has potent alpha amylase, anti-diabetic and antioxidant activities²¹.

According to Sangameswaran and Jayakar,²² the plant showed anti-diabetic, anti-hyperglycemic, anti-hyperlipidemic and spermatogenic effects in alloxan-induced diabetic rats. The investigation established some pharmacological evidence to support the folklore claim that it is used as an anti-diabetic agent²³.

Anti-inflammatory activity: The petroleum ether, ethanol extract of whole plant and methanol extract of leaves of *A. spinosus* exhibited anti-inflammatory activities in a dose dependent manner in carrageenan induced paw oedema, and produced significant inhibition of acetic acid induced increase in vascular permeability indicating that the extract

has anti-inflammatory activity. In the cotton pellet granuloma tests, rats were treated orally with the extract for 4 consecutive days after the subcutaneous implantation of a sterile pellets. The highest dose of the extract (100 mg/kg) was able to significantly reduce the post implantation weight of the cotton pellets compared to controls indicating its effectiveness against acute inflammation. *Amaranthus spinosus* extract also showed a highly specific prostaglandin synthesis inhibitory activity *in-vitro* in an anti-inflammatory model test system, indicating that it possess anti-inflammatory activities. The result suggested that the plant extract probably acts by the inhibition of prostaglandin biosynthesis^{24, 25, 26, 27}. The methanol extract of *Amaranthus spinosus* exhibited significant, dose dependent peripheral analgesic activity of the tested animals. The extract significantly reduced the acetic acid induced abdominal contractions²⁸.

Anthelmintic activity: The aqueous extracts of whole plant of *A. spinosus* Linn was evaluated for anthelmintic activity on adult Indian earthworms (*Pheritima Posthuma* & *Tubifex tubifex*), using piperazine citrate as reference standard. The aqueous extract showed anthelmintic activity in a dose dependent manner giving shortest time of paralysis (P) and death (D) with 50 mg/ml concentration, for both the worms. The extract showed more potent activity (15 mg/ml) against *Tubifex tubifex*^{27, 29}.

Anti-malarial activity: The *in-vivo* antimalarial activities of extracts from *A. spinosus* L. was reported in mice. The plant extract showed significant anti-malarial activities in the 4-day suppressive anti-malarial assay in mice inoculated with red blood cells parasitized with *Plasmodium Berghei*³⁰.

Heamatologic activity: Ethanol extract of *Amaranthus spinosus* leaf was administered orally to growing pigs to determine its effects on packed cell volume (PCV), red blood cell (RBC) and white blood cell (WBC) counts, and hemoglobin (Hb) concentration. The extract significantly reduced the elevated levels of PCV, RBC and Hb of pigs

albeit temporarily. The final weight and average weight gains of the pigs were significantly improved with the administration of the ethanol extract³¹.

Srivastava *et al.*³² showed that alteration in hematocellular components of albino rats due to methanolic extract of *Amaranthus spinosus*. The study was carried out by single daily dose administered for 5, 7 & 14 days. Results revealed that the RBC and WBC count as well as Hb% was significantly restored by the administration of methanolic extract of *A. spinosus*.

Akinloye and Olorede,³³ reported that the aqueous extract of *A. spinosus* leaf produced no significant changes in the value of haematological parameters such as RBC, WBC, packed cell volume (PCV), haemoglobin concentration (Hb) and blood coagulation time of the rats. Although a significant reduction in serum glucose and cholesterol levels was observed. Serum biochemical parameters showed no significant changes in the levels of the enzyme alkaline phosphatase (ALP), serum glutamate pyruvate transaminase (SGPT) and serum glutamate oxaloacetate transaminase (SGOT).

Immunomodulatory activity: The stimulatory effect of wild *A. spinosus* water extract was investigated on spleen cells from female mice. The extract significantly stimulated splenocyte proliferation. However, isolated B lymphocytes, but not T lymphocytes, could be stimulated by wild *A. spinosus* in a dose response manner. These results exhibited immuno-stimulating activity via directly stimulating B lymphocyte activation *in vitro*. Further, these results suggest that the immuno-stimulating effects of water extract might lead to B lymphocyte activation and subsequent T-cell proliferation *in-vitro*³⁴.

Lin *et al.*,³⁵ assessed the immuno-modulatory effects of wild *A. spinosus* water extract (WASWE) on spontaneous and dexamethasone (DEX)-induced apoptosis in murine primary splenocytes. The cultured splenocytes treated with WASWE products were harvested and analyzed to assess their apoptotic status according to DNA fragmentation by flow cytometry and agarose gel electrophoresis. The results showed WASWE inhibited the spontaneous and DEX-induced apoptosis of splenocytes.

Tatiya *et al.*,³⁶ carried out phytochemical investigation and immunomodulator activity of *Amaranthus spinosus* linn. They studied immunomodulatory activity by cell-mediated immune response (CMIR) measured by delayed type of hypersensitivity reaction to sheep red blood cells (SRBC) and humoral immune response (HIR) measured by hemagglutination antibody titre. Among the various leaf extracts the aqueous and alcoholic extracts revealed a significant elevation in humoral as well as cell-mediated response and pet. ether extract significantly reduced humoral as well as cell-mediated response.

Gastrointestinal activity: According to Ashok Kumar and Jayaveera,³⁷ investigated the effect of aqueous extract of *Amaranthus spinosus* on gastrointestinal tract in mice by using charcoal meal method. Results revealed significant gastrointestinal motility of *A. spinosus*.

Chaudhury *et al.*,³⁸ suggesting the presence of laxative effect in the plant mediated partly through cholinergic action.

Anti-diarrheal and anti-ulcer activity: The ethanol extract (50%) of the whole plant of *Amaranthus spinosus* Linn. (Amaranthaceae) (ASE) significantly inhibited travel of a charcoal meal at three different doses of ASE, but when 400 mg/kg of ASE was repeated in the presence of yohimbine, intestinal propulsive inhibition decreased, while morphine reversed the activity. Lipid peroxidation was also associated with a concomitant decrease in ulcer index³⁹.

Antigenic and allergenic activity: *Amaranthus spinosus* is an important aeroallergen in India and grows commonly in different parts of the country, specially significant in Type I hypersensitivity disorders. Investigated antigenic and allergenic properties of 5 pollen samples of *Amaranthus spinosus* collected from the Delhi area at fortnightly intervals. The observations will be helpful in standardizing pollen antigens for diagnosis and immunotherapy in India¹⁸.

Antitumor activity: The ethanol extract of *Amaranthus spinosus* leaves exhibit significant antitumor effects in EAC bearing mice⁴⁰. The Brine shrimp lethality bioassay method was used to determine the cytotoxicity activities²⁰.

Antibacterial activity: It was reported that ethanol and aqueous extracts of *Amaranthus spinosus* roots showed potential antibacterial activity against some bacterial strains including Gram-positive and Gram-negative bacteria using the agar well diffusion method. The ethanol extract showed significant results in comparison to the aqueous extract in inhibiting microbial growth^{20, 41, 42}.

Diuretic activity: The extract of *Amaranthus spinosus* increases the Na⁺, K⁺, Cl⁻ excretion, caused alkalization of urine, showed strong saluretic activity and carbonic anhydrase inhibition activity. These effects were observed predominantly at 500 mg/kg dose and there was no dose-response relationship.

This study strongly suggests that the *Amaranthus spinosus* is acting as a thiazide like diuretic with a carbonic anhydrase inhibitory activity which restates the claim as a diuretic herb in Siddha medicine⁴³.

Other activities: The biochemical role of methanolic extract of *Amaranthus spinosus* on the liver of Sprague Dawley rats indicate that significant change in protein and glycogen contents⁴⁴.

Ogunyemi *et al.*,⁴⁵ studies Competitive impact of *Amaranthus spinosus* in *Celosia argentea* and *Corchorus olitorius* production in Southwestern Nigeria.

The leaf residue of *Amaranthus spinosus* Linn., effect on the growth and metabolism of *Pertheneum hysterophorus* L., in pot culture. The leaf residue of *Amaranthus spinosus* inhibits the height of the plant, length of the leaves and the number of branches capitula and seeds per plant. The total sugar content was also decreased as well. The accumulation of organic acids reveals that respiration was hampered in *A. spinosus*. An increase in the amino acids might be an adaptation of plant in environmental stress⁴⁶. Chaudhary *et al.*,³⁸ spasmolytic effect was mediated through calcium channel blocking (CCB), while bronchodilator activity through a combination of -adrenergic and CCB pathways.

Table 2: Phyto constituents of *Amaranthus spinosus* Linn.

Therapeutic constituents	Plant part	References
Amaranthine, isoamaranthine, hydroxycinnamates, quercetin and kaempferol glycosides	stems	[49]
7-p-coumaroyl apigenin 4-O- -D-glucopyranoside, xylofuranosyl uracil, -D-ribofuranosyl adenine and -sitosterol glucoside.	whole plant	[50]
Rutin and quercetin	whole plant	[51, 52]
Amaranthoside- a lignan glycoside	whole plant	[53]
Amaricin- a coumaroyl adenosine stigmaterol glycoside		
-spinasterol	roots	[54]
hectriacontane	leaves and stem	
oleanolic acid, D-glucose and D-glucuronic acid aliphatic ester- -spinasterol octacosanoate	roots	[55]
saponin- -D- glucopyranosyl-(1-4)- -D-glucopyranosyl -(1-4)- -D-glucuronopyranosyl-(1-3)-oleonolic acid		
Saponin I- -D- glucopyranosyl-(1-2)- -D-glucopyranosyl -(1-2)- -D-glucopyranosyl-(1-3)- -spinasterol	roots	[56]
Saponin-II- -D-glucopyranosyl-(1-4)- -D-glucopyranosyl-(1-3)- -spinasterol		

Pharmacognostic Study: Baral *et al.*,⁴⁷ studied the pharmacognostic character of stem and leaves of *Amaranthus spinosus* Linn.

Jaya Mathur *et al.*,⁴⁸ investigated the macroscopic, microscopic and preliminary phytochemical investigation of the leaves of *Amaranthus spinosus* which includes leaf constants, physiochemical parameters like ash values, extractive values and moisture content. The total ash, acid insoluble ash, water-soluble ash values and sulfated ash were observed to be 6.33%, 3.60%, 2.44% and 0.80% w/w respectively. Alcohol soluble and water-soluble extracting values of the leaves were observed to be 6.40%, 3.30%, respectively. Powdered leaves were also subjected to fluorescence analysis with different chemicals. Phytochemical investigation of methanolic and petroleum ether extracts revealed the presence of Flavonoids, phytosterols, glycosides, tannins, phenolic compounds and carbohydrates.

Therapeutic Constituents: The main betalains in *A. spinosus* were identified as amaranthine and isoamaranthine. Extracts of *A. spinosus* were found to contain hydroxycinnamates, quercetin and kaempferol glycosides⁴⁹ (Fig. 1). The new coumaroyl flavone glycoside from the *n*-butanol fraction of the methanol extract of the whole plant of *Amaranthus spinosus* and assigned the structure 7-p-coumaroyl apigenin 4-O- -D-glucopyranoside on the basis of spectroscopic analysis. In addition -xylofuranosyl uracil, -D-ribofuranosyl adenine and -sitosterol glucoside have also been isolated for the first time from this species⁵⁰ (Fig. 1). Flavonoids present in the *Amaranthus spinosus* are rutin and quercetin. Vijay *et al.*,^{51, 52} has reported the isolation and structural determination of rutin in whole plant powder of *Amaranthus spinosus* Linn (Fig. 1). The phytochemical investigation of the *n*-butanol fraction of the methanolic extract of the whole plant of *Amaranthus spinosus* Linn., lead to the isolation of amaranthoside, a lignan glycoside,

and amaricin, a coumaroyl adenosine along with stigmaterol glycoside⁵³ (Fig. 1).

The -spinasterol and hectriacontane were isolated from a petroleum ether extract of leaves and stem of *A. spinosus*.

-spinasterol was also identified in roots. A saponin mixture was isolated in roots. Other constituents found oleanolic acid, D-glucose and D-glucuronic acid⁵⁴ (Fig. 1).

A new aliphatic ester, -spinasterol octacosanoate and a new saponin, -D- glucopyranosyl-(1-4)- -D-glucopyranosyl -(1-4)- -D-glucuronopyranosyl-(1-3)-oleonolic acid from the roots of *Amaranthus spinosus* Linn⁵⁵ (Fig. 1).

Two new saponin from the roots of *Amaranthus spinosus* were reported. The structure of saponins I and II were assigned to be as -D- glucopyranosyl-(1-2)- -D-glucopyranosyl -(1-2)- -D-glucopyranosyl-(1-3)- -spinasterol and -D-glucopyranosyl-(1-4)- -D-glucopyranosyl-(1-3)- -spinasterol, respectively⁵⁶ (Fig. 1).

Toxicities: The aqueous extract of the bark of *A. spinosus* has a relatively low toxicity LD₅₀ value of 1450 mg/kg, b.w. *A. spinosus* was reportedly the culprit in cases of spontaneous poisoning of cattle in Brazil during a severe drought. Clinical signs appeared after 30 days in 11 out of 35 adult cows and 8 out of 20 yearling calves which were introduced into a 15 ha maize plantation heavily infested with *A. spinosus*. However, only one calf died within 3-7 days. The clinical signs were depression, anorexia, marked weight loss, foul smelling diarrhea occasionally tinged with blood, and subcutaneous edema. Sub acute cases showed distended abdomens, the animals were reluctant to stand and walked with difficulty. Sloughing of the hooves occurred in some animals. The main post-mortem findings in 5 animals were moderately pale and swollen kidneys, perirenal oedema and varying degrees of oedema in several tissues and cavities. In some cases petechiae and suffusions were associated with the subcutaneous oedema. The mucosa of the digestive system showed necrotic glossitis, oesophagitis and pharyngitis, abomasal

hemorrhages and button-like ulcerations in the large intestine. The contents of ileum, colon and rectum were blood stained. Hemorrhagic diathesis was apparent by the presence of intra-abdominal hematomas. Histologically, there was marked tubular nephrosis associated with epithelial regeneration and hyaline intra-tubular casts. The mucosal lesions consisted of large necrotic areas in the epithelium which extended into the lamina propria and were associated with inflammatory reaction with massive infiltrations of mastocytes. The omasal mucosa had selective necrosis of the basal layer cells. Renal failure was suggested as the primary lesion which triggered the other changes.

A. spinosus also caused an outbreak of acute poisoning in ewes in southern Brazil. The clinical signs were uremic halitosis, loss of ruminal motility, dispnoea and abortion. The kidneys showed pale red spots, white streaks extending from the cortex to medulla and congestion. Histologically, there was severe acute tubular nephrosis, dispersed foci of coagulative necrosis in the liver, areas of coagulative necrosis in the myocardium and acute incipient interstitial pneumonia and secondary bronchopneumonia. Hyperkalemia secondary to renal insufficiency was the underlying cause of myocardial coagulative necrosis observed in seven sheep^{57, 58, 59}.

CONCLUSION

The claims of the efficacy of the plant in its traditional usage, therefore, require validation and accurate documentation. The pharmacological aspects of *A. spinosus* have been studied extensively; however, this plant has not yet been developed as a drug. Ongoing and detailed research are required for the identification, cataloguing and documentation of this herb, which may provide scientific information for further exploration and necessary development of this herb for the pharmaceutical industry.

Conflict of interest statement: Authors declare no conflict of interest.

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