Review Article
Curr. Pers. MAPs, (2023); 6(2): 66-77

Current Perspectives on Medicinal and Aromatic Plants

An International Journal
ISSN: 2619-9645 | e-ISSN: 2667-5722

Anticancer activity of *Amaranthus spinosus* L. (Tanduliya): A Review

Gangeshwar Kumar TRIPATHİ [1*], Manisha HARIWAL[2]

[1] Department of Rasa Shastra & Bhaishajya Kalpana, Shivalik Ayurvedic Medical College & Hospital, Bijarawa, Bankat, Azamgarh-276125, Uttar Pradesh India. Email: gangeshwar007@gmail.com, ORCID ID: 0009000892154520
[2] Centre of Advanced Study in Botany, Institute of Science, Banaras Hindu University, Varanasi-221005, Uttar Pradesh India. Email: hariwalmani.1993@gmail.com, ORCID ID: 0000000272656979
*Corresponding author : Gangeshwar Kumar Tripathi, gangeshwar007@gmail.com

https://doi.org/10.38093/cupmap.1324101
Received: 07/07/2023
Accepted: 31/07/2023

Abstract

Cancer is served typical life-threatening disease with common risk factors. Developing therapeutic measures for cancers has aroused attention for a long time. However, the problems with conventional treatments are in challenge, including side effects, economic burdens, and patient compliance. It is essential to secure safe and efficient therapeutic methods to overcome these issues. The current review portrays the functions of *Amaranthus spinosus* L. (Tanduliya), and its phytoconstituents against several types of cancers, and explores the possibility of developing these agents as a promising candidate for cancer treatment. *A. spinosus* is an edible plant, belonging to the family Amaranthaceae widely found in Asian countries like India, Sri Lanka, Japan, and Indonesia, and used for dietary and medicinal values. Among the various beneficial pharmacological effects of *A. spinosus*, anticancer activity is presumably less studied. *A. spinosus* contains several secondary metabolites like glycosides, phenolic compounds, steroids, terpenoids, saponin, carotenoids, tannins, etc. that strongly assure their anticancer activity. The effects of *A. spinosus* and its various derived phytoconstituents have been shown to anticancer activity against breast, hepatocellular, prostate, and colorectal cancer in various preclinical models. The in-depth review of existing studies has shown the promising anticancer activity of *A. spinosus* extract, and its bioactive molecules by inhibiting the different stages of cancer, including initiation, promotion, and progression. Besides valuable nutraceuticals, *A. spinosus* has multi-targeted actions like antioxidant, anti-inflammatory, immunomodulatory activity and the nontoxic nature of *A. spinosus* probably plays a crucial role in killing cancerous cells.

Key Words: Amaranthaceae, Amaranthus, Anti-inflammatory, Antioxidant, Cancer, Immunomodulatory

1. Introduction

The efficacy of anticancer therapeutics is limited by agent-specific adverse effects. Apart from impacting prognosis, acute or persisting therapy-induced normal tissue damage substantially impacts the patient´s quality of life (Temel et al., 2010). Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body (Doll and Peto, 1981). Multiple treatments are utilized for the cure of cancer like surgery with chemotherapy and/or radiation therapy which produced various side effects like anemia, nausea, vomiting, weight loss, infection, diarrhea, edema, fatigue, etc. Estimated national expenditures for cancer care in the United States in 2018 were $150.8 billion (Siegel, 2022). In future years, costs are likely to increase as the population ages and more people have cancer. Costs are also likely to increase as new, and often more expensive, treatments are adopted as standards of care.

Natural products play an important role in cancer prevention and treatment. Phenolic compounds from medicinal herbs and dietary plants include phenolic acids, flavonoids, tannins, stilbenes, curcuminoids, coumarins, lignans, quinones, and others. Various bioactivities of phenolic compounds are responsible for their chemopreventive properties (e.g., antioxidant, anticarcinogenic, or antimutagenic and anti-inflammatory effects) and also contribute to their inducing apoptosis by arresting the cell cycle, regulating carcinogen metabolism and ontogenesis expression, inhibiting DNA binding and cell adhesion, migration, proliferation or differentiation, and blocking signaling pathways (Huang et al., 2009; Sharma 2021).

Amaranthus spinosus L. species are widely distributed and cultivated in Asia, Africa, America, Australia, and Europe. Leaves and succulent stems of Amaranthus are inexpensive and excellent sources of protein with essential amino acids lysine and methionine, carotenoids, ascorbic acid, dietary fiber, and essential minerals, such as calcium, magnesium, potassium, phosphorus, iron, zinc, copper, and manganese (Sarker et al., 2019). *A. spinosus* belongs to the family Amaranthaceae and is a tropical and subtropical annual and perennial herb with a purple or greenish stem that grows up to 100-130 cm tall and is extensively found in India, Africa, Southeast Asia, and the United States of America. Branches and grooves of the spiny herb are widely distributed on erect glabrous herbs. Oval or elliptic-lanceolate leaves have an attenuate base and measure 3-8 x 2-4 cm. The petiole is up to 4 cm long, and the apex is obtuse or subacute. Flowers are found in axillary, sessile clusters, or terminal panicled spikes. Ovate-lanceolate bracts and bracteoles are small (Figure 1) (Kirtikar and Basu, 2001). *A. spinosus* leaves are used in traditional African medicine for skin disorders, gastrointestinal disorders, and inflammatory and painful conditions. *A. spinosus* is used to treat children's ophthalmitis, convulsions including nutritional deficiencies, in many parts of Africa (Ibewuike et al., 1997). The leaves of *A. spinosus* are used by the tribal people of Kerala, Sikkim, and Manipur in India to treat piles, leprosy, diabetes, high blood pressure, and rheumatic pain in addition to gastric disorders (including indigestion and peptic ulcer). The plant's decoction is described as being used to stop miscarriages in ancient Indian texts. To induce bowel movements in children, boil leaves and roots are used (Basu et al., 2019; The Wealth of India, 2006; Kirtikar and Basu, 2001).

Just a few previous reviews offer detailed knowledge of the progress of this significant research area. One of the previous review articles presents a brief overview of the compilation and exploration of the therapeutic properties of *A. spinosus* with various pharmacological activities like antioxidant, antidiabetic, immunomodulatory, antiprotozoal, anti-malarial, hepatoprotective, antigenic, and allergenic activity, etc. (Jhade et al., 2011). There are no publications on the overview of *A. spinosus* extract and its phytoconstituents in cancer. In this review, we discuss the possible health advantages of *A. spinosus* as well as the method by which it inhibits cancer progression. This review, in detail, portrays the functions of *A. spinosus* and its bioactive constituents against several types of cancers and explores the possibility of developing these agents as anticancer pharmaceuticals.

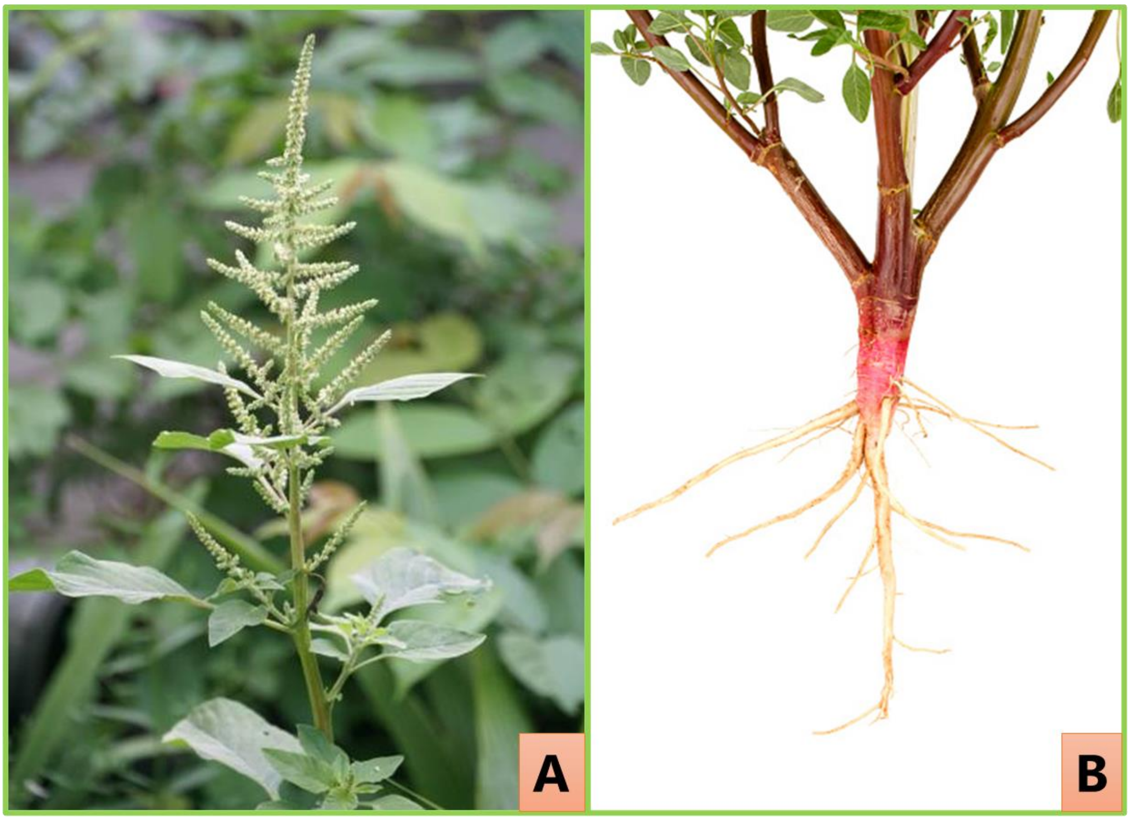

Figure 1. Photographs of *Amaranthus spinosus* L. (A) Natural habitat (B) Root.

Material and Methods

We thoroughly investigated Google Scholar and PubMed using relevant keywords like "*Amaranthus spinosus*," "Tanduliya," "Chaulai," "Prickly Amaranth", "Spiny amaranth", "Spiny pigweed", "Thorny amaranth," "Traditional use," "Ethnopharmacology," "Ethnobotany," "Phytoconstituents," "Chemical constituents," "Anticancer," "Anti-inflammatory," "Antioxidant", "Immunomodulatory" "cytotoxic" "Apoptosis" and "Toxicological study." Pertinent peer-reviewed research articles were retrieved from databases like Web of Science, Scopus, Embase, and MEDLINE. The articles were chosen for inclusion in the current review after all of the articles underwent authenticity, dependability, and relevance evaluations. ChemDraw Ultra 15.0 was used to illustrate the structures of all the phytoconstituents after they had all been verified using PubChem.

3. Results and Discussion

3.1. Nutraceutical properties

In a comparative study, the calcium content in dry leaves of *A. spinosus* was found to have a higher value (4500 mg/100 g dry weight) as compared to other species of Amaranthus (*A. tricolor*, *A. viridis*, and *A. blitum*) (Srivastava, 2011). As a leafy vegetable, weedy *A. spinosus* has remarkable protein, dietary fiber, carbohydrates, calcium, potassium, magnesium, phosphorus, sulphur, iron, manganese, copper, zinc, sodium, chlorophylls, β-cyanins, β-xanthin's, betalains, β-carotene, vitamin C, phenols, and flavonoids, etc. *A. spinosus* genotype WAS13 have high nutritional and antioxidant activity because it contains highest nutrients, pigments, vitamins, phenolics, flavonoids, and antioxidant (Figure 2, Table 1) (Sarker et al., 2019).

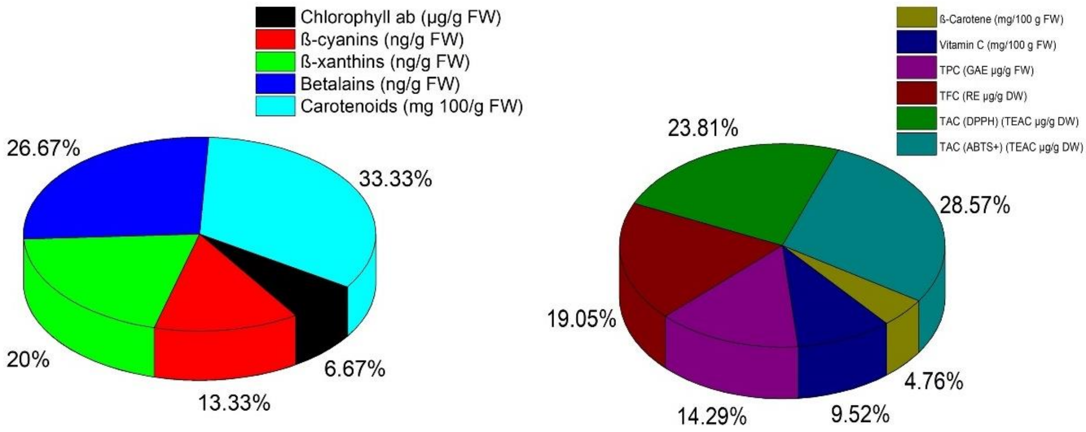

Figure 2. Nutraceutical value present in *A. spinosus*

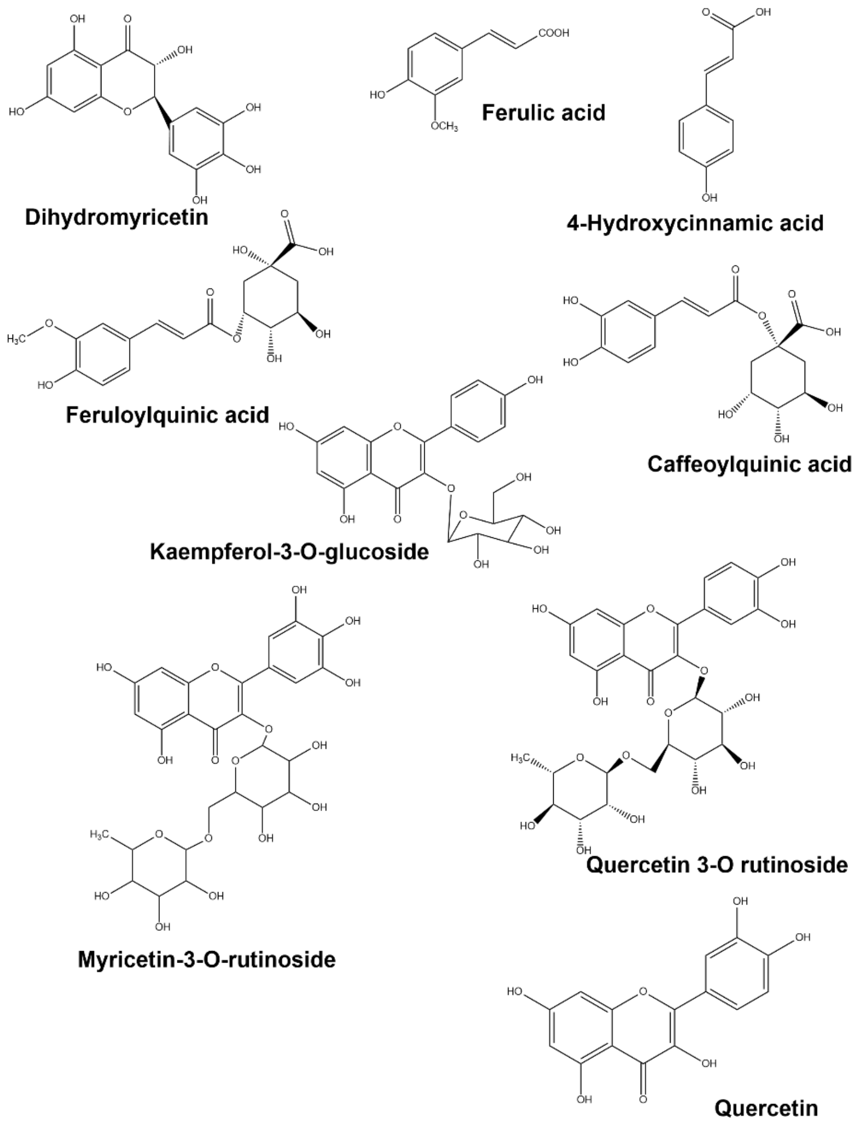

Figure 3. Chemical structures of major phytoconstituents isolated from *A. spinosus*

Table 1. Nutraceutical's composition of *A. spinosus*

Nutrients	Amount
Moisture (g/100 g)	84.47±1.34
Protein (g/100 g)	5.78±0.06
Fat (g/100 g)	0.63±0.02
Carbohydrates (g/100 g)	4.41±0.03
Energy (Kcal)	27.89±0.46
Ash (g/100 g)	5.18±0.04
Fiber (g/100 g FW)	11.24±0.72
K (mg/g FW)	6.48±0.04
Ca (mg/g FW)	2.44±0.05
Mg (mg/g FW)	3.02±0.05
P (mg/g FW)	0.68±0.005
S (mg/g FW)	1.25±0.04
Fe (μg/g FW)	15.34±0.09
Mn (μg g^{-1} FW)	10.23±0.06
Cu (μg/g FW)	2.04±0.07
Zn (μg/g FW)	10.99±0.13
Na (μg/g FW)	25.73±0.14
B (μg/g FW)	7.25±0.06
Mo (μg/g FW)	0.32±0.02

3.2. Phytochemistry

In an exclusive study, authors have reported alkaloids, glycosides, terpenes, and sugars as the major phytochemicals in the roots of *A. spinosus* (Jhade et al., 2011). Preliminary phytochemical screening of the 50% ethanolic leaves extract of *A. spinosus* showed the presence of carbohydrates, phenolic compounds, phytosterol, alkaloids, and flavonoids (Mishra et al., 2011). The hexane, chloroform, ethanolic and aqueous extract of aerial parts of *A. spinosus* showed the presence of saponin, carbohydrate, tannin, protein, glycoside, flavonoid, and phenol (Khanal et al., 2015). The total polyphenol content in the *A. spinosus* aerial methanolic extract was 194.21± 9.22 mg GAE/g extract, and the total flavonoid content in the extract was estimated to be 18.68± 3.67 mg QE/g. The LC-MS analysis showed the presence of various polyphenols in aerial methanolic *A. spinosus* extract like dihydromyricetin, ferulic acid, 4-hydroxycinnamic acid, feruloylquinic acid, kaempferol-3-O-glucoside, caffeoylquinic acid, myricetin-3-O-rutinoside, quercetin-3-O-rutinoside and quercetin (House et al., 2020) (Figure 3). Mondal et al. isolated (14E,18E,22E,26E)-methyl nonacosa-14,18,22,26 tetraenoate fatty acid from the whole plant of chloroform fraction of *A. spinosus* (Mondal et al., 2016).

3.3. Antioxidant activity

Free radicals are extremely reactive chemicals that can damage cells. They develop naturally in the body and are vital to many regular cellular processes (Diplock et al., 1998). Free radicals can damage DNA, proteins, and cell membranes when they are present in high concentrations, which is harmful to the body. Free radical damage to cells, particularly DNA damage, may lead to the formation of cancer and other illnesses (Valko et al., 2007). Chemicals known as antioxidants interact with and deactivate free radicals to stop them from harming. Most of the endogenous antioxidants that the body uses to combat free radicals are produced by the body. However, the body may obtain the remaining antioxidants it requires from exogenous sources, mainly the diet. Dietary antioxidants are a common name for these exogenous antioxidants and are abundant in fruits, vegetables, and grains. Vitamins A, C, and E (α-tocopherol) and β-carotene are a few examples of dietary antioxidants (Davis et al., 2012). Increased exogenous antioxidant levels inhibit the kinds of damage caused by free radicals that have been linked to the development of cancer *in vivo* studies.

The aerial methanolic extract of *A. spinosus* showed antioxidant activity by ferric reducing antioxidant power activity, scavenging 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical, and hydrogen peroxide (H_2O_2) activity (IC_{50}=24.38±1.44 mg/mL, 63.94± 3.72, and 28.55± 1.87 respectively) (House et al., 2020). Similarly, ethyl acetate leaves extract of *A. spinosus* possesses good radical scavenging activity (IC_{50} =53.68 μg/ml) (Bulbul et al., 2011). Leaves extracts of *A. spinosus* with and without vitamin C reverse the increased malondialdehyde (MDA), reduced glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD) levels in rats (Faponle et al., 2015).

The antioxidant capacity of *A. spinosus* extracts significantly reduced the amount of oxidative free radicals in rats and aided in rapid wound healing (Paswan et al., 2020). The methanolic seed extract of *A. spinosus* demonstrated concentration-dependent scavenging activity against DPPH and H_2O_2. Methanol seed extract had the highest radical scavenging activity value at 450 mg/mL (84.13%), but it was less effective than vitamin C (94.21%) (Rjeibi et al., 2016).

In addition, *A. spinosus* methanolic leaves extract showed antioxidant activity against DPPH radicals, nitric oxide radicals, and butylated hydroxyl anisole (Kumar et al., 2010). *A. spinosus* root extracts scavenged DPPH radicals in a dose-dependent manner (Barku et al., 2013). The oral administration of *A. spinosus* increases the hepatic antioxidants GSH, SOD, CAT, and glutathione peroxidase (GPx) levels (Prince et al. 2021).

The bioactive antioxidants potential of the major categories of phenolic acids and flavonoids derived from chalcone and cinnamate-dependent pathways of phenylpropanoid metabolism showed antioxidant properties of different plant parts of *A. spinosus* L. (Kar and Bhattacharjee, 2022).

3.4. Analgesic and Anti-inflammatory activity

Inflammation-generated oxidative stress and damage to macromolecules are prominent physiological features of all chronic diseases. Angiogenesis, tissue remodeling, stimulation of neoplastic transformation, and metastasis are all known to be induced by chronic inflammation and oxidative stress, in addition to being associated with tumor cell proliferation and growth (He et al., 2017; Grimm et al.,2013; De Oliveira et al., 2017).

When such normal tissue homeostasis is disrupted, cellular proliferation, as well as programmed cell death, becomes imbalanced, which leads to the development of a malignant state (apoptosis). It is known that activating the caspase cascade through the death receptors pathway or the mitochondrial death signaling, whose components have either been proapoptotic (Bax, Bad) or antiapoptotic (Bcl-2, Bcl-XL), can cause apoptosis (Huang and He, 2011; Yang et al., 2009; Laulier and Lopez, 2012). In order to combat cancer, one method used in the development of anti-cancer drugs is to cause programmed cell death in cancer cells (Ginwala et al., 2009). In particular, traditional uses of plants have drawn attention as plant-based foods, as their regular consumption may be linked to a lower cancer incidence (Aravindaram et al., 2010; Cerella et al., 2010; Ravishankar et al., 2013).

The ethyl acetate extract of *A. spinosus* leaves managed to prevent the compound 48/80 secretagogue's ability to induce systemic anaphylactic shock in an animal model. It inhibited the release of histamine, mast cell degranulation, and membrane disruption, suggesting a potential role in the avoidance and treatment of anaphylactic reactions (Patil et al., 2012). The whole plant of methanolic extract of *A. spinosus* had significant central and peripheral anti-nociceptive potency as well as anti-inflammatory activity (Baral, 2010; Olajide et al., 2004). Similarly, the extracts reduced inflammation-related pain, improved hot plate reaction times, and significantly increased tail immersion test results, all of which support further research into the clinical application of the extracts in conditions related to pain (Taiab et al., 2011). The methanolic aerial extract of *A. spinosus* inhibited lipoxygenase and scavenged nitric oxide (House et al., 2020). Leaves extracts of *A. spinosus* have demonstrated significant membrane stability, which improves anti-inflammatory responses (Rajasekaran et al., 2014). Research on castor oil-induced diarrhea and gastric mucosal integrity suggests that this plant extract's activity is likely mediated by the inhibition of prostaglandin biosynthesis (Olumayokun et al., 2004). A significant dose-dependent peripheral analgesic activity was demonstrated by *A. spinosus* methanolic extract. It significantly lessened the abdominal contractions brought on by acetic acid (Senthil Kumar et al., 2010). Methanolic extract of *A. spinosus* whole part exhibited significant anti-nociceptive and anti-inflammatory action in a mouse model. The extracts improved reaction times on a hot plate, decreased pain brought on by inflammation, and displayed a significant amount of activity in a tail immersion test (Md et al., 2011). The alcoholic extract and whole plant of *A. spinosus* possess both anti-inflammatory and analgesic activity in the carrageenan-induced paw edema model (Bharti et al., 2022; Jamaluddin et al., 2011).

3.5. Immunomodulatory activity

Previous studies have shown that tumor-bearing animals and cancer patients can both exhibit immunosuppressive effects, indicating that the immune system plays a significant role in immune surveillance against cancer cells (Chen et al., 2012). Therefore, it has been recognized that increasing the host's immune response may be a way to prevent tumor growth without endangering the host (Jiao et al., 2008). The immune system serves as the body's main line of defense against cancer because it can identify and eliminate developing tumors. Female BALB/c mouse spleen cells were significantly stimulated to proliferate by *A. spinosus* water extract. Studies conducted in vitro revealed that *A. spinosus* aqueous extracts had immunostimulant activity by directly promoting T cell proliferation and subsequent B lymphocyte activation in a dose-dependent manner (Lin et al., 2005). The immune-modulating effects of *A. spinosus* water extract on naturally occurring and dexamethasone (DEX)-induced apoptosis in murine primary splenocytes. The results demonstrated that the alcoholic extract prevented splenocyte apoptosis both naturally occurring and induced by DEX (Linn et al., 2008). The humoral and cell-mediated immune responses were both significantly increased by the alcoholic extract, but they were both significantly decreased by the petroleum ether extract (Tatiya et al., 2007).

3.6. Cytotoxicity and Anticancer activity

Despite advancements in technology and medicine over time, cancer remains a global concern (Seyed et al., 2016). It is the second major cause of death worldwide and accounts for thousands of fatalities annually. Despite the fact that the main reasons for chemotherapy failure continue to be target mutation, toxicity, and resistance, chemotherapy is still a vital treatment option for various cancers (Tiwari et al., 2016). Therefore, more study is needed to identify and create novel anti-cancer drugs that can resolve these chemotherapeutic failure causes.

In this context, the MTT assay demonstrated that the fatty acid significantly and dose-dependently inhibited cell proliferation of HepG2 cells (IC_{50}=25.52 μmol/L). This antiproliferative outcome was superior to linoleic acid (IC_{50} =38.65 μmol/L), but comparable to that of the standard drug, doxorubicin (IC_{50}= 24.68 μmol/L). The

G2/M transition was arrested as a result of the novel fatty acid induction of apoptosis, which was mediated by the downregulation of cyclin B1, the upregulation of Bax, and the downregulation of B-cell lymphoma 2 (Bcl-2) (Mondal et al., 2006). The most common type of liver cancer, hepatocellular carcinoma, accounts for the majority of cancer deaths worldwide (Parkin et al., 2002). The fatty acid (14E,18E,22E,26E)-methyl nonacosa-14,18,22,26 tetraenoate) isolated from *A. spinosus* showed significant antiproliferative activity that was mediated by the induction of apoptosis in HepG2 cells. The second most frequent form of cancer in men is prostate cancer. Scientists are working hard to identify potential sources in the commonly consumed foods that prevent the growth of prostate cancer. Ethanolic extract of *A. spinosus* was tested for its cytotoxic and anticancer properties using lymph node carcinoma of the prostate (LNCaP) cell lines and the brine shrimp lethality assay. The findings indicated the cytotoxic activity of *A. spinosus* against Artemia salina (LC_{50}= 920 µg/mL). However, at the 400 µg/mL tested concentration of *A. spinosus* failed to inhibit cell proliferation (Octaviani et al., 2013).

Apoptosis is a physiological process that is characterized by DNA fragmentation, membrane blebbing, chromatin condensation, and cell shrinkage (Sharma et al. 2007). Apoptosis is a crucial regulator of tissue homeostasis, and an imbalance between cell death and proliferation can lead to the development of tumors (Fulda and Debatin 2003). The water extract of *A. spinosus* exhibited apoptosis induction and cytotoxic activities in *Allium cepa* L. root meristematic cells and human erythrocytes (Prajitha and Thoppil, 2013). The standard crude extract showed cytotoxic activity against HeLa cancer cell lines. It was found that crude extract showed a significant effect on the estimated cell counts of apoptotic death of HeLa and HeLa-R cells (Sharma et al., 2020). The hydroalcoholic extract of *A. spinosus* roots extract showed a non-cytotoxic effect (LC_{50} = 1.178 mg/mL). Almost twelve percent of those with confirmed cases of breast cancer later develop metastatic illness, or breast cancer which has moved from the breast to other regions of the body, despite advancements in detection of breast cancer, diagnosis, and treatment (Peart, 2017). Methanolic aerial extract of *A. spinosus* showed cytotoxicity (IC_{50}=64.90± 3.91 mg/mL) against the breast cancer cell line (MCF-7). While the aerial methanolic extract displayed greater antiproliferative potential (IC_{50}=82.11± 7.02 mg/mL) in triple-negative breast cancer cell lines (MDA-MB-231) (House et al., 2020). In breast, colorectal (HT-29), liver (HEPG2), and normal cell lines, the methanol extracts of *A. spinosus* leaves significantly inhibited the growth of tumors. The amount of tumor growth and the number of viable cells is significantly reduced by the methanol leaves extract (Rajasekaran et al., 2014; Joshua et al., 2010). *A. spinosus* leaf methanol extract exhibited chemo-protective action in rats by reducing oxidative stress and inflammation in response to doxorubicin-induced multi-organ damage (Akinloye et al., 2023).

3.7. Toxicity studies

Acute oral toxicity testing with *A. spinosus* leaves extract at the highest dose (2000 mg/kg) did not reveal any animal lethality or behavioral changes (Kumar et al., 2010). A single oral dose of the extract (5000 mg/kg/b.w.) did not result in any fatalities or toxicological symptoms in a gross necropsy. Repeated doses of the extract (500 and 1000 mg/kg, b.w.) did not result in any deaths or notable changes in body weight or the relative weight of the vital organs in sub-chronic oral toxicity. Additionally, there was no discernible change in the hematological, biochemical, or histopathological parameters. Blood glucose levels were found to reduce, but this did not result in organ damage, demonstrating the plant's safety (Atchou et al., 2021).

4. Limitations and Future Perspectives

The nutrient-rich food *A. spinosus* may offer enormous opportunities for the community who suffer from nutrient deficiency to overcome hidden hunger and achieve nutritional sufficiency. The different pharmacological properties of this plant could be attributed to its bioactive compounds and nutritional value. *A. spinosus* pharmacological activity was greatly aided by the antioxidant activity of its pigments, β-carotene, vitamin C, phenolics, and flavonoids. The current study indicates that *A. spinosus* has undergone less pharmacological research, but it is a great source of phenolics, flavonoids, and antioxidants that have a wide range of pharmacological and therapeutic effects.
Therefore, more research on the bioactive components of *A. spinosus* is required to assess its therapeutic efficacy in animal models and clinical studies to verify its anticancer activities at the cellular and molecular level, and also ensure its status as a functional food.

5. Conclusion

A. spinosus has been used for its dietary and therapeutic benefits. It is a perennial herb used to treat and prevent a number of ailments including cancer, inflammation, pain. *A. spinosus* bioactive substances demonstrated significant anticarcinogenic effects through a number of mechanisms, including cancer cell apoptosis, cell cycle arrest, and activation of the angiogenic cascade. Bioactive phytochemicals from *A. spinosus* inhibit cell growth, apoptosis evasion, adhesion, invasion, migration, and metastasis in a diverse array of preclinical models of breast, hepatocellular, prostate, and colorectal cancer.

Acknowledgments

The authors express their gratitude to Dr. Vineet Sharma for his valuable contributions to content research, writing support, technical editing, and proofreading before submission.

Author Contribution

GKT conceptualized and designed the study, while the first draft of the manuscript was collaboratively written by GKT and MH. MH provided critical revisions to the work. All authors thoroughly reviewed and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no conflict of interest.

References

1. Abir, M. H., & Ahmad, M. (2021). Phytochemical, Nutritional and Pharmacological Potentialities of Amaranthus spinosus Linn.: A review. Archives of Ecotoxicology, 3(2), 49-59. https://doi.org/10.36547/ae.2021.3.2.49-59
2. Akinloye, O. A., Sulaimon, L. A., Ogunbiyi, O. E., Odubiyi, A. E., Adewale, A. A., Toriola, M. A., & Boyenle, I. D. (2023). Amaranthus spinosus (Spiny Pigweed) methanol leaf extract alleviates oxidative and inflammation induced by doxorubicin in male sprague dawley rats. Advances in Traditional Medicine, 1-18. https://doi.org/10.1007/s13596-022-00677-9
3. Aravindaram, K., & Yang, N. S. (2010). Anti-inflammatory plant natural products for cancer therapy. Planta Medica, 76(11), 1103-1117. DOI: 10.1055/s-0030-1249859
4. Atchou, K., Lawson-Evi, P., Diallo, A., & Eklu-Gadegbeku, K. (2021). Toxicological evaluation of the dried hydroethanolic extract of Amaranthus spinosus L. roots in Artemia salina larvae and Sprague Dawley rats. Clinical Phytoscience, 7, 1-9. https://doi.org/10.1186/s40816-021-00304-1
5. Baral, M. A. N. I. K., Chakraborty, S., & Chakraborty, P. (2010). Evaluation of anthelmintic and anti-inflammatory activity of Amaranthus spinosus Linn. International Journal of Current Pharmaceutical Research, 2(4), 44-47.
6. Barku, V. Y. A., Opoku-Boahen, Y., Owusu-Ansah, E., & Mensah, E. F. (2013). Antioxidant activity and the estimation of total phenolic and flavonoid contents of the root extract of Amaranthus spinosus. Asian Journal of Plant Science and Research, 3(1), 69-74.
7. Bharti, R. K. S., Kumar, S., & Kumar, S. (2022) Pharmacological evaluation of analgesic, anti-inflammatory and anti-pyretic activities of amaranthus spinosus stem.Volume 21, pp. 1048-1059
8. Bulbul, I. J., Laizuman, N., Ripa, F. A., & Obaydul, H. (2011). Antibacterial, cytotoxic and

antioxidant activity of chloroform, n-hexane and ethyl acetate extract of plant Amaranthus spinosus. International Journal of PharmTech Research, 3(3), 1675-1680.
9. Cerella, C., Sobolewski, C., Dicato, M., & Diederich, M. (2010). Targeting COX-2 expression by natural compounds: a promising alternative strategy to synthetic COX-2 inhibitors for cancer chemoprevention and therapy. Biochemical Pharmacology, 80(12), 1801-1815. https://doi.org/10.1016/j.bcp.2010.06.050
10. Davis, C. D., Tsuji, P. A., & Milner, J. A. (2012). Selenoproteins and cancer prevention. Annual Review of Nutrition, 32, 73-95. https://doi.org/10.1146/annurev-nutr-071811-150740
11. de Oliveira, G. A., Cheng, R. Y., Ridnour, L. A., Basudhar, D., Somasundaram, V., McVicar, D. W., ... & Wink, D. A. (2017). Inducible nitric oxide synthase in the carcinogenesis of gastrointestinal cancers. Antioxidants & Redox Signaling, 26(18), 1059-1077. https://doi.org/10.1089/ars.2016.6850
12. Diplock, A. T., Charuleux, J. L., Crozier-Willi, G., Kok, F. J., Rice-Evans, C., Roberfroid, M., ... & Vina-Ribes, J. (1998). Functional food science and defence against reactive oxidative species. British Journal of Nutrition, 80(S1), S77-S112. https://doi.org/10.1079/BJN19980106
13. Doll, R., & Peto, R. (1981). The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. Journal of the National Cancer Institute, 66(6), 1192-1308.
14. Faponle, A. S., Atunnise, A., Adegbesan, B. O., Ogunlabi, O. O., Odufuwa, K. T., & Ajani, E. O. (2015). Separate and co-administration of Amaranthus spinosus and vitamin C modulates cardiovascular disease risk in high fat diet-fed experimental rats. Journal of Pharmacognosy and Phytotherapy, 7(3), 27-34. https://doi.org/10.5897/JPP2014.0340
15. Fulda, S., & Debatin, K. M. (2003). Apoptosis pathways in neuroblastoma therapy. Cancer Letters, 197(1-2), 131-135. https://doi.org/10.1016/S0304-3835(03)00091-0
16. Ginwala, R., Bhavsar, R., Chigbu, D. G. I., Jain, P., & Khan, Z. K. (2019). Potential role of flavonoids in treating chronic inflammatory diseases with a special focus on the anti-inflammatory activity of apigenin. Antioxidants, 8(2), 35. https://doi.org/10.3390/antiox8020035
17. Grimm, E. A., Sikora, A. G., & Ekmekcioglu, S. (2013). Molecular pathways: inflammation-associated nitric-oxide production as a cancer-supporting redox mechanism and a potential therapeutic target. Clinical Cancer Research, 19(20), 5557-5563. https://doi.org/10.1158/1078-0432.CCR-12-1554
18. He, L., He, T., Farrar, S., Ji, L., Liu, T., & Ma, X. (2017). Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species. Cellular Physiology and Biochemistry, 44(2), 532-553. https://doi.org/10.1159/000485089
19. House, N. C., Puthenparampil, D., Malayil, D., & Narayanankutty, A. (2020). Variation in the polyphenol composition, antioxidant, and anticancer activity among different Amaranthus species. South African Journal of Botany, 135, 408-412. https://doi.org/10.1016/j.sajb.2020.09.026
20. Huang, S., & He, X. (2011). The role of microRNAs in liver cancer progression. British Journal of Cancer, 104(2), 235-240.
21. Huang, W. Y., Cai, Y. Z., & Zhang, Y. (2009). Natural phenolic compounds from medicinal herbs and dietary plants: potential use for cancer prevention. Nutrition and Cancer, 62(1), 1-20. https://doi.org/10.1080/01635580903191585
22. Ibewuike, J., Ogundaini, A. O., Bohlin, L., & Ogungbamila, F. O. (1997). Anti-inflammatory activity of selected Nigerian medicinal plants. Nigerian Journal of Natural Products and Medicine, 1, 10-14. https://doi.org/10.4314/njnpm.v1i1.11790
23. Jhade, D., Ahirwar, D., Jain, R., Sharma, N. K., & Gupta, S. (2011). Pharmacognostic standardization, physico-and phytochemical evaluation of Amaranthus spinosus Linn. root. Journal of Young Pharmacists, 3(3), 221-225. https://doi.org/10.4103/0975-1483.83770
24. Joshua, L. S., Pal, V. C., Kumar, K. S., Sahu, R. K., & Roy, A. (2010). Antitumor activity of the ethanol extract of Amaranthus spinosus leaves against EAC bearing swiss albino mice. Der Pharmacia Lettre, 2(2), 10-15.
25. Kar, A., & Bhattacharjee, S. (2022). Bioactive polyphenolic compounds, water-soluble vitamins, in vitro anti-inflammatory, anti-diabetic and free radical scavenging properties of underutilized alternate crop Amaranthus spinosus L. from Gangetic plain of West Bengal. Food Bioscience, *50*, 102072. https://doi.org/10.1016/j.fbio.2022.102072
26. Khanal, D. P., Raut, B., & Dangol, K. S. (2015). Phytochemical screening, pharmacognostic evaluation and biological activity of Amaranthus spinosus L. Journal of Manmohan Memorial Institute of Health Sciences, 1(4), 29-34.
27. Kirtikar, K. R., Basu, B. D. (2001) Indian Medicinal Plants, (2nd ed), vol. I, Oriental Enterprises, New Connaught Place, Dehradun, Uttranchal, India, 2832-2836.
28. Kumar, B. S. A., Lakshman, K., Jayaveera, K. N., Shekar, D. S., Kumar, A. A., & Manoj, B. (2010). Antioxidant and antipyretic properties of methanolic extract of Amaranthus spinosus

leaves. Asian Pacific Journal of Tropical Medicine, 3(9), 702-706. https://doi.org/10.1016/S1995-7645(10)60169-1
29. Laulier, C., & Lopez, B. S. (2012). The secret life of Bcl-2: apoptosis-independent inhibition of DNA repair by Bcl-2 family members. Mutation Research/Reviews in Mutation Research, 751(2), 247-257. https://doi.org/10.1016/j.mrrev.2012.05.002
30. Lin, B. F., Chiang, B. L., & Lin, J. Y. (2005). Amaranthus spinosus water extract directly stimulates proliferation of B lymphocytes in vitro. International Immunopharmacology, 5(4), 711-722. https://doi.org/10.1016/j.intimp.2004.12.001
31. Lin, J. Y., Li, C. Y., & Lin, B. F. (2008). Amaranthus spinosus L. inhibits spontaneous and dexamethasone-induced apoptosis in murine primary splenocytes. Journal of Food and Drug Analysis, 16(4), 10. https://doi.org/10.38212/2224-6614.2345
32. Taiab M. J. A., Q. Nazmul, A.M. Asif, H.M. Amran, K.M. Shams-Ud-Doha, S.A. Apurba (2011). Analgesic activity of extracts of the whole plant of Amaranthus spinosus linn. International Journal of Drug Development and Research, 3(4), 189-193.
33. Jamaluddin, A. T. M., Qais, N., Ali, M. A., Howlader, M. A., Shams-Ud-Doha, K. M., & Sarker, A. A. (2011). Analgesic activity of extracts of whole plants of Amaranthus spinosus Linn. International Journal of Drug Development and Research, 3(4), 189-193.
34. Md JA, Nazmul Q, Asif AM, Amran HM, Shams-Ud-Doha KM, Apurba SA. Analgesic activity of extracts of the whole plant of Amaranthus spinosus linn. International Journal of Drug Development and Research, 3(4), 189-193.
35. Mishra, S. B., Verma, A., Mukerjee, A., & Vijayakumar, M. (2011). Pharmacognostic Standardization and Phytochemical screening of Leaves of Amaranthus spinosus L. Pharmacognosy Journal, 3(26), 34-38. https://doi.org/10.5530/pj.2011.26.6
36. Mondal, A., Guria, T., Maity, T. K., & Bishayee, A. (2016). A novel tetraenoic fatty acid isolated from Amaranthus spinosus inhibits proliferation and induces apoptosis of human liver cancer cells. International Journal of Molecular Sciences, 17(10), 1604. https://doi.org/10.3390/ijms17101604
37. Octaviani, C. D., Lusiana, M., Zuhrotun, A., Diantini, A., Subarnas, A., & Abdulah, R. (2013). Anticancer properties of daily-consumed vegetables Amaranthus spinosus, Ipomoea aquatica, Apium graveolens, and Manihot utilisima to LNCaP prostate cancer cell lines. Journal of Natural Pharmaceuticals, 4, 67-70.
38. Olajide, O. A., Ogunleye, B. R., & Erinle, T. O. (2004). Anti-inflammatory properties of Amaranthus spinosus leaf extract. Pharmaceutical Biology, 42(7), 521-525. https://doi.org/10.3109/13880200490893285
39. Parkin, D. M., Bray, F., Ferlay, J., & Pisani, P. (2005). Global cancer statistics, 2002. CA: A Cancer Journal for Clinicians, 55(2), 74-108. https://doi.org/10.3322/canjclin.55.2.74
40. Paswan, S. K., Srivastava, S., & Rao, C. V. (2020). Wound healing, antimicrobial and antioxidant efficacy of Amaranthus spinosus ethanolic extract on rats. Biocatalysis and Agricultural Biotechnology, 26, 101624. https://doi.org/10.1016/j.bcab.2020.101624
41. Patil, S. D., Patel, M. R., Patel, S. R., & Surana, S. J. (2012). Amaranthus spinosus Linn. inhibits mast cell-mediated anaphylactic reactions. Journal of Immunotoxicology, 9(1), 77-84. https://doi.org/10.3109/1547691X.2011.631609
42. Peart, O. (2017). Metastatic breast cancer. Radiologic Technology, 88(5), 519M- 539M.
43. Prajitha, V., & Thoppil, J. E. (2017). Cytotoxic and apoptotic activities of extract of Amaranthus spinosus L. in Allium cepa and human erythrocytes. Cytotechnology, 69, 123-133. 133 DOI 10.1007/s10616-016-0044-5
44. Rajasekaran, S., Dinesh, M. G., Kansrajh, C., & Baig, F. H. A. (2014). Amaranthus spinosus leaf extracts and its anti-inflamatory effects on cancer. Indian Journal of Research in Pharmacy and Biotechnology, 2(1), 1058.
45. Ravishankar, D., Rajora, A. K., Greco, F., & Osborn, H. M. (2013). Flavonoids as prospective compounds for anti-cancer therapy. The International Journal of Biochemistry & Cell Biology, 45(12), 2821-2831. https://doi.org/10.1016/j.biocel.2013.10.004
46. Rjeibi, I., Saad, A. B., & Hfaiedh, N. (2016). Oxidative damage and hepatotoxicity associated with deltamethrin in rats: The protective effects of Amaranthus spinosus seed extract. Biomedicine & Pharmacotherapy, 84, 853-860. https://doi.org/10.1016/j.biopha.2016.10.010
47. Sarker, U., & Oba, S. (2019). Nutraceuticals, antioxidant pigments, and phytochemicals in the leaves of Amaranthus spinosus and Amaranthus viridis weedy species. Scientific Reports, 9(1), 20413. https://doi.org/10.1038/s41598-019-50977-5
48. Senthil, M. K., Venugopalan, R., Shanmugam, S. K., & Perumal, P. (2010). Evaluation of analgesic activity of Amaranthus spinosus Linn leaves in mice. Journal of Pharmacy Research, 3(12), 3088-3089.
49. Sharma, I., Kasture, P., Umrao, A., Rao, J., Rao, G. (2020). A study to determine the anti-cancer and pro-apoptotic properties of Amaranthus spinosus

Linn. Extract, AS20. Journal of Emerging Investigators, 3, 1-6.
50. Sharma, M., Sharma, P. D., Bansal, M. P., & Singh, J. (2007). Lantadene A-induced apoptosis in human leukemia HL-60 cells. Indian Journal of Pharmacology, 39(3), 140. DOI: 10.4103/0253-7613.33433
51. Sharma, V., Firdaus, Z., Rai, H., Nayak, P. K., Singh, T. D., & Gautam, D. N. S. (2021). Consumption of Ashtanga Ghrita (clarified cow butter added with herb extracts) improves cognitive dysfunction induced by scopolamine in rats via regulation of acetylcholinesterase activity and oxidative stress. Drug Metabolism and Personalized Therapy, 36(4), 337-350. https://doi.org/10.1515/dmpt-2021-0108
52. Siegel RL, Miller KD, Hannah EFBS, Jemal A. Cancer statistics, 2022. CA: a cancer journal for clinicians. 2022;72(1):7-33. https://doi.org/10.3322/caac.21708
53. Srivastava, R. (2011). Nutritional Quality of Some Cultivated and Wild Species of Amaranthus L. International Journal of Pharmaceutical Sciences and Research, 2(12), 3152.
54. Tatiya, A. U., Surana, S. J., Khope, S. D., Gokhale, S. B., & Sutar, M. P. (2007). Phytochemical investigation and Immunomodulator activity of Amaranthus spinosus Linn. Indian Journal of Pharmaceutical Education and Research, 41(4), 337-341.
55. Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T., Mazur, M., & Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. The International Journal of Biochemistry & Cell Biology, 39(1), 44-84. doi:10.1016/j.biocel.2006.07.001
56. Yang, B. F., Lu, Y. J., & Wang, Z. G. (2009). MicroRNAs and apoptosis: implications in the molecular therapy of human disease. Clinical and Experimental Pharmacology and Physiology, 36(10),951-960. https://doi.org/10.1111/j.1440-1681.2009.05245.x