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# Exploring nature's potential: A traditional and phytopharmacological review of Amaranthaceae family targeting JAK–STAT signalling pathway

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## Abstract

The Amaranthaceae family, encompassing more than 175 genera and over 2000 species, represents one of the most diverse groups of angiosperms with profound ethnomedicinal, nutritional, pharmacological and ecological significance worldwide. Medicinally important species, including *Amaranthus viridis* L., *Achyranthes bidentata* Blume, *Alternanthera sessilis* (L.) DC. and *Celosia argentea* L., have been extensively utilised in Ayurveda, Siddha, traditional Chinese medicine (TCM) and numerous indigenous healthcare systems for the management of inflammatory disorders, diabetes mellitus, gastrointestinal diseases, reproductive ailments and wound healing. This critical review comprehensively elucidates the ethnobotanical relevance, phytochemical diversity, nutritional attributes and pharmacological potential of Amaranthaceae species, with particular emphasis on their modulation of the Janus kinase–signal transducer and activator of transcription (JAK–STAT) signalling pathway, a pivotal regulator of inflammation, immunity, cellular proliferation and apoptosis. Phytochemical investigations have revealed an extensive repertoire of bioactive metabolites, including flavonoids, alkaloids, saponins, terpenoids, phenolic acids and betalains, which collectively exhibit potent antioxidant, anti-inflammatory, antidiabetic, hepatoprotective, antimicrobial and immunomodulatory activities. Emerging experimental evidence suggests that several Amaranthaceae-derived phytoconstituents effectively regulate aberrant JAK–STAT signalling, thereby highlighting their potential as promising natural alternatives or complementary adjuncts to synthetic JAK inhibitors for the management of chronic inflammatory and immune-mediated disorders. Beyond their therapeutic applications, numerous species serve as nutrient-dense leafy vegetables and pseudocereals enriched with high-quality proteins, essential amino acids, dietary fibre, vitamins and minerals, contributing substantially to global food and nutritional security. Nevertheless, significant challenges persist regarding phytochemical standardisation, optimisation of bioavailability, comprehensive toxicological assessment, pharmacokinetic characterisation and rigorous clinical validation. Future multidisciplinary investigations integrating advanced phytochemical profiling, molecular pharmacology, systems biology, nanotechnology and well-designed clinical trials are indispensable to accelerate the translational development of Amaranthaceae-derived nutraceuticals and phytopharmaceuticals for inflammatory and immunological diseases.

**Keywords:** Amaranthaceae, ethnomedicine; JAK–STAT pathway; nutraceuticals; phytochemicals

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## Introduction

The *Amaranthaceae* family represents one of the most taxonomically diverse and ecologically resilient lineages of angiosperms, comprising more than 175 genera and over 2000 species distributed predominantly throughout tropical and subtropical regions worldwide. Renowned for their exceptional nutritional, ornamental, ethnomedicinal and pharmacological significance, *Amaranthaceae* species have long occupied a prominent position in traditional healthcare systems and have increasingly attracted scientific interest as valuable reservoirs of bioactive phytoconstituents. Their remarkable adaptability to extreme environmental conditions, particularly drought, salinity and nutrient-deficient soils, reflects profound evolutionary plasticity, underscoring their immense potential for sustainable agriculture, climate-resilient crop development, nutraceutical innovation and phytopharmaceutical applications (1). Conventionally, numerous *Amaranthaceae* species, including *Amaranthus viridis* L., *Amaranthus tricolor* L., *Achyranthes aspera* L., *Achyranthes bidentata* Blume, *Alternanthera sessilis* (L.) DC and *Celosia argentea* L, have been extensively employed in Ayurveda, Siddha, traditional Chinese medicine and diverse indigenous healthcare systems for the management of inflammatory disorders, diabetes mellitus, gastrointestinal ailments, wound healing, menstrual irregularities, respiratory diseases and dermatological conditions. Their extraordinary therapeutic versatility is attributed to a rich repertoire of flavonoids,

alkaloids, saponins, phenolic acids, terpenoids, steroids and glycosides, exhibiting potent antioxidants, anti-inflammatory, antidiabetic, hepatoprotective, antimicrobial, antinociceptive and immunomodulatory activities. Moreover, their exceptional nutritional profile establishes these species as promising nutraceuticals, contributing substantially to global food security and integrative healthcare (2). Over the past several decades, Amaranthaceae has garnered substantial scientific attention owing to the systematic isolation, structural elucidation and pharmacological characterisation of its diverse bioactive phytoconstituents, accompanied by extensive investigations into their molecular mechanisms of action and therapeutic potential. Contemporary experimental and toxicological studies have increasingly validated many of the traditional ethnomedicinal claims associated with these species. Nevertheless, despite their rich ethnobotanical heritage and remarkable phytochemical diversity, a considerable proportion of Amaranthaceae taxa remain pharmacologically underexplored and therapeutically under utilised. This translational disparity between traditional medicinal knowledge and rigorous pharmaceutical validation underscores the urgent necessity for comprehensive phytochemical standardisation, mechanistic investigations, toxicological profiling and well-designed clinical studies (3). The lack of standardisation of the extraction process, the lack of clinical trials and the inadequate knowledge about the bioavailability and toxicity profiles also do not allow the full therapeutic exploitation of these plants (4). In this respect, the family *Amaranthaceae* should be reconsidered in detail to consolidate the existing sources of information about their botanical properties, ethnomedicinal use, phytochemical composition and pharmacological prospectus.

Furthermore, the family is also considered as the possible source of phytochemicals that might interfere with the Janus kinase–signal transducer and activator of transcription (JAK-STAT) signalling pathway vital in the control of immune responses, inflammatory agents and cell multiplication. Disruption of the JAK-STAT pathway has been implicated in a wide range of chronic diseases and synthetic JAK inhibitors have been found to be effective; however, their long-term use has been impeded by their side effects (5, 6). This reiterates the importance of safer and natural substitutes. Different representatives of the family Amaranthaceae exhibit activities that can regulate this signalling pathway, providing the basis for the future development of these natural products as additions or alternatives to existing treatments (7). Through the systematic literature review of the convergence of traditional and modern pharmacological studies, the proposed review will serve to emphasise the therapeutic value of Amaranthaceae species to promote future studies that could provide new therapeutic interventions against JAK-STAT-mediated diseases. Such an integrative assessment does not only imply the massive potential of such a family in the context of traditional medical systems, but it also suggests the potential utility of the same family in the discovery of new medications and nutraceuticals. During a time when the use of synthetic drugs is slowly being opposed and natural therapeutics are becoming more popular, Amaranthaceae plants provide a biologically rich source for the development of cost- and eco-friendly substitutes (8). This review can help fill the gap between the traditional and contemporary scientific understanding of the family and motivate additional interdisciplinary studies that may lead to the identification of new pharmacologically active substances and therapeutic uses of the found drugs applicable to modern medical issues (9).

## Methodology of literature search

This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to systematically evaluate the ethnomedicinal values, phytochemicals, pharmacological activities and potential modulation of the JAK–STAT pathway by the Amaranthaceae family. A comprehensive literature search was performed using PubMed, Scopus, Web of Science, ScienceDirect, SpringerLink and Google Scholar for studies published up to 2025. In addition, phytochemical and natural product information was further explored using specialised databases, including Natural Products Occurrence Database (LOTUS), OSADHI and Indian Medicinal Plants, Phytochemistry and Therapeutics (IMPPAT). Combinations of keywords such as Amaranthaceae, *Amaranthus*, *Achyranthes*, *Alternanthera*, *Celosia*, ethnomedicinal uses, phytochemical constituents, pharmacological activities, anti-inflammatory, immunomodulatory and JAK–STAT pathway were applied. Eligible studies included peer-reviewed articles published in English reporting detailed traditional uses, phytochemical profiling, biological or pharmacological activities and direct or indirect involvement in the JAK–STAT signalling cascade. Duplicate records, non-medicinal studies, conference abstracts and articles lacking methodological clarity were excluded. Study selection was conducted through title and abstract screening followed by full-text evaluation. Relevant data on botanical identity, plant parts used, bioactive compounds, pharmacological activities, JAK–STAT pathway modulation and toxicological findings were extracted and qualitatively synthesised. Due to heterogeneity in study design and reported outcomes, a narrative synthesis approach was adopted.

## Botanical description and taxonomic classification

Amaranthaceae is a family of flowering plant species (Order Caryophyllales) of about 175 genera and more than 2000 species that are distributed globally. Taxonomically, Amaranthaceae includes several important genera, including *Amaranthus*, *Achyranthes*, *Alternanthera*, *Celosia*, *Chenopodium*, *Aerva*, *Gomphrena, Beta and Spinacia*, many of which hold significant ethnomedicinal, nutritional and pharmacological importance (10). Table 1 presents the hierarchical taxonomic classification of the family Amaranthaceae. Members of the family are characterised by simple, alternate or opposite leaves that

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are typically exstipulate and by the presence of betalain pigments rather than anthocyanins, which impart vivid red, purple, or green coloration (11). This is an impressive family of morphological diversity with herbs, shrubs and some small trees, several of which are well-adapted to grow in temperate, subtropical and tropical environments. The plants are usually herbaceous, although there are also genera, like *Aerva* and *Achyranthes*, that look shrubby. The stems are commonly erect or spreading, occasionally angular or striate and most species have a propensity towards succulence, which is an adaptation to arid or saline conditions. Inflorescences are frequently tight spikes or panicles of small, inconspicuous flowers which can be made of papery or spiny textures by the presence of persistent bracts and bracteoles (12). These flowers are typically actinomorphic, bisexual or unisexual and lack true petals, having a perianth of 3–5 tepals (13). The number of stamens is usually 1–3 or 5 and the ovary is superior and single with a basal ovule, forming a unilocular fruit either an utricle or capsule with one or few small seeds (14).

**Table 1.** Taxonomic classification of the family Amaranthaceae from kingdom to family

| Taxonomic rank | Classification |
|---|---|
| Kingdom | Plantae |
| Subkingdom | Tracheobionta |
| Superdivision | Spermatophyta |
| Division | Magnoliophyta |
| Class | Magnoliopsida |
| Subclass | Caryophyllidae |
| Order | Caryophyllales |
| Family | Amaranthaceae Juss. |

The Amaranthaceae were originally differentiated taxonomically as distinct from Chenopodiaceae, though recent molecular phylogenetic work has lumped the two into a wider Amaranthaceae sensu lato. This more rigorous classification has subfamilies Amaranthoideae, Gomphrenoideae, Chenopodioideae and Salsoloideae. Amaranthus, Achyranthes, Alternanthera, Celosia and Chenopodium are some of the important genera of medicinal and economic value.

Amaranthus is the genus which includes cultivated wild species and is a common leafy vegetable, pseudo-cereal and an ornamental plant. *Achyranthes aspera* and *A. bidentata* are famous due to the wide range of applications in traditional medicine and A. sessilis is appreciated as a source of therapeutic and nutritional value.*Celosia argentea* is cultivated as an ornamental crop and medicinally to treat eye and liver diseases, whereas *Chenopodium quinoa* Wild. has become recognised as a nutritious pseudo-cereal in world markets (15). Amaranthaceae have a high degree of ecological flexibility in harsh conditions, including drought, salinity and non-fertile soil, due to the $C_4$ photosynthetic pathway which is associated with greater efficiency in water-use and carbon-fixation. Through these adaptations, the family ecologically becomes significant in the sustenance of soil fertility and erosion prevention in the arid lands. In general, the botanical and taxonomic diversity of Amaranthaceae indicates its evolutionary success, the ability to withstand the ecological situation and the enormous opportunities for nutritional and pharmacological application (16).

## Ethnomedicinal and traditional uses

Listing of traditional medicinal uses of Amaranthaceae species in different traditional medicines (Ayurveda, Siddha, traditional Chinese medicine, African and South American folk medicine) has applications in inflammation, diabetes, reproductive disease, gastrointestinal disease and wound healing.

### Ethnomedicinal uses

Ethnomedicinal uses of Amaranthaceae family have traditionally played a leading role in the traditional medicine systems of many parts of the world, both in Asia and Africa and in the Americas, where they have been used in a wide range of conditions. The ethnobotanical surveys and more recent reviews show that the members of this family are used in the treatment of skin disorders, wounds and inflammations, gastrointestinal disturbances, respiratory problems, urinary problems, diabetes and reproductive or circulatory disorders. As an illustration, the sub-family Gomphrenoideae (Amaranthaceae) has historically been used in the treatment of chronic diseases, infectious diseases, wounds, burns, snakebites and scorpion stings and renal, gastrointestinal and respiratory conditions (17, 18).

## *Achyranthes bidentata* (Medicinal genus)

A medicinal herb in the Amaranthaceae family, used in traditional Chinese medicine to strengthen bones and tendons, promote blood circulation, relieve lower-back pain and dysmenorrhea. More than 270 metabolites have been identified, supporting its therapeutic potential (19, 20).

The genus *Achyranthes* is also well-documented within this family: an example of this is *A. bidentata*, which is used in traditional Chinese medicine to invigorate the blood and dispel blood stasis, to treat amenorrhea, dysmenorrhoea, lumbar and knee-pain, oedema and urinary stagnation. A closely related species, *A. aspera*, is used in Indian folk medicine in the stimulation of childbirth, snake bites, insect bites, gynaecological conditions, asthma, hemorrhoids and the treatment of a broad range of diseases. Likewise, edible plants like *Amaranthus spinosus* L. have two folds, that is, as wild leafy vegetables and as medicinal plants. An illustration is that in India, its leaves and roots are applied as emollient poultices in abscesses, boils and burns, its extract is used in constipation and its root decoction with honey is used as an aphrodisiac. *Amaranthus dubius* Mart. ex-Thell. (red spinach) is an example of a species traditionally used in tropical/subtropical areas to treat such ailments as anaemia, inflammation, digestive disorders and fever, where nutritional properties supplement its medicinal usefulness (21).

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The genus *Chenopodium* is also a source of valuable medicinal plants: for example, *Chenopodium ambrosioides* L. (wormseed) is a widely used medicinal herb and edible plant in the world, traditionally against parasitic worms, gastrointestinal ills, respiratory illness and other ailments (22).

### *Alternanthera sessilis* (leafy herb with dual food/medicine role)

A dual-purpose leafy herb consumed as a vegetable and used medicinally for dysentery, skin disorders, hemorrhoids and urinary problems. Its young shoots are eaten like spinach, while traditional uses include diuretic and wound-healing applications (23).

Another recent updated review of the genus Amaranthaceae called some wild plants highlighted that ethnobotanical applications are rich and diverse: most of the species find application in urinary disorders, hypertension, skin disorders, wounds and as anti-inflammatory agents. Notably, it was pointed out that despite the many plants in the family being used traditionally, only a fraction of their traditional uses has been laboratorial validated: in the Gomphrenoideae review it was apparent that only an approximate 21 % of traditional uses had been tested in the lab and 79 % were not. These folk uses indicate various organ systems and types of diseases: skin and wound healing (e.g., poultices of *A. spinosus*), urinary and diuretic (e.g., Achyranthes spp.), female reproductive (menstrual, childbirth), anti-inflammatory and analgesics (joint pains, lumbar pain), gastrointestinal (constipation, ulcers), respiratory and infection (asthma, respiratory complaints), metabolic (anaemia, diabetes, hypertension) and even the ethnomedicinal endowment of the Amaranthaceae, therefore, highlights its significance as a source of medicinal biodiversity, particularly in regional health systems which utilise local plants (24).

## Traditional uses

The family Amaranthaceae has traditionally been used in many species to provide a broad range of treatment for numerous ailments. To give an example, *A. viridis* (green amaranth) is employed in folk medicine as a decoction or poultice in case of inflammation, dysentery, urinary complaints and liver disorders; leaves are applied to boils and abscesses and roots or whole-plant products are used in cases of constipation, venereal diseases and even as an emollient. Likewise, another traditional Chinese and Indian medicine, *A. bidentata*, has been applied in the treatment of blood invigoration and stasis extermination, tendon and bone strengthening, liver and kidney care, dysmenorrhea, joint pains, muscular weakness and urinary stagnation (20). In yet another instance, *A. sessilis* (sessile joyweed) is both consumed and used as a traditional medicine: as a leafy vegetable (25), it is also used to promote digestion, gastrointestinal disorders (diarrhoea, dysentery), as a wound dressing, eye disorders and skin irritations and in a few localities as a lactagogue (to stimulate the flow of breast milk). These customary applications cut across organ systems, including skin and wound healing, digestive and urinary dysfunction, inflammatory conditions, metabolic problems and reproductive health and are indicative of the way that the Amaranthaceae plants are utilised as food and as medicine in most indigenous contexts (26, 27). The ethnomedicinal use of specific species of Amaranthaceae with relation to the part of the plant used and the traditional therapeutic suggestions in various cultural systems are summarised in Table 2.

## Phytochemical profile of Amaranthaceae species

The family Amaranthaceae is a wonderful and diverse source of phytochemicals and this fact says much about its pharmacological and nutritional prospects. Phytochemical studies of several genera (e.g. *Amaranthus, Achyranthes, Celosia, Aerva*) demonstrate a great variety of secondary metabolites such as flavonoids, phenolic acids, alkaloids, saponins, steroids/terpenoids, glycosides, cardiac glycosides, tannins and fatty acids. In the recent review of wild Amaranthaceae herbs, the scientists identified that these plants are good sources of various phytochemicals such as flavonoids, alkaloids, saponins, terpenoids and phenolic compounds that form the basis of their bioactivities to a large extent (38). The examination of particular genera showed that over 270 metabolites have been isolated in *A. bidentata* and terpenoids and steroids dominate the chemical profile of the plant, with alkaloids and flavonoids being other significant products. Meanwhile, *C. argentea* was discovered to contain more than 79 compounds, of which saponins are typical components of it, as well as phenols, fatty acids and peptides.

**Table 2.** Traditional uses of selected Amaranthaceae species

| Plant species | Common/traditional name | Parts used | Traditional medicinal uses | Reference |
|---|---|---|---|---|
| *Amaranthus viridis* | (green amaranth) | Leaves, whole plant | Diuretic, laxative, wound healing, anti-inflammatory | (28, 29) |
| *Achyranthes aspera* | Prickly chaff flower | Whole plant, roots, leaves | Piles, boils, wound healing, diuretic, dropsy, hepatoprotective | (30, 31) |
| *Alternanthera sessilis* | Sessile joyweed | Leaves | Eye disorders, anaemia, diabetes, anti-inflammatory | (32, 33) |
| *Celosia argentea* | Cockscomb | Leaves, seeds | Liver tonic, menstrual regulator, anti-haemorrhagic | (34, 35) |
| *Chenopodium album* | Lamb's quarters | Leaves, seeds | Vermifuge, digestive aid, rheumatic disorders | (36) |

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|---|---|---|---|---|
| *Digera muricata* | (Wild spinach) | Leaves, entire herb | Antidiabetic, anthelmintic, antioxidant | (37) |
| *Gomphrena celosioides* | – | Whole plant | Medicinal weed; less explored | |
| *Cyathula prostrata* | – | Whole plant | Traditional medicinal uses (less documented) | |

With *A. viridis*, chemical screening showed flavonoids and steroids, tannins, cardiac glycosides, saponins and terpenoids were present; quantitative analysis showed a total phenolic content (TPC) of approximately 16.4 mg catechin eq/g and total flavonoid content (TFC) of approximately 5.28 mg quercetin eq/g in a single sample (29). These secondary metabolites have various uses. The antioxidant, anti-inflammatory and antimicrobial properties of flavonoids and phenolic compounds are associated with the antioxidant activity of scavenging free radicals and the regulation of oxidative stress signalling. Cytotoxic, antidiabetic and hepatoprotective effects are often based on alkaloids, glycosides and saponins. Steroids and terpenoids can play a role in hormonal and regulatory processes and fatty acids, tocopherols and phytosterols in the seeds (especially in *Amaranthus* spp.) are also indicative of nutritional, as well as bioactive, functions. The phytochemical profiling of Amaranthaceae has been conducted, methodologically, as phytochemical screening (to cover broad classes), quantitative estimates (total phenolic content (TPC), total flavonoid content (TFC), saponin/alkaloid content), gas chromatography–mass spectrometry (GC-MS) and liquid chromatography–mass spectrometry (LC-MS) to determine individual compounds and bioactivity-directed isolation (39). Nevertheless, there are still issues: most species have not been studied in detail, active compounds are frequently isolated without complete mechanistic characterisation and no uniform preparations of extracts have been made. Some of these plants, as noted in a recent review, remain to be less exploited in terms of their pharmacological potential. To conclude, the family Amaranthaceae is a rich area to study chemically: species of this family contain a wide range of phytochemicals, which accounts for a large fraction of their ethnomedicinal applications, as well as those which hold potential nutraceutical and drug-lead opportunities. Future studies should involve systematic isolation of active constituents, structure–activity relationship studies, the standardisation of extracts and the integration of phytochemistry and pharmacology as well as toxicology (40). Table 3 provides a summary of the major phytochemical components found in some of the Amaranthaceae species together with the chemical classes.

**Table 3.** Major phytochemical compounds identified in selected Amaranthaceae species

| Plant name | Phytochemicals identified | Type of compounds | Reference |
|---|---|---|---|
| *Amaranthus spinosus* | Quercetin, Oleic acid, Aspinasterol, Assamicin, Rutin, Amaranthine, 5'-O-trans-p-Coumaroyladenosine, Amaranthoside, Betacyanins, Trigonelline | flavonoids, phytosterol, alkaloid | (41, 42) |
| *Achyranthes aspera* | Ecdysterone, Hyperoside, Saponin B, Acetylursolic acid, Tritriacontanol, 4-Methylheptatriacont-1-en-10-ol, Betaine, Brassidic acid, Achyranthine, Oleanolic acid | steroids, triterpenoids, phenolic glycosides | (43, 44) |
| *Chenopodium album* | Coumarin, Dehydrovomifoliol, Phenylacrylic acid, Cinnamic acid, 3,6,9-Trihydroxy-4-megastigmene, Kaempferitrin, Chenoalbuside, N-trans-Feruloyl tyramine, Ascaridole, Apo-9-zeaxanthinone, Kaempferol | monoterpenes, flavonoids, saponins | (45, 46) |
| *Alternanthera sessilis* | Luteolin, Robinetin 7-glucoside, Tetracontane-1,40-diol, 2,3,4-Trimethylpentanoic acid, 1-Chlorooctadecane, Apigenin, β-sitosterol | flavones, phytosterols | (47, 48) |
| *Celosia argentea* | Celosianin, Amaranthin, 3,4-Dihydroxyphenylalanine, Celosian, Miraxanthin V, Celogenamide A, Moroidin, Celogentin D, Phytosterol, Campesterol, 24-methylenecycloartanol, Isorhamnetin 3-o-glucoside, Betalamic acid, Betanin, Chlorogenic acid | glycoproteins, phenolics, pigments, triterpenoids, flavonoids | (49, 50) |
| *Beta vulgaris* | Protocatechuic acid 4-glucoside, Apigenin 7-O-beta-D-glucoside, melilotic acid, Betavulgarin, quercetin-3-o-beta-d-xylopyranoside, Betalains, Castasterone, Syringic acid, 3,4-dihydroxycinnamic acid, Geosmin, Cryptoxanthin, Indole - 3 carboxylic acid, Para-coumaric acid, Nicotianamine, Myricetin, Betanidin, Portulacaxanthin iii, Carotenoid, Succinic acid, Chamomile, Avenasterol, Rutin, α-carotene, Betanin, 3-rutinosyl quercetin, betaxanthin | pigments, antioxidants, phenolics, flavonoids, sterols | (51, 52) |

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## Nutritional and functional importance

A lot of the Amaranthaceae family have dual purposes such as food and medicine and are therefore very valuable in terms of nutritional and functional food outlook. *Amaranthus tricolor* is one of the edible species that is commonly used in Asia and Africa as a leafy vegetable. As an example, *A. tricolor*, 100 g of fresh leaves, contains approximately 2.86 g of protein, 3.63 g of carbohydrate and 0.39 g of fat and 99 mg of calcium (Ca), 79 mg of magnesium (Mg), 28.1 mg of vitamin C and 2.03 mg of vitamin E (53, 54). In a larger net of vegetable amaranths, *A. tricolor* had a protein of 3.5 g, carbohydrate of 6.5 g and 267 mg Ca per 100 g fresh leaves, potassium (K) 411 mg and iron (Fe) of 3.9 mg. *Amaranthus viridis*, another species, has been reported to have the highest amounts of crude protein in the leaf tissue up to about 24 % and is also a good source of essential amino acids, as well as micronutrients like Mg, zinc (Zn), linolenic and linoleic fatty acids. These nutritional analyses suggest that amaranth leaves are a high-value vegetable food, which is rich in protein, vitamins and minerals and may play a significant role towards the meeting of dietary needs in resource-deprived environments (55).

To the pseudo-cereal, the genus *C. quinoa* (though occasionally included in a related family or sub-group) can also be found as the subject of wider discourse of crops related to Amaranthaceae. The quinoa seeds are known to contain quality proteins (22 % by weight) and a complete amino acid profile (containing all nine essential amino acids). Quinoa seeds and greens are also abundant in minerals, including K, phosphorus (P), Ca, Mg, Fe and Zn. In fact, protein contents (~37 g/100 g dry weight) of quinoa leaves have been reported to be higher than the corresponding amaranth or spinach leaves; at the same time, the essential amino acids are also high. Their nutritive value, coupled with the fact that they can adapt to marginal soils and the stresses they face, presents them as potential food-security and functional-food options (56).

In addition to the raw nutrients, there is the functional significance of the bioactive compounds that are available: phenolics, flavonoids, carotenoids and micronutrients confer antioxidants, anti-inflammatory and health-promoting effects. Indicatively, total carotenoids, vitamin C, phenolic and flavonoid levels in the *A. tricolor* leaves were increased in the presence of drought stress, which suggests the possibility of such leafy vegetables as nutritious and bioactive food sources. To conclude, Amaranthaceae family species provide nutritionally rich leafy greens and grains/pseudo-grains that are nutritionally rich in macro- and micronutrients and are functional/health-promoting, which can be used as nutraceuticals, dietary supplements and for food resilience in changing climates. Table 4 summarises the nutritional composition of the chosen edible species of Amaranthaceae family in terms of their protein, mineral and vitamin C contents.

**Table 4.** Nutritional composition of selected edible species from the Amaranthaceae family (57, 58)

| Species | Plant part | Protein (g/100 g) | Calcium (mg/ 100 g) | Iron (mg/ 100 g) | Vitamin C (mg/ 100 g) |
|---|---|---|---|---|---|
| *Amaranthus tricolor* | (leaves) | 3.5 g (fresh) | 267 mg | 3.9 mg | 80 mg |
| *Amaranthus viridis* | (leaves) | 2.46 g | 215 mg | — | 43.3 mg |
| *Chenopodium quinoa* | (seeds) | 14.1 % protein | — | — | — |

## Pharmacological and biological activities

The Amaranthaceae family exhibits an extraordinary spectrum of pharmacological and biological activities, providing compelling scientific validation for its extensive ethnomedicinal applications and highlighting its immense potential as a prolific source of nutraceuticals, phytopharmaceuticals and novel therapeutic lead molecules.

Numerous genera within this botanically diverse family, including *Amaranthus*, *Achyranthes*, *Alternanthera* and *Celosia*, have been comprehensively investigated for their multifaceted pharmacological properties, encompassing antioxidant, anti-inflammatory, antidiabetic, antimicrobial, hepatoprotective, immunomodulatory, anticancer, neuroprotective and cardioprotective activities. These remarkable bioactivities are principally attributed to the synergistic actions of structurally diverse phytoconstituents, including flavonoids, phenolic acids, alkaloids, terpenoids, saponins, betalains and glycosides, thereby positioning the Amaranthaceae family as an invaluable reservoir for future drug discovery and functional food innovation. (59)

## Antioxidant and free-radical scavenging activities

Numerous species within the Amaranthaceae family possess exceptional antioxidant potential, primarily attributable to their abundant repertoire of phenolic compounds, flavonoids, saponins, betalains and other redox-active phytoconstituents (39). These bioactive metabolites effectively scavenge reactive oxygen and nitrogen species, inhibit lipid peroxidation, enhance endogenous antioxidant defense systems and mitigate oxidative stress-mediated cellular injury. Among them, *A. viridis* demonstrated remarkable pharmacological efficacy, exhibiting potent 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitory, antihyperglycemic and antioxidant activities, thereby underscoring its therapeutic significance in managing metabolic disorders. Furthermore, contemporary systematic reviews of wild Amaranthaceae species consistently recognise antioxidant activity as a predominant pharmacological attribute, reinforcing the family's immense potential as a valuable source of natural antioxidant agents for nutraceutical and phytopharmaceutical development (60).

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### Anti-inflammatory, analgesic and wound-healing effects

Numerous members of the Amaranthaceae family, traditionally employed for the management of pain, inflammation, oedema and wound healing, have undergone extensive pharmacological validation, thereby substantiating their longstanding ethnomedicinal applications. Among these, species belonging to the *Alternanthera* genus have demonstrated remarkable therapeutic versatility, exhibiting potent anti-inflammatory, antihyperglycemic, antioxidant, wound-healing and anticancer activities through the modulation of multiple inflammatory and metabolic signalling pathways (41). Likewise, comprehensive pharmacological investigations of the *Achyranthes* genus have corroborated with its traditional use in alleviating lumbago, gonalgia, oedema and other inflammatory disorders. These therapeutic effects are primarily attributed to diverse bioactive phytoconstituents that collectively confer significant anti-inflammatory, analgesic, immunomodulatory and tissue-reparative properties, thereby reinforcing the translational potential of Amaranthaceae species as promising candidates for evidence-based phytopharmaceutical development (61).

### Antidiabetic or hypoglycaemic effects

Several edible leafy vegetables belonging to the Amaranthaceae family, particularly *A. tricolor* and *A. viridis*, have demonstrated substantial antihyperglycemic efficacy in experimental animal models, thereby providing robust scientific evidence supporting their traditional dietary and medicinal applications in the management of metabolic disorders. These species are enriched with a diverse array of bioactive phytoconstituents, including flavonoids, phenolic acids, betalains, saponins and terpenoids, which collectively regulate glucose homeostasis through multiple complementary mechanisms. Notably, *A. tricolor* has exhibited pronounced antihyperglycemic, anti-inflammatory, antioxidant and antinociceptive activities by modulating oxidative stress, suppressing pro-inflammatory mediators, enhancing insulin sensitivity and preserving pancreatic β-cell function. These multifaceted pharmacological properties underscore its considerable promise as a functional food and a prospective phytopharmaceutical candidate for the prevention and management of diabetes and its associated inflammatory complications (62).

### Hepato-, nephro- and organ-protective activities

Several members of the Amaranthaceae family have demonstrated remarkable organ-protective properties, underscoring their considerable therapeutic potential in the prevention and management of chronic metabolic and degenerative disorders. Among these, *C. argentea* has emerged as a pharmacologically versatile medicinal species exhibiting pronounced hepatoprotective, antihyperglycemic, anti-hypertensive, antioxidant and tumour-modulating activities. These diverse biological effects are primarily mediated through the synergistic actions of bioactive phytoconstituents, including flavonoids, phenolic compounds, saponins, triterpenoids and betalains, which collectively attenuate oxidative stress, suppress inflammatory signalling cascades, regulate cellular proliferation and preserve tissue architecture. Consequently, *C. argentea* represents a promising phytotherapeutic candidate for the development of multifunctional nutraceuticals and evidence-based phytopharmaceuticals targeting complex chronic diseases through multitarget pharmacological mechanisms (63).

### Antimicrobial, antiparasitic and antimicrobial-resistance activities

A substantial proportion of species within the Amaranthaceae family have been extensively utilised in traditional medicine for the treatment of infectious diseases and contemporary pharmacological investigations have unequivocally substantiated their broad-spectrum antimicrobial efficacy. These medicinal plants possess a rich diversity of bioactive phytoconstituents, including flavonoids, phenolic acids, alkaloids, saponins, terpenoids and betalains, which collectively exert potent antibacterial, antifungal, antiviral and antiparasitic activities through multiple complementary mechanisms. Furthermore, comprehensive evaluations of wild Amaranthaceae species have consistently demonstrated the coexistence of significant antimicrobial and antihyperglycemic properties, thereby highlighting their multifunctional therapeutic potential. Such pharmacological versatility underscores the immense value of the Amaranthaceae family as a promising reservoir of bioactive compounds for the development of novel anti-infective agents, functional foods and evidence-based phytopharmaceuticals (45).

### Miscellaneous activities (antitumour, hypolipidemic, immunomodulatory)

Emerging pharmacological evidence has further expanded the therapeutic repertoire of the Amaranthaceae family, revealing pronounced antitumor, antiproliferative, hypolipidemic and immunomodulatory activities. Notably, *A. viridis* has demonstrated significant lipid-lowering efficacy, whereas *A. spinosus* exhibits remarkable immunomodulatory potential through the regulation of innate and adaptive immune responses. Collectively, the family encompasses an extensive spectrum of pharmacological activities, including antioxidant, anti-inflammatory, antihyperglycemic, antimicrobial, organ-protective, cardiometabolic and anticancer effects (46, 47). Nevertheless, despite encouraging preclinical evidence, substantial translational challenges remain, including inadequate mechanistic elucidation, insufficient phytochemical standardisation, dose optimisation, comprehensive toxicological evaluation, pharmacokinetic characterisation and rigorous clinical validation. Table 5 summarises the diverse pharmacological activities of representative Amaranthaceae species while identifying critical gaps in mechanistic understanding and standardisation that warrant future investigation.

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**Table 5.** Pharmacological activities of selected Amaranthaceae species

| Plant species | Pharmacological activity | Model / notes | Reference |
|---|---|---|---|
| *Amaranthus* spp. | Antioxidant, anti-inflammatory, antidiabetic, hepatoprotective | Review reports rich phytochemistry, but mechanism often not fully defined. | (64, 65) |
| *Achyranthes aspera* | Wound healing, anti-arthritic, hepatoprotective, antimicrobial | *In-vivo* hepatoprotective study reported. | (66, 67) |
| *Alternanthera* spp. | Anticancer, antioxidant, antibacterial, anti -inflammatory, central nervous system (CNS) depressant, immunomodulator, antidiabetic | Many species still poorly standardised, crude extracts dominate. | (68, 69) |
| *Aerva lanata* (L.) Juss. ex Schult. | Diuretic, anti-inflammatory, anti-urolithiasis, antidiabetic, hepatoprotective | Traditional use validated in multiple pharmacological models. | (70–72) |
| *Digera muricata* (L.) Mart. | Antidiabetic, anthelmintic, antioxidant | Less explored; more work needed. | (73) |

Clinical trials involving the Amaranthaceae family, notably the genus *Amaranthus*, are increasingly confirming their therapeutic potential for complex metabolic and cardiovascular disorders, building upon extensive preclinical research. Recent findings, including a retrospective study published in 2025, demonstrated that amaranth extracts improved dyslipidemia and glycemic control in patients with metabolic syndrome over 12 weeks (74). This supports a Phase 2 clinical trial (NCT06769035) aimed at evaluating the impacts of amaranth seed supplementation on insulin resistance, inflammation and oxidative stress in overweight patients, expected to complete in mid-2025. However, caution is advised, as earlier studies revealed that amaranth oil could increase cholesterol levels (75).

Additional preclinical studies from 2024 and 2025 indicate amaranth's broader therapeutic potential, such as regulating biomarkers for ovarian hyperthecosis and exhibiting anti-Alzheimer's activity. Investigations of Amaranthaceae plants highlight their diverse therapeutic effects; for instance, *Amaranthus cruentus* L. showed anti-anaemic properties (76), while *Amaranthus blitum* L. demonstrated anti-platelet and anti-coagulant activities (77). Safety evaluations of amaranth extracts established a No Observed Adverse Effect Level (NOAEL), indicating their promise for future development (78). Furthermore, studies on *A. aspera* revealed anti-diabetic effects and its potential utility in chronic conditions (79). Recent mechanistic research on *Chenopodium album* L. found an antithrombotic effect (80).

Collectively, the evidence for Amaranthaceae plants in addressing diseases like anaemia, metabolic syndrome, thrombosis and inflammatory disorders is growing, although the translation into human clinical trials remains limited. Ongoing and future studies aim to leverage bioactive compounds from various Amaranthaceae species for developing adjunct therapies for chronic inflammatory and metabolic diseases, highlighting their significant role in potential treatment strategies.

## Overview of JAK-STAT signalling pathway

The (JAK-STAT) pathway is an indispensable intracellular signalling cascade. It transmits signals to the nucleus, which regulates gene expression from external cytokines, growth factors and hormones. The pathway consists of Janus kinases (JAKs) such as JAK1, JAK2, JAK3, TYK2 and signal transducers and activators of transcription (STATs).

The STAT family consists of seven members such as STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6. In response to growth factors or cytokines binding to cell surface receptors, JAKs become activated via trans-phosphorylation, which leads to the phosphorylation of tyrosine residues on the receptors. These phosphorylated sites act as docking points for STAT proteins; these proteins are also phosphorylated by JAKs. This leads to their dimerisation, nuclear translocation and binding to specific DNA elements to regulate genes associated with cell proliferation, differentiation, survival and immune functions. Dysregulation of the JAK-STAT pathway has been linked to chronic inflammatory diseases, autoimmune disorders and malignancies, where constitutive STAT activation may cause aberrant immune responses and abnormal cell growth. Hence, targeting the JAK-STAT pathway has been recognised as a promising therapeutic strategy, particularly using phytochemicals derived from medicinal plants like Amaranthaceae species that are conventionally used for inflammatory and immune-mediated disorders. Discovered in 1991, the JAK-STAT pathway illuminates the relay of signals from cell surface receptors to the nucleus that regulates essential cellular functions like immune responses and apoptosis. Each member of the JAK and STAT family has unique structural domains that play specific functions in signalling. JAKs are frequently the target of therapeutic strategies to prevent unnecessary activation. As a result, STAT3 inhibitors are created; immune cell differentiation depends on STAT3 and STAT5, whereas antiviral responses depend on STAT1 and STAT2. The pathway's intricacy and the regulation through negative feedback mechanisms like suppressors of cytokine signalling (SOCS) proteins and protein tyrosine phosphatases are critical for maintaining balanced gene expression crucial for immunity, growth and overall development. Misregulation can result in various pathological conditions (6). The integrated JAK-STAT signalling cascade and its functions in immune control and the pathogenesis of diseases are illustrated in Fig. 1.

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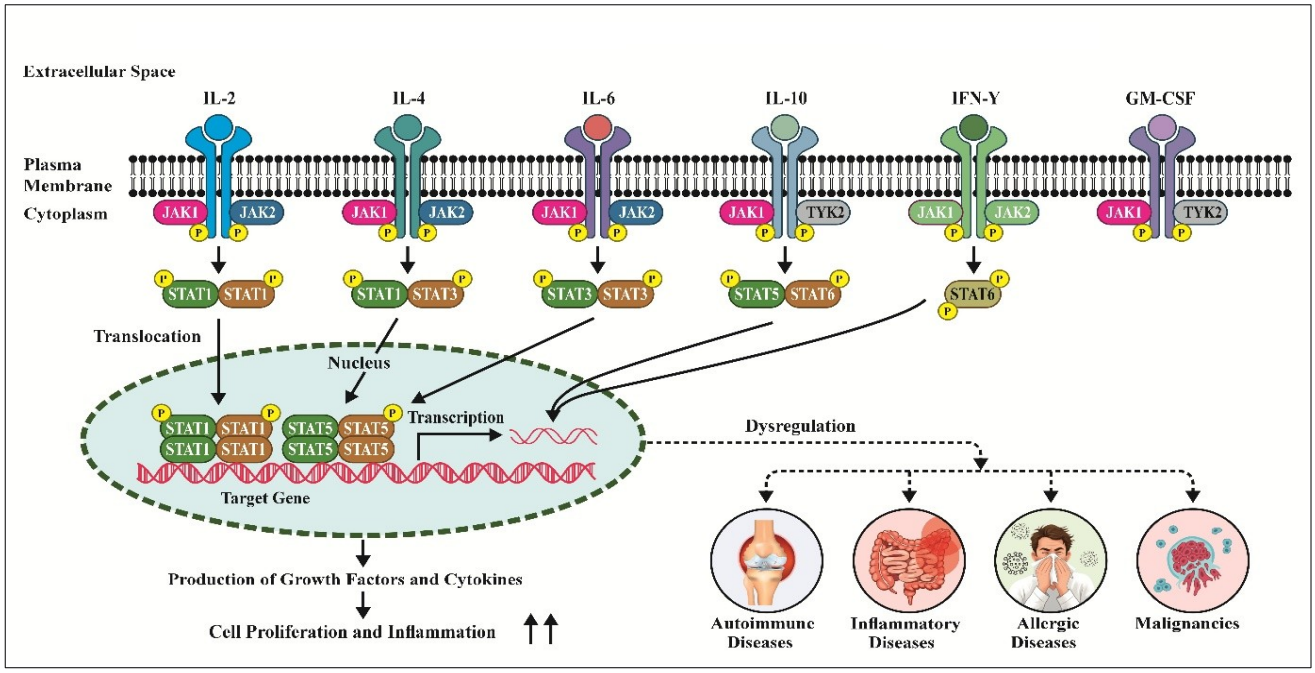



**Fig. 1.** Integrated JAK-STAT signalling pathway in health and immunological disorders.

## Amaranthaceae-derived compounds as JAK-STAT inhibitors

Research has shown that specific compounds within the Amaranthaceae family inhibit the JAK-STAT pathway, marking them as potential candidates for therapeutic development. The bioactivities of these phytochemicals, including flavonoids, alkaloids and terpenoids, often feature anti-inflammatory and immunomodulatory actions.

Flavonoids, a varied category of plant secondary metabolites, hold promise for therapeutic use, notably in regulating the JAK-STAT signalling pathway. Notably, their inclusion in the Amaranthaceae family makes them prospective sources of new JAK-STAT inhibitors via direct kinase inhibition and downstream signalling regulation. Apigenin, a flavonoid, has been shown to lower p-JAK1/2 and p-STAT3 levels in breast cancer cells, hence inhibiting tumorigenesis and angiogenesis. Other flavonoids in the Amaranthaceae family may be discovered to have comparable or stronger inhibitory effects on this pathway. Furthermore, green tea catechins have chemoprotective mechanisms via suppressing STAT1 and STAT3, which reduces iNOS and ICAM-1 expression after cancer treatment. The isoflavone formononetin from *Astragalus membranaceus* (Fisch.) Bunge. also inhibits JAK1-STAT1 phosphorylation and cancer cell proliferation by inactivating p-STAT3. Other substances, such as isorhamnetin and isoliquiritigenin, have shown high STAT3 affinities, implying a direct inhibitory effect on inflammatory bowel injury. Citrus flavanones hesperidin and its derivative, 5,7,3'-triacetyl hesperetin, have strong anti-inflammatory effects by lowering p-JAK2 and p-STAT3 expression levels. Flavonoids such as baicalin treat cardiac damage and target the JAK2/STAT3 pathway, suggesting its therapeutic potential.

Another widely distributed flavonoid, quercetin, significantly reduces JAK2 and STAT3 phosphorylation, which has implications for autoimmune diseases by inhibiting IL-12-induced T cell proliferation and differentiation. Similarly, astragalin inhibits JAK1, STAT1 and STAT3 phosphorylation in lung cancer cells, indicating its therapeutic potential. Other flavonoids, including luteolin, kaempferol and naringenin, interfere with JAK-STAT signalling through a variety of ways. Kaempferol 7-O-β-D-glucoside reduces inflammation in activated macrophages via decreasing JAK1 and JAK2 phosphorylation. As demonstrated in Fig. 2, plant-based phytochemicals derived from the Amaranthaceae, especially polyphenols and betalains, are multi-targeted inhibitors of the JAK stimulating pathway because they disrupt cytokine receptor attachment, JAK phosphorylation, STAT dimerisation and consequent nuclear translocation.

Saponins, amphipathic glycosides discovered in the Amaranthaceae family, have substantial anti-inflammatory and immunomodulatory activities, possibly via JAK-STAT pathway suppression. These molecules, which contain steroidal or triterpenoid aglycones connected to sugar chains, have a wide range of biological activities, including anticancer properties, which are often achieved by regulating cell signalling pathways. By preventing JAK and STAT protein phosphorylation, several saponins lessen proliferative and inflammatory reactions. For instance, triterpenoid saponins from a variety of therapeutic plants can inhibit nuclear translocation and STAT3 phosphorylation, which stops the transcription of genes that promote inflammation and angiogenesis. Due to this, several saponins are turning into promising treatment options for conditions like cancer and chronic inflammation that are marked by aberrant JAK-STAT activation. The significant binding efficacy of

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hederagenin and quinovic acid 3-O-glycosides against JAK2 suggests that they may disrupt the kinase activity of JAK2 and the initiation of the JAK-STAT signalling cascade. Saikosaponins also alter the STAT pathway; for example, saikosaponin A promotes STAT4 signalling, which increases Th1 immune responses against breast cancer. Alkaloids, nitrogen-containing compounds belonging to the Amaranthaceae family, exhibit strong biological activities, like immunomodulatory, anti-inflammatory and anticancer properties. They play a crucial role in regulating the JAK-STAT signalling pathway. These effects, which include the inhibition of JAK kinases and STAT protein phosphorylation, are frequently mediated by interactions with important signalling molecules in the JAK-STAT cascade. Although sanguinarine lowers STAT3 phosphorylation that kills cancer cells resulting in its antineoplastic effects. Berberine downregulates JAK2 and STAT3 levels, which interrupts the pathway in several kinds of malignancies. Molecular docking investigations reveal that quaternary alkaloids such as chelerythrine, a selective JAK1, JAK2 and JAK3 inhibitor. Indole, isoquinoline and tropane, which make them promising options for the development of tailored treatments against illnesses brought on by JAK-STAT. Because of their complex structure, which offers perspectives into feasible JAK-STAT inhibitors, they may be extensively examined in drug discovery.

Bufothionine, an indole alkaloid, has been effective in reducing JAK2 and p-STAT3 levels, preventing proliferation and triggering autophagy in hepatocellular carcinoma cells.

Along with alkaloids and saponins, the Amaranthaceae family contains a range of bioactive compounds, such as polyphenols and essential oils, that may modify the JAK-STAT pathway. These phytochemicals provide an important resource for the creation of new therapeutic drugs due to their roles in immune regulation and cellular communication. Flavonoids like quercetin and kaempferol disrupt JAK-STAT signalling by targeting upstream kinases and changing STAT phosphorylation, which may have anti-inflammatory and anti-cancer properties. Polyphenols, including resveratrol and oleanolic acid, have been reported to be potent kinase inhibitors in the JAK-STAT pathway, interfering with cytokine-induced gene expression and cellular proliferation. Additionally, artemisinins, a class of sesquiterpene lactones, inhibit STAT3 dimerisation and STAT3-related gene expression in cancer cells and preadipocytes by binding to the SH2 domain. The Western blot analyses have shown that artemisinins cause the down regulation of STAT3 phosphorylation to make it clear that this pathway is critical in the inhibitory action of the artemisinins. Most substances such as baicalin and dihydroartemisinin can control multiple STAT proteins and have a broad-spectrum effect on the JAK-STAT pathway. However, physalin A only suppresses JAK/STAT3 signalling, indicating a JAK-dependent mechanism of action by which physalin A leads to anti-tumor effects. Cardamonin decreases nitric oxide generation associated with the JAK-STAT pathway by hindering ERK1/2 and STAT1-4 activation. Additionally, cryptotanshinone influences the phosphorylation of JAK2 and STAT3, which demonstrates the wide range of phytochemicals that can alter this crucial signalling pathway. In quest of discovering new medications that may identify the JAK-STAT system and heal a broad range of inflammatory and cancerous illnesses related to JAK-STAT dysregulation. The potential of malvidin and some chalcones as specific therapeutic agents is supported by the direct inhibition of JAK2 and STAT5 phosphorylation by them.

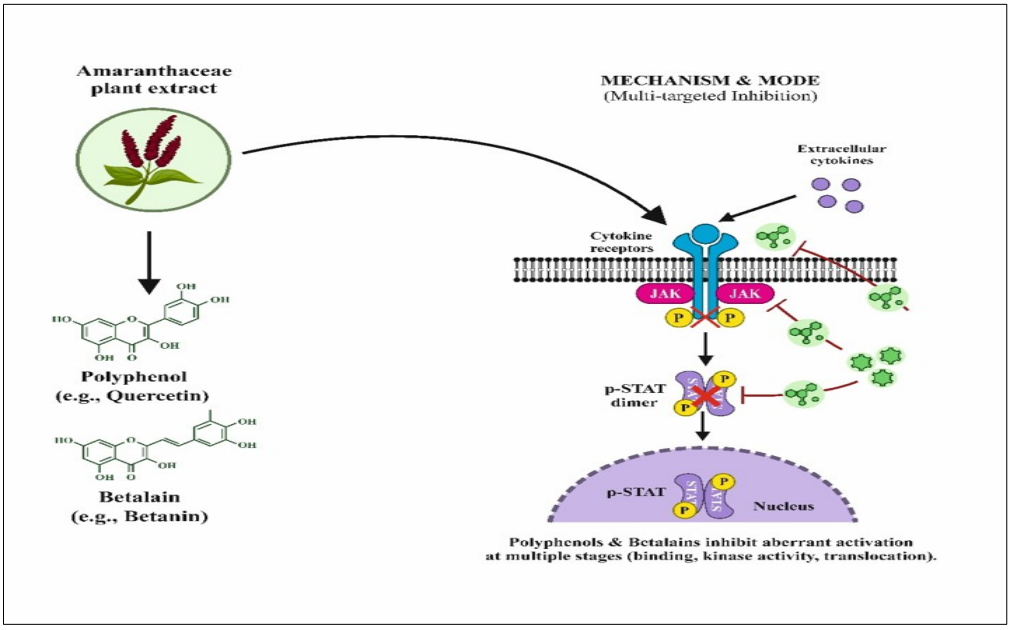



**Fig. 2.** Mechanism of JAK-STAT pathway inhibition by Amaranthaceae phytochemicals.

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The *in vivo* experiments on the study of extracts made of *A. spinosus, A. viridis, C. album* and *Beta vulgaris* L. demonstrate significant anti-inflammatory and antiproliferative effects through the reduction of pro-inflammatory cytokines like IL-6 and TNF-a. Flavonoids such as quercetin and rutin interfere with the JAK2 and STAT3 phosphorylation that inhibits the translocation of the STAT to the nucleus and increases interferon levels. It also reduces anti-survival and inflammatory genes. The *in vivo* research works reported that Amaranthaceae extracts have anti-inflammatory and tumor-inhibitory actions, which are explained by a decrease in the activation of STAT3. Antioxidant effects of betalains in *B. vulgaris* lower the oxidative stress-induced STAT activation. Triterpenoid saponins in *A. aspera* have immunosuppressive effects, which disrupt JAK-STAT signalling. Also, computational studies show that Amaranthaceae compounds may effectively suppress the activity of the JAK kinases by favourable interactions with their active sites.

Amaranthaceae compounds offer a more balanced therapeutic profile compared to synthetic JAK inhibitors like tofacitinib, which are specific but may cause immunosuppression and side effects. These compounds are medium-potency compounds that have an impact on JAK–STAT signalling, NF-κB pathways, oxidative stress and cytokine dynamics and thus have the potential to be used in chronic inflammatory and autoimmune diseases. The diverse actions of these natural compounds could minimise side effects linked to single-target therapies. As Fig. 3 demonstrates, the Amaranthaceae plant extracts can address the shortcomings of single-target JAK monotherapy with multi-target effects and increase their therapeutic potential by being used as part of combinatorial and personalised therapy. Continued exploration through bioactivity-guided isolation and mechanistic studies is essential to validate their potential as safer alternatives or complementary therapies to synthetic JAK inhibitors.

Further research into the stereochemical structure-activity relationships of these compounds could reveal important molecular determinants for inhibitory effects. Overall, the link between JAK/STAT pathway modulation and chronic inflammatory diseases places the Amaranthaceae family as a valuable source for drug discovery.

**Toxicological studies and safety evaluation**

A toxicological study is an important process in confirming the safe usage of Amaranthaceae family herbaceous plants as drugs and nutraceuticals. Acute, sub-chronic and chronic toxicity of a few species have been studied, but extensive gaps exist. As an example, sub-acute studies of *A. spinosus* (root hydroethanolic extract) at 200, 400 and 600 mg/kg over 28 days revealed no significant changes in haematology, biochemistry, or histology parameters (81, 82). Orally, a single dose of 2000 mg/kg of an extract of *A. viridis* leaves showed no death or negative behavioural effects in the rats. The NOAEL was 1000 mg/kg repeated orally in rats over 28 days and the acute LD50 was greater than 5000 mg/kg. Conversely, research conducted on *A. lanata* found that oral acute toxicity was low; however, long-term exposure for 90 days produced cellular alterations in the vital organs and a decrease in sperm count in male rats at high dosages and this points to the possibility of moderate toxicity, given specific conditions. Equally, the sub-acute toxicity of the species *A. aspera* was also tested and the intra-peritoneal LD50 was found to be approximately 1224.7 mg/kg; furthermore, the extract also produced significant alterations in clotting/bleeding parameters in rats when administered over a period of 21 days. The other issue is associated with the build-up of heavy or toxic metals: *A. viridis* that was growing on polluted soils had high levels of cadmium (Cd), nickel (Ni) and Zn, which posed a human-health risk should it be used for edible purposes. These results highlight the importance of the fact that although most plants of the Amaranthaceae family display favourable toxicity profiles at some dose and exposure durations, safety cannot be assured in all species and extract types or exposure conditions. Among the important safety factors are standardisation of extract composition (varying phytochemical profiles), establishing dose-response relationships and chronic exposure effects (reproductive, genotoxic and neurotoxicity endpoints) and the consideration of external contamination (heavy metals, environmental toxins). According to Table 5, the toxicological assessment of the Amaranthaceae species reveals the overall positive acute safety profiles, but shows the possible sub-chronic and reproductive, organ-specific and heavy-metal-related hazards that should be carefully evaluated and subject to long-term safety evaluation (Table 6). A recent review pointed out that even though there is ethnomedicinal use of many wild Amaranthaceae plants, toxicological and safety information is limited in a big percentage of species. To be of clinical use in the future, strict safety assessment is essential: standardised extracts, properly designed animal and human studies, chronic toxicity experiments and observation of possible contaminants are necessary to warrant safe extrapolation to therapeutic or functional-food applications (83).

## Conclusion

The natural agents that can modulate Janus kinase–signal transducer and activator of transcription (JAK–STAT) signalling, oxidative stress and related inflammatory pathways like NF-κB could provide a more balanced approach to managing chronic inflammatory and immune-mediated diseases. The family of Amaranthaceae is one of the best demonstrations of nature's diversity with nutritional, medicinal and ecological benefits. Among the species that were emphasised in the review as being endowed with a broad spectrum of phytochemicals, namely, flavonoids, alkaloids, saponins, terpenoids and phenolic compounds, are *Amaranthus tricolor, Achyranthes bidentata, Alternanthera sessilis* and *Celosia argentea*, that have therapeutic potential. These plants have significantly demonstrated pharmacological activities like antioxidant, anti-inflammatory, antimicrobial, antidiabetic, hepatoprotective and anticancer effects, which justify their long-term ethnomedical use by different cultures.

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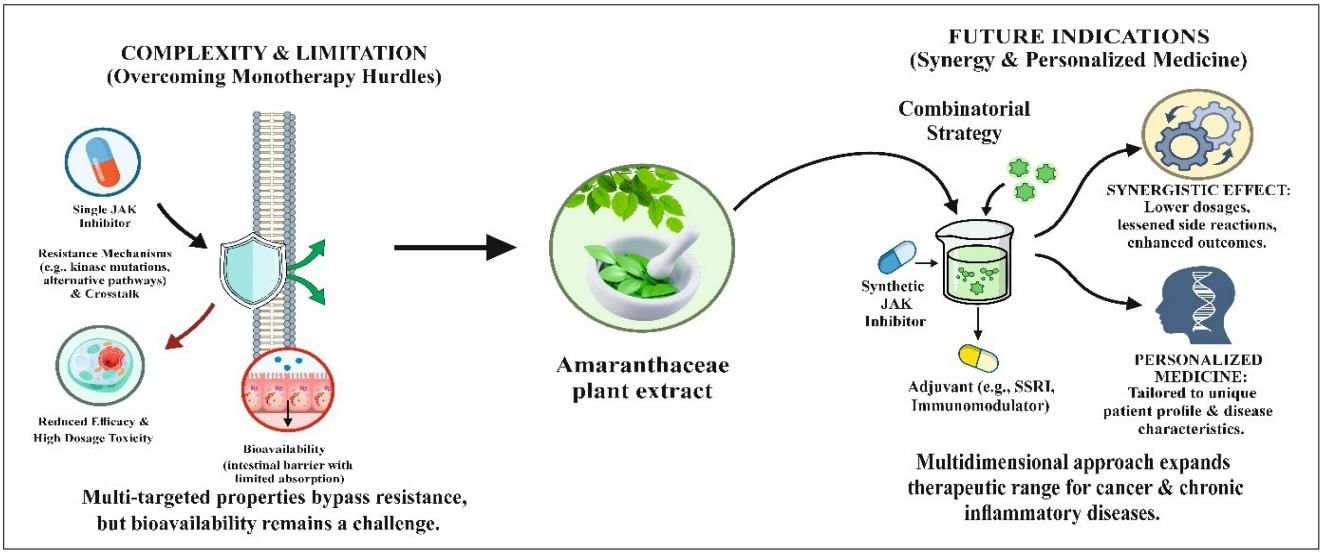



**Fig. 3.** Overcoming monotherapy limitations: Combinatorial and personalised therapeutic potential of Amaranthaceae plant extract.

**Table 6.** Toxicological and safety data of selected Amaranthaceae species

| Species | Study type and dose | Findings | Safety implications | Reference |
|---|---|---|---|---|
| *Amaranthus viridis* (leaf aqueous extract) | Acute (2000 mg/kg) and sub-acute in rats | No mortality or visible adverse effects at 2000 mg/kg in acute test | Indicative of high acute oral safety in animals; further studies needed for chronic use. | (84) |
| *Aerva lanata* (aqueous extract) | Acute (oral up to 30 g/kg), Sub-chronic (40–1000 mg/kg for 90 days) in rats | $LD_{50}$ oral = ~22.6 g/kg. Sub-chronic: organ weight changes (lungs, brain, pancreas), reduced sperm count (85, 86) | While acute exposure appears safe, longer-term use may affect reproductive and organ systems—caution needed. | (86) |
| *Pupalia lappacea* (leaf hydro-ethanol extract) | Sub-chronic (10, 50, 250 mg/kg for 90 days) in rodents | Higher dose (250 mg/kg): reduced sperm motility/testosterone; liver and spleen histological changes(87) | Suggests that even moderate doses may have reproductive and organ-toxicity risks—dose optimisation required. | (88) |
| *Amaranthus spp.* (accumulation in contaminated soils) | Meta-analysis of heavy-metal uptake in *Amaranthus* species | High potential for cadmium (Cd) accumulation [leaf bioaccumulation factor (BAF)] high) (89, 90) | Edible species may pose risk of heavy-metal exposure when grown in polluted soils—monitoring recommended. | (91, 92) |

They are also rich in nutrients such as proteins, vitamins, minerals and essential amino acids; hence, their functional food and nutraceutical properties. However, direct investigations into many Amaranthaceae species are still limited, indicating critical gaps in mechanistic understanding, standardisation, bioavailability and clinical validation. In conclusion, merging traditional medicinal knowledge with contemporary experimental and computational pharmacology elevates Amaranthaceae as a prime candidate for novel, safer JAK–STAT pathway modulators. But, notwithstanding the positive pharmacological and nutritional data, there is a tremendous gap in standardised toxicology studies and clinical validation. The area of research to be considered in the future is bioactive compound isolation, mechanism of action pharmacological studies, dose optimisation and testing safety in human beings since the Amaranthaceae family has vast potential in the field of contemporary phytotherapy, food security and universal health.

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## Authors' contributions

AM collected the literature and wrote the original draft. UPP and BB reviewed and edited the manuscript. All authors have read and approved the final manuscript.

## Compliance with ethical standards

### Conflict of interest

Authors do not have any conflict of interests to declare.

### Ethical issues

None

### Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used grammarly (grammar verification), paperpal (academic language refinement) and quillbot (text paraphrasing for clarity).

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