Rediscovering the therapeutic potential of *Amaranthus* species: A review

Kavita Peter a, Puneet Gandhi b,⇑

⇑Corresponding author at: Department of Research, Bhopal Memorial Hospital and Research Centre, Karond Chouraha, Raisen Bypass Road, Bhopal, Madhya Pradesh, India.

E-mail address: puneetgandhi67@yahoo.com (P. Gandhi).

**Abstract**

Extracts of *Amaranthus* have been used to treat several ailments since ancient times. However, *Amaranthus* spp. has seen a resurgence of interest in recent decades. Literature summarization of *in vitro* and *in vivo* studies established that *Amaranthus* spp. has several protective and curative properties attributed majorly to strong antioxidant activity. This comprehensive review critically analyzes folklore claims of *Amaranthus* with scientific evidences, delineating its phytochemical based nutraceutical properties and emphasizes clinical utility of the plant in various chronic diseases, also defining gap areas for future clinical research. Data on 13 edible *Amaranthus* spp. was acquired via an electronic search including regional scientific journals, theses, books and government reports. These results provide an in-depth analysis of biological effects of major bioactive ingredients present in crude extracts of specific bioparts. However, bioavailability and underlying mechanism of action of constituents isolated from *Amaranthus* spp. have not been worked out, thus necessitating focused research in this arena.

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1. Background

Recent decades have witnessed a resurgence of interest in *Amaranthus* spp. as nutraceutical and natural protector against chronic ailments. A native of tropical America, *Amaranthus* (meaning immortal in Greek) was a staple crop in the Aztec, Mayan, Incan civilizations. Currently it is widely cultivated and consumed throughout India, Nepal, China, Indonesia, Malaysia, Philippines; whole of Central America, Mexico; Southern and Eastern Africa.

Genus *Amaranthus* belongs to order Caryophyllales, family Amaranthaceae, sub-family Amaranthoideae. It includes branched annual herbs with about 70 different species, 17 of which are edible. National Botanical Research Institute of India (NBRI) has built up perhaps, one of the best qualitative collections of Amaranth ‘germplasm’ in the world, comprising nearly 400 accessions, referable to 20 species, of which nearly half belong to the grain type [1].

*Amaranthus* extracts have been used in ancient Indian, Nepalese, Chinese and Thai medicine to treat several conditions including urinary infections, gynecological conditions, diarrhea, pain, respiratory disorders, diabetes and also as diuretic [2–4]. In India, root extract of *A. spinosus* is given as a vermicide among the Santhali and Paharia tribes of eastern Bihar, while an aqueous decoction of the plant is used for chronic diarrhea in southern Orissa [5]. Some tribes apply *A. spinosus* to induce abortion. The juice of *A. spinosus* is used by tribes of Kerala to prevent swelling around stomach while leaves are boiled without salt and consumed for 2–3 days to cure jaundice [6]. However, anti-cancerous, anti-inflammatory, hepatoprotective, neuroprotective, cardioprotective and antidiabetic properties, of *Amaranthus* with relevance to current global health scenario are currently in the limelight.

Natural crude extracts from plants have been used in traditional medicine to treat various ailments, *Amaranthus* spp. is one of them; though its complete therapeutic uses are still unexplored. Scientific interest in *Amaranthus* and its health promoting benefits has increased significantly in the recent past with various reviews presenting nutraceutical properties of Amaranth [7]; its composition, antioxidant properties, applications, and processing [8]. The present review provides a comprehensive updated account of scientific data of the current decade on phytochemical constituents and *in vivo/in vitro* pharmacological activities (Fig. 1) of different bioparts of 13 *Amaranthus* spp. with special emphasis on the need for clinical studies, highlighting the gaps in research areas.

2. Active components of *Amaranthus* spp

Extracts of all plant parts of *Amaranthus* seem to have medicinal benefits; hence the focus of recent studies has been to identify therapeutic constituents of *Amaranthus* from different bioparts. High antioxidant activity of most *Amaranthus* spp., along with anti-inflammatory property, has increased interest in investigating its nutraceutical and clinical potential as functional food. Phytochemical analysis of aerial parts of various *Amaranthus* spp. has established presence of active constituents like alkaloids, flavonoids, glycosides, phenolic acids, steroids, saponins, amino acids, vitamins, minerals, terpenoids, lipids, betaine, catechuic tannins and carotenoids [9–13]. Also documented are amaranthoside, a lignan glycoside; amaricin, a coumaroyl adenosine [14], betalains such as betacyanins (amaranthine, isoamaranthin), betaxanthin; hydroxycinnamates, quercitin and kaempferol glycosides as flavonoids and phenolic acids [15]. Amaranth extracts isolated sequentially by acetone and methanol/water from defatted plant leaves, flowers, stem and seeds yield rutin, nicotiflorin, isoquercitrin, 4-hydroxybenzoic and p-coumaric acids as major components [16].

In species specific studies, evaluation of bioactive substances and phenolic contents of *A. tricolor* and *A. hypochondriacus* leaves revealed high content of betacyanins and betaxanthins while isoqueretin and rutin were the most abundant flavonoids; salicylic, syringic, gallic, vanillic, ferulic, p-coumaric, ellagic and sinapic acid were the most common phenolic acid [17]. In addition to the
known betalains, red-violet amaranthin, a novel betaxanthin, methyl derivatives of arginine betaxanthin and betalamic acid were detected in *A. tricolor* leaves [18]. Rutin and quercitin content was determined in individual plant parts of five *Amaranthus* spp. Only *Amaranthus* leaves sampled at maturity stage contained quercetin or quercetin derivatives. *A. hybrid* and *A. cruentus* were the best source of rutin [19]; while amount of rutin and quercetin in methanolic leaf extract of *A. viridis* was found to be 58.52 and 9.12% w/v respectively [20]. In an exclusive study, Jhade et al. [21] reported alkaloids, glycosides, terpenes, and sugars as the major phytochemicals in roots of *A. spinosus*.

The role of active components bioflavonoids, rutin and quercetin mitigating radiation induced oxidative stress has been investigated by Patil et al. [22], but lack of similar studies on rutin and quercetin sourced from *Amaranthus* delineates the need for clinical research in this area. These compounds possess multifarious properties and are thought to be the main compounds responsible for *Amaranthus* spp. beneficial health effects. In addition, synergistic action of these components and their bio-absorption is not well worked out.

3. Nutraceutical/supplementary food

A study by Dlamini et al. concluded that *A. cruentus* is potentially a good dietary source of the pro-vitamin A carotenoid (β-carotene). Carotenoid content was highest in leaves, followed by seeds, stem and roots. The major carotenoid identified in the leaves was canthaxanthin (antitumor agent), followed by β-carotene and lutein (retardant for age related eye diseases). The level of β-carotene (28.5 mg/100 g) in *A. cruentus* was seven times higher than in tomatoes and thus may help to treat anaemia in African countries [23].

In a comparative study, calcium content in dry leaves of *A. spinosus* was found to have higher value (4500 mg/100 g dry weight) followed by *A. tricolor, A. viridis* and *A. blitum*, while iron content was maximum in *A. viridis* (15 mg) followed by *A. spinosus, A. tricolor* and *A. blitum*. Thus *Amaranthus* spp. can be used as a source of biogenic calcium and in antacid preparations [24].

Amaranth grain, also called Rama's grain (Rajgira) in India, is highly nutritious and a good source of anthocyanins and polyphenolics [25]. The grain has high protein content, well balanced amino acid profile with 8 essential amino acids and very high levels of minerals such as calcium, iron, etc. [26]. It doesn't contain gluten and its high content of quality protein and unsaturated fatty acids is one of its advantages as food supplement. *Amaranthus* seeds are also carrier of valuable fiber and an alternative natural source of squalene (a triterpene); which is a superior antioxidant and known for its wide biological efficacy; against cancer [27] hypercholesterolemia [28]; and as cardioprotectant [29]. *A. caudatus* and *A. paniculatus* seeds are documented to possess antioxidant potential [30]. Silva and co-workers [31] reported the presence of a lunasin-like peptide (11.1 µg/g of total extracted protein) in four genotypes of mature amaranth seeds showing a match for more than 60% with soybean lunasin peptide sequence which is known to possess anti-cancerous properties.

The studies mentioned above conclusively indicate that *Amaranthus* spp. contains appreciable amount of nutrients and can be included in diet to supplement daily nutritional requirements to combat diseases, hence serving as a nutraceutical for fortification of food.

4. Antioxidant potential of *Amaranthus* spp

Antioxidants, molecules that reduce effect of free radicals; important for protection against cancer and degenerative disorders; are in abundance in *Amaranthus* spp. (Table 1). Antioxidant potential has been attributed to the presence of appreciable levels of phenolics and flavonoids. Leaves and flowers of *Amaranthus* as well as their extracts were shown to possess highest antioxidant activities compared to other parts; rutin being the major radical scavenger [16]. Total antioxidant activity assay of dry leaf powder of *A. tricolor* revealed 1 g equivalent to 0.035 g/ml of ascorbic acid [12]. Evaluation of pure and aqueous-methanolic leaf and seed extracts from *A. viridis* [32]; ethyl acetate leaf extracts of *A. spinosus* [33], revealed that they possess good radical scavenging activity with IC₅₀ value of 14.25–83.43 µg/ml and 53.68 µg/ml respectively, confirming their superior antioxidant activity. A study based on hydroacetic, methanolic and aqueous extracts prepared from aerial parts of *A. cruentus* and *A. hybridus*; conducted by Nana et al. [9] described these extracts as having antioxidant and xanthine oxidase inhibitory activities in *vitro*.

The antioxidant potential of aqueous boiled leaf extract of *A. gangeticus* was investigated by Dutta and Singh [34] and their results confirmed protective effect of the extract, on calf thymus genomic DNA and anti-lipid peroxidation activity in goat liver homogenates, suggesting potential against free-radical associated

| Table 1 |
|---|
| Biochemical studies validating antioxidant property of *Amaranthus* spp. |

| Latin name of plant | Plant part used | Extract type/active component | Antioxidant activity |
|---|---|---|---|
| *A. spinosus* | Leaves | Chloroform, n-hexane, ethyl- acetate | DPPH |
| *A. caudatus* | Leaves | Methanolic | Alpha-amylose inhibition assay by CNPG3 |
| *A. hybridus* | Whole plant | Methanolic | Alpha-amylose, ABTS, DPPH, SOD,SH . NO |
| *A. cruentus* | Aerial parts | Hydroacetic, methanolic, aqueous | Xanthine oxidase inhibitory |
| *A. cruentus* | Seeds | 3 novel purified peptides | HMG-CoA reductase assay in terms of NADPH |
| *A. tricolor* | Leaves | Dry leaf powder | Ascorbic acid |
| *A. tricolor* | Stem | Methanol, ethanol, hexane | DPPH, TPC |
| *A. viridis* | Leaves | Petroleum ether, dichloromethane & methanol | DPPH, ABTS, ALPO |
| *A. viridis* | Leaves & seeds | Pure & aqueous methanolic | DPPH, TPC, TPC |
| *A. viridis* | Leaves | Methanolic | SOD, GST, Catalase, Acorobic acid, Lipid-peroxidation |
| *A. gangeticus* | Aqueous | Sequentially extracted by acetone & then methanol/ water | DPPH and superoxide radical by Hematoxilin |
| *Amaranth* (A. cruentus) | Leaves, seeds, stem & flowers | | ABTS, DPPH, ORAC, TPC |

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oxidative damage and related degenerative diseases involving metabolic stress, genotoxicity and cytotoxicity. Amornrit and Santiyanont [39], demonstrated that pretreatment with A. lividus and A. tricolor extracts can significantly decrease cell toxicity and intracellular ROS production by downregulating the expression of oxidative stress genes such as HMOX-1, RAGE, and RelA/ NF-kB in SH-SYSY cells, and may be beneficial for age-related diseases and neurodegenerative disorders. In another experimental study on human erythrocytes, partially purified alkaloids (PPA) from A. viridis prevented the decline of antioxidant status, in turn decreasing LPO levels by preventing MDA formation thus confirming the protective role of these alkaloids against free radical induced oxidative damage [36]. The methanolic extract of A. caudatus presented significant antioxidant activity in all the studies in vitro antioxidant models by Kumar et al. [37] but was found to be extremely effective in scavenging ABTS (2,2′-azino-bis(3-ethylbenzothiazole line-6-sulfonic acid-diammonium salt) radical activity (IC$_{50}$ 48.75 ± 1.1 µg/ml). While comparing, two species A. viridis (green stem) and A. tricolor (red stem), it was found that the latter had higher phenolic content and antioxidant capacity, due to the presence of red anthocyanin pigment [38].

4.1. Anti-inflammatory and anti-nociceptive properties

Inflammation generated oxidative stress and damage to macromolecules is a prominent physiological feature of all chronic diseases. Ethyl acetate fraction of A. spinosus leaves completely inhibited the compound 48/80 secretagogue-induced systemic anaphylactic shock in mouse model. It also stabilized the mast cell lipid bilayer membrane, thereby preventing perturbation of membrane, release of histamine and mast cell degranulation in rat peritoneal mast cells in vitro, suggesting a role in prophylaxis and management of anaphylactic reactions [39]. Kumar et al. [11] provided scientific evidence that whole plant methanolic extracts of A. caudatus and A. viridis and methanolic leaf extracts of A. spinosus exhibit significant antipyretic effect by reducing yeast-induced elevated body temperature in rats and the results were comparable to standard antipyretic drug paracetamol (Table 2). Hydroalcoholic leaf extract of A. tricolor [40] showed anti-nociceptive activity against acetic acid induced writhing model; anti-inflammatory activity against carrageenan induced rat paw edema and cotton pellet induced granuloma in rats. In a similar study, methanolic whole plant extract of A. tricolor demonstrated a dose-dependent significant reduction in the number of writhings induced in mice by intraperitoneal administration of acetic acid; with maximum antinociceptive activity observed at a dose of 400 mg extract/ kg BW, which was comparable favourably with aspirin (200 mg/ kg BW) [41]. In addition, whole plant methanolic extract of A. viridis L. [42], ethanolic and aqueous root extracts of A. hybridus L. [43], whole plant methanolic extract of A. spinosus [44], methanolic extract of A. caudatus L. [45] were shown to possess significant central and peripheral anti-nociceptive potential and anti-inflammatory activity, in mouse model. The extracts also blocked pain emanating from inflammation, increased reaction time on hot plate and significant activities were observed in tail immersion test; justifying further studies on clinical use of the extracts in pain related conditions.

4.2. Anticancerous properties

Efficacy of polyphenols for chemoprevention and as antiproliferative is documented in vitro. Gandhi et al. [46] tested the antiproliferative activity of A. cruentus aqueous extract on human peripheral lymphocytes and suggested that it could be used as an inexpensive, biocompatible, commercial alternate to available anti-proliferative therapeutics. Hexane, ethyl-acetate and methanolic extracts of A. tristis Roxb. showed antiproliferative properties with minimum side effects as determined in human colon adenocarcinoma cell line (COLO-320-DM) [47]. In an in vivo study, ethanolic extract of A. spinosus leaves given orally to Swiss albino mice bearing EAC (Ehrlich’s ascites carcinoma), was evaluated for its antitumor potential. A decrease in tumor volume and viable cell count, with concomitant increase in mean survival time and non-viable tumor cell count along with restoration of hematological and biochemical parameters towards normal was observed [48]. Bulbul et al. [33] used brine shrimp lethality bioassay to determine the cytotoxicity activities of chloroform, n-hexane and ethyl acetate leaf extracts of A. spinosus wherein LC$_{50}$ values were 18.15 µg/ml, 29.51 µg/ml & 18.15 µg/ml respectively; which were much higher than standard vincristine sulphate. Sreelatha and co-workers [49] showed that oral administration of A. paniculatus leaf extract causes a significant decrease in tumor volume, viable cell count, tumor weight and elevated the lifespan of EAC-treated mice with an increase in cellular antioxidant defence system. A. caudatus and A. hybridus feed possess anticarcinogenic properties as evident from reduced micronuclei formation and also protects detoxifying enzymes such as, GGT and alkaline phosphatase (ALP) in sodium arsenite treated albino Wistar rats [50]. Protein isolate from seeds of A. mantegazzianus produced morphological changes and caused rearrangement of the cytoskeleton, inhibited cell adhesion and induced apoptosis and necrosis in UMR106 cell line, exhibiting potential antitumor properties [51]. Maldonado et al. [52] reported that a cancer-preventive peptide in Amaranth had activities similar to those of soybean lunasin which inhibited the transformation of NIH-3T3 cells to cancerous foci and histone acetylation H3 and H4 by 70% and 77%, respectively. Administration of A. hybridus seed and A. lividus stem extract led to 45 and 43% growth inhibition of EAC cells, with up-regulation of p53, Bax and caspase-3 and down-regulation of Bcl-2 mRNA in Amaranthus treated mice indicating mitochondria mediated apoptosis of EAC cells in comparison with control [53]. In another study it was shown that 50% ethanolic extracts of A. viridis Linn. leaves had better antiproliferative activity, against Jurkat, CEM and HL-603 (human leukemic cell lines) than its stem (Table 3). It was also observed that, both extracts enhanced the proliferation of normal cells while the standard curcumin had an anti-proliferative effect on both leukemic and normal cells. Leaf extract could further be explored as a novel source of cancer therapy [54].

4.3. Hepatoprotective

Hepatotoxicity is caused by toxic drugs, excess of alcohol consumption, infection or autoimmune response. Oral administration of methanolic extract of A. spinosus significantly increased the protein and glycogen contents in liver of Sprague Dawley rats thus indicating it to be safe for treatment of liver problems [55]. Escudero et al. [56] based on their observations of lipid profile and liver histoarchitecture in Wistar rats, concluded that presence of pheno- nols in flour and protein concentrate of A. cruentus seeds provokes an increase in antioxidant defenses, thus playing a protective role in liver. A. hypochondriacus seed feed significantly increased activity and gene expression of Cu, Zn-SOD; decreased activity of aspar- tate aminotransferase (SGOT) and content of malondialdehyde (MDA) (< 0.001) in serum; decreased NADPH oxidase transcript levels (< 0.05) in liver, suggesting its protective effect in rats intoxicated with ethanol [57]. Oral administration of ethanolic leaf extracts of A. tricolor for 3-w significantly reduced elevated levels of serum GOT, GPT, GGT, ALP, bilirubin, cholesterol, LDL, VLDL, TG, and MDA induced by CCl$_4$ in rats; which were supported by liver histopathology status. Moreover, extract treatment was also found to significantly increase activities of NP-SH and TP in liver tissue [58]. Results of an another study revealed that 50% ethanolic
| Latin name of plant | Plant part used                          | Extract type/active component | Model                         | Pharmacological activity                                      | Dosage/toxicity | Refs. |
|---------------------|----------------------------------------|------------------------------|-------------------------------|---------------------------------------------------------------|-----------------|-------|
| A. spinosus         | Whole plant                            | Methanolic                   | Mouse                         | Anti-nociceptive, anti-inflammatory                           | 500 mg/kg       | [44]  |
|                     | Whole plant                            | 50% ethanolic                | Rats                          | Hepatoprotective                                             | 400 mg/kg       | [59]  |
|                     | Whole plant                            | Methanolic                   | Wistar rats                   | Hepatoprotective                                             | 200 & 400 mg/kg, 14 d | [60]  |
|                     | Whole plant                            | Petroleum-ether, chloroform, methanolic, aqueous | Rats                          | Anti-diabetic                                                | 200 & 400 mg/kg | [67]  |
|                     | Whole plant except roots               | Methanolic                   | Sprague Dawley rats           | Hepatoprotective                                             | 250 mg/kg       | [55]  |
|                     | Whole plant                            | Aqueous, methanolic          | Mice                          | Anti-diabetic, anti-inflammatory                             | 0.01-10 mg/ml   |       |
|                     | Plant material                         | Methanolic                   | Male Swiss Wistar rats        | Anti-depressant                                              | 100 & 200 mg/kg | [91]  |
|                     | Leaves                                 | Ethyl -acetate               | Mouse                         | Anti-anaphylactic                                            | –               | [39]  |
|                     | Leaves                                 | Powder                       | Wistar-albino rats            | Gastroprotective                                             | 1 g/kg & 2 g/kg | [65]  |
|                     | Leaves                                 | Ethanolic                    | Rats                          | Anti-diabetic                                                | 450 mg/kg       | [71]  |
|                     | Leaves                                 | Chloroform, n-hexane, ethyl-acetate – hexane most effective |                   | Anti-diabetic                                                | 250 & 500 mg/kg for 21 d | [72]  |
|                     | Leaves                                 | Extract                      | Eggs of brine shrimp          | Cytotoxic                                                    | LC 50–29.15 μg/ml (for hexane) | [33]  |
|                     | –                                     | Hydro-ethanolic              | Rat urinary bladder & rabbit jejunum | Anti-diabetic, anti-cholesterolemic | 400 mg/kg for 21 d | [66]  |
| A. caudatus         | Whole plant                            | Ethanol                      | Swiss albino mice             | Anti-cancer                                                  | 100 & 200 mg/kg BW for 16 d | [48]  |
|                     | Whole plant                            | Methanolic                   | Mice & rats                   | Anti-nociceptive,anti-pyretic                                | 200 & 400 mg/kg | [45]  |
|                     | Whole plant                            | Methanolic                   | Rats                          | Anti-pyretic                                                 | 400 mg/kg       | [11]  |
|                     | Aerial parts                           | 96% ethanolic & hydro-alcoholic extract | Male New Zealand rabbits     | Anti-atheroscleromic                                          | 150 mg/kg daily for 2 mo | [76,77] |
|                     | Leaves                                 | Aqueous                      | Albino Wistar rats            | Anti-carcinogenic                                            | 1 ml of 0.2 g/ml for 14 d | [50]  |
|                     | Leaves                                 | Methanolic                   | Rats                          | anti-diabetic, hypercholesterol-licem                      | 400 mg/kg for 21 d | [66]  |
| A. hypochondriacus  | Seeds                                  | Whole                        | Rats                          | Hepatoprotective                                            | –               | [57]  |
| A. cruentus         | Seeds                                  | Flour & protein concentrate  | Wistar rats                   | Hepatoprotective                                            | –               | [56]  |
| A. viridis          | Whole plant                            | Methanolic                   | Mouse                         | Anti-nociceptive, anti-pyretic                                | 200 mg/kg       | [42]  |
|                     | Whole plant                            | Methanolic                   | Rats                          | Anti-diabetic                                                | 400 mg/kg       | [11]  |
|                     | Whole plant                            | Methanolic                   | Albino Wistar rats            | Anti-diabetic                                                | 200 & 400 mg/kg for 15 d | [69]  |
|                     | Whole plant                            | Whole plant                  | Male Wistar rats              | Cardioprotective                                             | 300 mg/kg BW for 45 d | [74,75] |
|                     | Leaves                                 | Methanolic                   | Rats                          | Anti-diabetic, hypercholesterol-licem                      | 400 mg/kg for 21 d | [66]  |
| A. paniculatus      | Leaves                                 | Aqueous: ethanolic 4:1       | Rats                          | Anti-diabetic, anti-hyperlipidemic                            | 100, 200, 400 mg/kg for 30 d | [70]  |
| A. tricolor         | Whole plant                            | Methanolic                   | Mice                          | Anti-cancer                                                  | 100 & 200 mg/ml | [49]  |
|                     | Leaves                                 | Ethanolic                    | Mice                          | Anti-nociceptive,anti-diabetic                              | 400 mg/kg BW     | [41]  |
|                     | Leaves                                 | Aqueous                      | Rats                          | Hepatoprotective                                             | 3 w             | [58]  |
|                     | Leaves                                 | Ethanolic, ethyl-acetate     | Rats                          | Anti-diabetic, hypocholesterol-licem                      | 400 mg/kg for 21 d | [12]  |
|                     | Leaves                                 | Hydro-alcoholic              | Rats                          | Gastroprotective                                             | 200 mg/kg       | [62,63] |
| A. hybridus         | Roots                                  | Aqueous                      | Albino Wistar rats            | Hepatoprotective                                             | 400 mg/kg       | [61]  |
|                     | Leaves                                 | Aqueous                      | Albino Wistar rats            | Anti-carcinogenic                                            | 1 ml of 0.2 g/ml for 14 d | [50]  |
|                     | Mature plant with ripened seed         | Methanolic                   | EAC cellstreated mice          | Anti-cancer                                                  | 25, 50 & 100 μg/ml/d for 6 d | [53]  |
| A. lividus          | Roots                                  | Aqueous, ethanolic           | Mouse                         | Anti-nociceptive, anti-inflammatory                          | 200 mg/kg       | [43]  |
| A. roxburghianus    | Young plant                            | Methanolic                   | –                             | Anti-cancer                                                  | 25, 50 & 100 μg/ml/d for 6 d | [53]  |
|                     | Roots                                  | Hydro-alcoholic              | Rats                          | Treatment for ulcerative colitis                            | 50 and 100 mg/kg | [64]  |

* All the studies mention: no acute toxicity at 2000 mg/kg BW
whole plant extract of *A. spinosus* could afford a significant protection against d-galactosamine/lipopolysaccharide-induced liver injury in rats [59]. Whole plant methanolic extract of *A. spinosus* showed significant (*p < 0.001*) hepatoprotective activity against paracetamol induced hepatotoxicity in Wistar rats [60]. Pretreatment with the aqueous extract of *A. tricolor* roots significantly prevented physical, biochemical, histological and functional changes induced by paracetamol in Wistar albino rats (Table 2). The extract showed significant hepatoprotective effects as evidenced by decreased serum enzyme activities like SGPT, SGOT, ALP, and TB, which was supported by histopathological studies of liver and the results were comparable with standard drug silymarin as against hepatotoxic drug paracetamol [61].

### 4.4. Gastroprotective

There are various plant-originated “gastroprotectors” with different composition that have been used in clinical and folk medicine due to their beneficial effects on the mucosa of gastro-intestinal tract. Ethanolic and ethyl-acetate leaf extracts of *A. tricolor* showed gastric-ulcer healing effect in acetic acid-induced chronic gastric ulcers; gastric cytoprotective effect in ethanol and indomethacin-induced gastric ulcers. The extract also inhibited gastric secretion in pylorus-ligated rats [62]. As an extension of their work, the authors prepared a poly-herbal formulation containing leaf extracts of *A. tricolor* and two other herbs, which exhibited antiulcer properties [63]. Another poly-herbal formulation with a combination of hydroalcoholic extract of *A. roxburghianus* roots and piperine showed minimal ulceration, hemorrhage, necrosis and leucocyte infiltration in histopathological observation, decreased levels of myeloperoxidase and MDA, increased glutathione levels in blood and colon tissue in rats with ulcerative colitis [64]. A study by Ghosh et al. [65] established that powdered leaves of *A. spinosus* could protect Wistar albino rats significantly (*p < 0.001*) from ethanol induced gastric ulcers and cytoseamine induced duodenal ulcers (Table 2).

### 4.5. Antidiabetic properties

Impairment in glucose metabolism leads to physiological imbalance with the onset of hyperglycemia and subsequently diabetes mellitus. Methanolic extracts of *A. caudatus*, *A. spinosus* and *A. viridis* leaves showed significant anti-diabetic and anti-cholesterolemic activity, in streptozotocin (STZ) induced diabetic rats [66], Clemente and Desai [12], showed that oral administration of aqueous leaf extracts of *A. tricolor* significantly reduced (*p < 0.001*) serum glucose, serum TG, total cholesterol, LDL and VLDL, but elevated HDL (*p < 0.05*) in alloxan-induced diabetic rats, as compared to diabetic control. The extract prevented decrease in BW of treated diabetic rats and promoted improvement in Hb-levels. Petroleum-ether, chloroform, methanolic and aqueous extracts of *A. spinosus* was found to exert preventive effect on haemoglobin glycosylation [67]. Methanolic leaf extracts of *A. caudatus* [36] and *A. spinosus* [68] exhibited significant in vitro inhibition of α-amylase enzyme (Table 1) even at very low concentration (IC50 19.233 μg/ml and IC50 46.02 μg/ml, respectively). Oral administration of methanol leaf extract of *A. spinosus* [68] and methanolic whole plant extract of *A. viridis* [69] showed significant reduction in elevated blood glucose, MDA and restored GSH, CAT, TG levels in alloxan-induced oxidative stress in diabetic rats as compared to diabetic control. Oral administration of *A. viridis* stem aqueous extract in STZ induced diabetic rats, significantly decreased blood glucose level and modulated lipid profile [70]. Ethanolic extract of leaves of *A. spinosus*, significantly decreased plasma glucose levels (*p < 0.01 and *p < 0.001*), hepatic glucose-6-phosphatase activity (*p < 0.01 and *p < 0.001*), increased the hepatic glycogen content (*p < 0.01*) with a concurrent increase in hexokinase activity in both type 1 and 2 diabetic rats (*p < 0.01 and *p < 0.001*). It also significantly lowered the plasma and hepatic lipids, urea, creatinine levels (*p < 0.001*) and LPO with an improvement in the antioxidant profiles (*p < 0.001*) of both type-1 and type-2 diabetic rats [71]. Mishra and group cogitated that administration of *A. spinosus* 50% ethanolic leaf extract caused significant reduction in blood glucose in STZ induced diabetes in albino mice, with significant increase in activities of both enzymatic and non-enzymatic antioxidants. Also degenerative changes of pancreatic cells in STZ induced diabetic rats were minimized to near normal morphology [72]. Results presented by Rahmatullah et al. [41], indicated significant oral hypoglycemic activity of methanolic whole plant extract of *A. tricolor* on glucose-loaded Swiss albino mice at all doses of the extracts tested. Maximum antihyperglycaemic activity was shown at 400 mg extract/kg BW, which was comparable to glibenclamide (10 mg/kg BW). Among the betalains identified from *A. tricolor* leaves, betalamic acid (250 μg/mL) significantly inhibited the porcine pancreatic α-amylase activity by 22% compared to that of standard acarbose, while amaranthin and betaxanthin did not show any inhibition [18]. The above mentioned studies present evidence that *Amaranthus* spp. is a potential natural source of ingredients for management of hyperglycemia, associated lipidemia, prevention of diabetic complications and for overall health of diabetic patients. Following clinical trials *Amaranthus* extracts thus can be used for preparation of prospective nutraceuticals for diabetes (Table 2).

### 4.6. Cardioprotective

A number of studies demonstrate that consumption of polyphenolic rich diet limits the incidence of coronary heart disease. Amaranth products, like defatted amaranth flour and protein concentrate have the ability to bind bile acids that has been hypothesized as a possible mechanism by which dietary fiber lowers blood cholesterol level [73]. Oral administration of dried *A. viridis* whole plant altered C-reactive protein, total protein, albumin, globulin, ceruloplasmin and glycoprotein levels in serum and heart of isoproterenol-induced myocardial infarcted rats [74]. It also lowered levels of serum enzymes (AST, ALT, LDH, CPK), cardiac troponin, GSSG and LPO of membrane and elevated levels of antioxidant enzymes (CAT, SOD, GPX, GST and GSH), bringing back all the parameters to near normal [75], exemplifying its cardioprotective effect. anti – atherosclerotic effect of ethanolic extract of *A. caudatus* L. on male New Zealand rabbits was studied by Kabiri and group [76]. On the 30th and 60th day of experiment, rabbits fed with high cholesterol diet and *A. caudatus* extract had significantly decreased cholesterol, LDL-C, triglyceride, oxidized LDL, apolipoprotein A &B, CRP, HDL-C and athereogenic index. The fatty streak formation evaluated on 60th day, showed significant decrease in lesion severity, establishing that *A. caudatus* extract was more effective thanLovastatin. In an extended study, hydroalcoholic extracts of *A. caudatus* and *Hypericum perforatum* L. were investigated and found to possess significant anti-fatty streak effect in hyper-cholesterolemic rabbits [77]. Leaf extracts of *A. spinosus* singularly and in combination with vitamin C reversed unfavorable alterations (increased MDA but reduced GSH, CAT and SOD of heart) in adult rats on high fat diet [78]. Soares et al. [79] cited in their work, three novel peptides from grain of *A. cruentus* and two other herbs, significantly inhibited HMG-CoA reductase, a key enzyme in cholesterol biosynthesis; suggesting a possible hypocholesterolemic effect. Unprocessed and extruded amaranth hydrolysates (EAH) from *A. hypochondriacus* showed a reduction in the expression of interleukins involved in atherosclerosis in THP-1 lipopolysaccharide (LPS)-induced human macrophages. Also, EAH reduced the expression of LOX-1, ICAM-1 and MMP-9, important molecular markers in the atherosclerosis pathway [80] (Table 2).
model based Pharmacological activity of is endemic) to treat malaria[82].
Msambweni community of Kenyan South Coast (where the disease L. to be one of the plant species used traditionally by the
cidal activity, exerting an anti-malarial effect comparable to
in gain of BW, increased hemoglobin content and blood schizonti-
of chemical insecticides; along with evidences of resistance develop-
4.7. Antimalarial properties

On account of eco-hazardous nature and non-target specificity of chemical insecticides; along with evidences of resistance development in the exposed species; the importance of usage of secondary plant metabolites for vector control is being acknowledged. In an animal model study, ethanolic formulation of A. spinosus given to Plasmodium berghei infected mice resulted in gain of BW, increased hemoglobin content and blood schizontidal activity, exerting an anti-malarial effect comparable to chloroquine [81] (Table 2). Another study has documented A. hybridus L. to be one of the plant species used traditionally by the Msambweni community of Kenyan South Coast (where the disease is endemic) to treat malaria [82].

4.8. Antimicrobial properties

The antimicrobial properties of Amaranthus spp. have been exploited by mankind for decades. In a study by Islam et al. [83], chloroform leaf extracts of A. viridis showed antibacterial activity against Bordetella bronchiseptica, Bacillus pumilus, Staphylococcus aureus and Proteus vulgaris. The ethanolic extract displayed antibacterial activity against Bacillus subtilis, B. bronchiseptica, Bacillus cereus, B. pumilus, Micrococcus flavus, S. aureus, Sarcina lutea, Escherichia coli and P. vulgaris. Aqueous extract and polar mass exhibited notable antibacterial activity against B. bronchiseptica. In another study Bulbul et al. [39], showed chloroform, n-hexane and ethyl-acetate leaf extracts of A. spinosus possess moderate to good activity against a range of Gram positive and Gram negative bacteria.

In vitro antibacterial potential of root extracts in petroleum-ether, ethyl- acetate, ethanol and water were screened. Although all extracts exhibited inhibitory effect against the tested bacterial strains; ethyl-acetate root extract of A. hybridus showed highest antibacterial activity against B. subtilis and S. aureus while alcoholic extract showed greater inhibition of E. coli [84]. Vardhana et al. [85], tested ethanolic and aqueous A. spinosus root extracts against ten clinically isolated bacterial strain, documenting high activity against Gram positive and moderate activity against Gram negative bacteria; with ethanolic extract demonstrating better results. Evaluation of pure and aqueous/methanolic leaf and seed extracts [31]; methanolic dried leaf and seed extracts [86] from A. viridis demonstrated considerable antimicrobial activity against selected pathogenic bacterial and fungal strains (Table 3). Hexane, ethyl acetate, dichloromethane and methanolic leaf extracts of A. hybridus, A. spinosus and A. caudatus showed broad spectrum anti-bacterial activity. The MIC of A. spinosus extracts against S. typhi was 129 mg/ml. MIC of A. hybridus extracts against the tested organisms ranged from 200 mg/ml to 755 mg/ml whereas that of A. caudatus was between 162.2 mg/ml and 665 mg/ml [87]. Bioparts, namely, root, stem, leaves and flower from A. spinosus L. extracted in distilled water, hexane and methanol were assayed against Staphylococcus spp., E. coli, Pseudomonas spp., Klebsiella spp., Paracoccus spp. and three fungal strains of Fusarium spp., Aspergillus spp. and Alternaria spp. in which stem and flower extracts displayed better antibacterial activity [88].

4.9. Other properties

Apart from above mentioned pathological conditions, Amaranthus spp. has shown health benefits for several other ailments. The aqueous-methanolic crude extract of A. spinosus was studied in vivo in mice and in vitro using isolated tissue preparations and

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**Table 3**

In vitro model based Pharmacological activity of Amaranthus spp.

| Latin name of the plant | Plant part used | Extract type/active component | Model | Pharmacological activity | Refs. |
|-------------------------|----------------|-------------------------------|-------|--------------------------|-------|
| A. spinosus             | Leaves         | Hexane, ethyl -acetate, dichloromethane, methanolic | S. typhi | Anti-bacterial | [87] |
|                         | Leaves         | Chloroform n-hexane, ethyl- acetate | 4 Gram +ve & 6 gram –ve strains | Anti-microbial | [33] |
|                         | Leaves         | Ethyl-acetate                  | Rat peritoneal mast cells | Anti-anaphylactic | [39] |
|                         | Stem & flower  | Distilled water, hexane, methanol | 5 bacterial & 3 fungal strains | Anti-bacterial & anti-fungal | [88] |
| A. caudatus             | Root           | Ethanoic, aqueous              | Against 10 pathogenic strains | Anti-bacterial | [85] |
|                         | Leaves         | Hexane, ethyl acetate, dichloromethane, methanolic | S. typhi | Anti-bacterial | [87] |
| A. gangeticus           | Leaves         | Ethanol -aqueous               | Calf thymus genomic DNA, goat liver homogenate | Degenerative diseases | [34] |
| A. cruentus             | Leaves & stem  | Aqueous                        | Peripher blood lymphocytes | Anti-cancer | [46] |
|                         | Seeds          | Deflated flour and protein     | Bile acid binding activity | Hypcholesterolemic | [73] |
| A. viridis              | Leaves         | Chloroform, hexane, aqueous   | 9 bacterial, & 2 fungal strains | Anti-bacterial | [83] |
|                         | Seeds          | Pure aqueous, methanolic       | S. aureus, E. coli, R. oligosporus, F. solani | Anti-bacterial, anti-fungal | [31] |
|                         | Dried leaves & seed extracts | Methanolic                    | S. aureus, E. coli, R. oligosporus, F. solani | Anti-bacterial, anti-fungal | [86] |
|                         | Leaves & stem  | 50% ethanolic extract          | 3 human leukemic cell lines (Jurtkat, CEM and HL60) | Antiproliferative | [54] |
| A. hypochondriacus      | Seeds          | Unprocessed & extruded         | Lipopolysaccharide (LPS)-induced THP human macrophage cell line | Anti-atherosclerotic | [80] |
| A. tricolor             | Leaves         | Betalamic acid (250 µg/ml)     | Porcine pancreatic α-amylase activity | Anti-diabetic | [18] |
|                         | Leaves         | Petroleum ether, dichloromethane & methanol | SH-SY 5V cells | Neuroprotective against AGES-induced oxidative stress | [35] |
| A. hybridus             | Leaves         | Hexane, ethyl -acetate, dichloromethane, methanolic | S. typhi | Anti-bacterial | [87] |
|                         | Roots          | Petroleum-ether, ethyl- acetate, ethanol, water | B. subtilis, S. aureus, E. coli | Anti-bacterial | [84] |
| A. tristis Roxb.        | –              | Hexane, ethyl-acetate, methanolic extracts | Human colon adenocarcinoma cell line | Anti-cancer | [47] |
| A. mante-gazzianus      | Seeds          | Protein isolate                | UMIR106 cell- line | Anti-tumor | [51] |
| A. lividus              | Leaves         | Petroleum ether, dichloromethane & methanol | SH-SY 5V cells | Neurotrophic gainst AGES-induced oxidative stress | [35] |
| Amaranthus (A. cruentus) | Seeds          | Isolated peptide              | NIH-3T3 cell line | Anti-cancer | [52] |
was validated to possess laxative, spasmyloytic and bronchodilator properties [89] (Table 2). According to Koffuor et al. [90], hydroethanolic extract of A. spinosus had contractile effect on rat urinary bladder (similar to acetylcholine and nicotine) and rabbit jejunum, possibly mediated via nicotinic, histaminic and muscarinic receptor stimulation. The extract was not lethal and a 240 mg/kg dose had no adverse effect on blood, liver and kidney metabolic function; thus being safe for use in ischuria. At higher concentration methanolic extract of A. spinosus showed significant (p ≤ 0.01) reduction in immobility in tail suspension and forced swim model of depression comparable to escitalopram and imipramine, as observed by Kumar et al. [91].

5. Clinical studies

Despite numerous traditional claims and scientific literature available on Amaranthus spp. there are very few clinical studies available for reference. Chávez-Jáuregui et al. [92] evaluated the effects of defatted Amaranth snacks of A. caudatus on plasma lipids in moderately hypercholesterolemic patients. An intake of 50 g of extruded amaranth daily for 60 days did not significantly reduce LDL in these subjects; but there was a significant reduction in HDL (Table 4).

In a study by Kushwaha et al. [93], ninety postmenopausal women were supplemented daily with 9 g A. tricolor leaf powder, for a period of 3 months. Biochemical analysis revealed significant increase in serum retinol (5.0%), serum ascorbic acid (5.9%), haemoglobin (5.3%) GST Px (11.9%), SOD (10.8%), decrease in MDA (9.6%) and a significant decrease (p ≤ 0.01) in fasting blood glucose levels (10.4%) in postmenopausal women, indicating that the leaves possess antioxidant and therapeutic potential for prevention of complications post-menopause. In a study conducted in Kenya, Nawiri et al. [94] showed that intervention with sun-dried Amaranthus leaf formulation significantly improved bioavailability of serum β-carotene and retinol levels, while improving baseline hemoglobin levels by 4.6%; among preschool children; reflecting its utility in fighting vitamin-A deficiency and anaemia, among children and lactating mothers in developing countries. A single oral dose of amaranth extract is able to increase the NO3 and NO2 levels in the body for at least 8 h. The increase in NO3 and NO2 levels can help to improve the overall performance of people involved in vigorous physical activities or sports [95].

6. Bioavailability of individual components

The high antioxidant capacity of Amaranthus spp. has been attributed to high levels of polyphenolic compounds specially flavonoids. Till date no published study has directly compared the relative bioavailability of components of Amaranthus, though there are studies available on these individual components isolated from other sources. Bioavailability of oral quercetin was shown to be 17% compared to 100% in intravenously administered quercetin, as reported in pigs [96]. In rats, rutin was monitored to be absorbed slower than quercetin as it is probably hydrolysed to quercetin by the coecal microflora, whereas quercetin was absorbed directly from the small intestine and in the large bowel [97]. Absorption and bioavailability was shown to be highest for isoquercetin, lower for quercetin and lowest for rutin as observed in humans [98]. In humans, about 93% of rutin is metabolized in the gut, while ingestion of isoquercetin, quercetin and rutin; quercetin aglycone is not detectable in human plasma and body tissues in significant amounts, though its conjugates, glucuronated, sulphated and methylated-quercitin are documented in humans and animals [99,100]. Flavonols are only partially bioavailable in humans, even though portal blood facilitates removal of absorbed material to maintain a favourable concentration gradient [101]. Calcium bioavailability of raw and extruded amaranth grains (A. caudatus) was assessed in a biological assay in rats. The results showed that amaranth can be a complementary source of dietary calcium; bioavailability of which is favorably modified by the extrusion process [102].

7 Conclusion

Amaranthus is an important traditional herb widely used in folk medicine for centuries. Current scientific opinion advocates consumption of whole plant instead of isolated compounds, the way nature prepared it with full compliments of naturally occurring synergetic phytonutrients to attain holistic wellbeing. Polyphenolic rich Amaranthus based diet can provide significant protection against many chronic disease conditions. Results of studies outlined in this review provide an in-depth analysis of health effects of extracts from different bioparts and with reference to major bioactive ingredients of Amaranthus spp. However, bioavailability and underlying mechanism of action of constituents from this source has not been looked into and warrants focused clinical research in future.

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