The Dual Nature of Amaranth

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The beneficial health-promoting properties of plants have been known to mankind for generations. Preparations from them are used to create recipes for dietary supplements, functional food, and medicinal products. Recently, amaranth has become an area of increasing scientific and industrial interest. This is due to its valuable biological properties, rich phytochemical composition, and wide pharmacological activity. Amaranth is a pseudo-cereal crop with a dual character, combining the features of food and health-promoting product.

amaranth | pseudo-cereals | functional food | biological activity | pharmacological activity | health benefits

1. Introduction

In recent years, there has been noticed a growing interest in plant raw materials whose properties allow them to be used in both food and medicines. Various cereal grains are widely used in the food and beverage industry. There is a fairly broad group of plants that are classified as so-called pseudo-cereals. This means that the edible parts of these plants are the seeds and they usually are consumed in a similar way to cereals, being processed into flour. They also have similar nutritional values and taste to cereals. These are not typical cereals, but due to their similar composition and nutritional value mentioned above, they can be a good alternative. Pseudo-cereals have been the staple food of our ancestors for thousands of years, and all over the world. In different regions of the world, different pseudocereals predominate. Even today, pseudo-cereals still form the basis of nutrition in the poorest parts of the world. They have been increasingly appreciated in European countries for a long time. The best-known pseudo-cereals are amaranth, buckwheat, sorghum, millet, chia as well as khorasan. Actually, the most widely studied pseudocereals are quinoa, amaranth, chia, and buckwheat [1]. They present great potential as a natural source of a wide spectrum of biologically active compounds. Recent work suggests that first and foremost peptides and protein hydrolysates derived from these beneficial species for the human health are worth considering [1]. The first study on an amaranth protein deriving bioactive peptide with cholesterol esterase and pancreatic lipase inhibitory activities was published in 2021 by Ajayi and colleagues [2].

2. Status of Amaranth as a Food or Food Ingredient

The seeds, oil, and leaves of this plant are used as food [3][4]. Amaranth seeds were consumed as early as the time of the Incan, Mayan, and Aztec Empires. According to the EU Novel Food Catalogue, in the case of *Amaranthus caudatus, Amaranthus cruentus, Amaranthus hypocondriacus* as food, only the use of grains from the plant is known in the EU. This product was present on the market as a food or food ingredient and was consumed to a significant degree before 15 May 1997, when the first regulation on novel food came into force. Thus, its access to the market is not subject to the Novel Food Regulation (EU) 2015/2283. However, other specific legislation may restrict the placing of this product as a food or food ingredient on the market in some Member States.

3. Biological and Pharmacological Activity

This plant has many valuable health benefits. Amaranth has been used as an astringent. This effect probably originates from the content of saponins, protoalkaloids, and betacyans [5]. According to PDR for Herbal Medicines, amaranth has been used for the treatment of diarrhea, ulcers, and in cases of pharyngitis. There are also reports on the use of the plant in excessive menstruation, skin problems such as acne and eczema, and as a mouthwash for sore mouths [6]. Saponins, protoalkaloids, and betacyans are responsible for the pharmacological activity of amaranth [5]. There are reports in the scientific literature regarding the beneficial activity of amaranth on the cardiovascular and nervous systems, hypoglycemic effect, antimicrobial activity, antioxidant activity. Amaranth is widely used in the pharmaceutical industry to produce medicinal products against atherosclerosis, stomach ulcers, tuberculosis, as well as antiseptic, antifungal, and anti-inflammatory preparations [7]. According to Khare 2004, the seeds of *Amaranthus hypochondriacus* L. in Unani medicine are considered as a spermatogenetic drug and tonic. A decoction is used in heavy menstrual bleeding, flowers are treated as remedium for diarrhea, dysentery, cough, and hemorrhages. *Amaranthus polygamus* Willd. is used as a spasmolytic, emmenagogue, galactagogue factor [8]. *Amaranthus spinosus* Linn. is taken to reduce heavy menstrual bleeding and in cases of excessive vaginal discharge, also as a diuretic medium. The whole plants of *Amaranthus blitum* Linn., *Amaranthus gangeticus* Linn., *Amaranthus mangostanus* Linn., and *Amaranthus tricolor* Linn. are considered as astringent, diuretic, demulcent, and cooling [8]. *Amaranthus* tricolor Linn. is placed and described in the Ayurvedic Pharmacopoeia of India. Amaranth seed oil exhibits hypolipemic, anti-atherosclerotic, hypotensive, and antioxidant activity [9]. Therefore, its consumption may lead to inhibition or delay in the development of diet-related diseases of civilization.

3.1. Hepatoprotective Activity

Various species of amaranth exhibit hepatoprotective activity. Information on such activity can be found in many scientific papers. Zeashan et al., (2009) demonstrated the hepatoprotective activity of whole plant extract, which was evaluated at 6, 7, 8, 9, and 10 mg/mL concentrations against CCl_4-induced toxicity in freshly isolated rat hepatocytes and HepG2 cells. Ethanolic extract of *Amaranthus spinosus* showed hepatoprotective activity in a dose-dependent manner [10]. In the study by Aneja et al., (2013), the hepatoprotective activity of aqueous extract of roots of *Amaranthus tricolor* Linn. was analyzed in paracetamol overdose-induced hepatotoxicity in a Wistar albino rat model [11]. The extract examined significantly prevented the physical, biochemical, histological, and functional changes induced by paracetamol in the liver of rats, thereby exhibiting hepatoprotective activity [11]. Other researchers also mention the hepatoprotective activity of amaranth, which is attributed to the oil and extracts of the plant [9]. Enrichment of the diet with amaranth oil regulates the lipid profile and has a protective effect on the liver. Primarily, amaranth oil modulates physicochemical properties of lipids and cell membranes of hepatocytes. As a result, it stabilizes cell membranes and acts as a hepatoprotective agent [9]. Squalene is known to exhibit antioxidant and hepatoprotective properties, and also regulates cholesterol levels and helps remove toxic substances from the body [7]. Since a significant squalene content has been found in amaranth oil [12], this liver-protective activity is probably due to this.

3.2. Antioxidant Activity

Zeashan and colleagues documented the antioxidant activity of amaranth extract (obtained from the whole plant). In the study conducted by Zeashan et al., (2009), this extract showed significant antioxidant activity in the DPPH assay. In the next study by Lucero-Lopez et al., antioxidant properties of *Amaranthus hypochondriacus* seed extract were also examined. The study was conducted on the liver of rats sub-chronically exposed to ethanol. The results obtained in the experiments confirm the beneficial effect of the tested extract, which as a rich source of polyphenols, had a protective effect on the livers of rats [13]. Sarker and Oba's work characterized the phytochemical composition of *Amaranthus gangeticus* L. species. They particularly focused on the identification of phenolic compounds responsible for the antioxidant activity of these plants. Twenty-five different phenolic compounds were identified in the plant. Antioxidant components of *A. gangeticus* genotypes exhibited good radical scavenging activities [14]. In another study, the same researchers presented chemical compounds found in amaranth *A. tricolor* (betaxanthins, betalains) that exhibit antioxidant activity [15]. In the study by Al-Mamun et al., the antioxidant activity of the methanol extract derived from the seed and stem of *A. hybridus* and *A. lividus* was tested. The DPPH radical scavenging assay showed that both extracts examined possessed significant dose-dependent antioxidant potential, exhibiting IC_{50} values of 28 ± 1.5 and 93 ± 3.23 μg/mL, respectively [16]. In a subsequent scientific paper, two polysaccharides from *A. hybridus* named AHP-H-1 and AHP-H-2 were characterized and examined as potential antioxidant factors. The results obtained in the study confirmed that the two polysaccharides purified from *A. hybridus* have strong antioxidant activity (DPPH radical scavenging activity and superoxide anion free radical scavenging activity) [17]. Kumari and colleagues confirmed the antioxidant properties of another amaranth species, *A. viridis.* Aqueous, chloroform, methanol, and hexane extracts were examined in several in vitro model systems. *A. viridis* exhibited dose-dependent effective antioxidant properties. Major components responsible for his antioxidant activity are gulonic and chlorogenic acids and also kaempferol [18]. In another paper describing the antioxidant activity of amaranth, the phenolic composition of the aerial part of *Amaranthus caudatus* was tested using ABTS+, DPPH, and O_2 scavenging activity, ferric-reducing antioxidant power (FRAP), and Fe_2+ chelating ability methods. Different levels of antioxidant activity were observed depending on the stage of plant development and the content of biologically active substances (mainly a wide range of phenolic composition) responsible for generating such activity [3]. Studies focusing on the antioxidant capacity of amaranth over the period 2015–2020 were collected and summarized in Park et al.'s work. Here, current knowledge on the antioxidant properties of different amaranth species was systematized and consolidated. These properties resulted not only from the presence of phenolic compounds but were also derived from hydrolysates and active peptides with superior antioxidant activity [4].

3.3. Anticancer Potential

Water extracts of two amaranth species (*A. lividus* and *A. hybridus*) were examined as anticancer factors. Female Swiss albino mice divided into a few groups were injected with EAC cells and received 25, 50, or 100 μg/mL/day/mouse of test extracts after 24 h of EAC cells injection. The measurement of cancer cells growth inhibition was conducted. Administration of *A. hybridus* and *A. lividus* extracts led to 45 and 43% growth inhibition of EAC cells [16]. The seed extract of *A. hybridus* possessed higher growth inhibitory activity than the stem extract of *A. lividus* and exhibited 14, 26, and 45% growth inhibition at 25, 50, and 100 μg/mL, respectively. In animals treated with amaranth extracts, morphological changes suggestive of apoptosis were also observed in EAC cells. Amaranth preparations can be considered as a potential target for cancer cure studies [16].

3.4. Antihyperglicemic and Hypolipidemic Activity

There are scientific papers in the databases on the sugar-lowering and cholesterol-lowering effects of amaranth-containing products. Methanolic extract of *Amarantus viridis* leaves (at the dose of 200 mg/kg and 400 mg/kg per day, 21 days) reduced blood sugar levels in streptozotocin-induced diabetic rats. The administration of the extract also reduced serum cholesterol and triglyceride levels [19]. Girija et al. investigated the anti-diabetic and anti-cholesterolemic activity of the methanol extract of leaves (200 and 400 mg/kg, for 21 days) from three species of amaranth: *A. caudatus, A. spinosus,* and *A. viridis* [20]. Experiments were conducted in streptozotocin-induced diabetic rats. Methanol extracts of all three species of amaranth showed significant glucose and cholesterol-lowering activity at a dose of 400 mg/kg [20]. Similar issues are presented in another paper published in 2011. Antihyperglycemic and hypolipidemic activity of the methanolic extract of leaves of *Amaranthus viridis* was investigated. Normal and streptozotocin-induced diabetic rats were fed with 200 mg/kg and 400 mg/kg of extract *per os* for 21 days. Here proved that the tested extract showed antiglycemic activity and improved the lipid profile in rats [19]. Studies on the activity of selected proteins from amaranth (*Amaranthus cruentus*) suggest hypocholesterolemic activity of this plant. Manolio Soares and colleagues showed that proteins from the plant affect the action of a key enzyme in cholesterol biosynthesis, 3-hydroxy-3-methyl-glutaryl-CoA reductase [21]. The hypolipemic effect of amaranth oil is associated with its significant squalene content. The mechanism of activity of squalene relies on the inhibition of HMG-CoA activity—a liver enzyme responsible for cholesterogenesis. Such activity has been demonstrated in both rat and clinical studies [9]. In another paper, the effects of consumption of the *Amaranthus mangostanus* on lipid metabolism and gut microbiota in high-fat diet-fed mice were examined. Amaranth powder supplementation significantly reduced the levels of triglycerides, total cholesterol, and phospholipids in the liver of rats and also downregulated the expression of a few lipogenesis-related genes [22]. Recent research findings suggest that the aqueous extract obtained from steamed red amaranth leaves might be used as a potent nutritional supplement to prevent diabetic retinopathy. Anti-glycative and anti-oxidative action of that extract against a high glucose-induced injury was examined in a human lens epithelial cell line HLE-B3 [23].

3.5. Neuroprotective and Antidepressant Action

An attempt was made to determine the neuroprotective effect of *A. lividus* L. and *A. tricolor* L. extracts against AGEs-induced cytotoxicity and oxidative stress. Advanced glycation end-products (AGEs) caused oxidative stress and cytotoxicity in neuronal cells. It was found that examined extracts protect human neuroblastoma SH-SY5Y cells against AGEs-induced cytotoxicity [24]. The researchers suggest that amaranth may be useful for treating chronic inflammation associated with neurodegenerative disorders [24]. In another paper by the same researchers, the neuroprotective effect of amaranth was again described. The methanol extracts of *A. lividus* and *A. tricolor* leaves were found to decrease cell toxicity and intracellular ROS production in human neuronal immortalized SH-SY5Y cells. Examined extracts decreased oxidative stress by suppressing gene expression of HMOX-1, RAGE, and RelA. Because of such activity and the high content of antioxidant substances, amaranth extracts may be a potential neuroprotective factor [25]. The methanol extract of *Amaranthus spinosus* (100 and 200 mg/kg, orally) was investigated for antidepressant activity. In the study, forced swimming test (FST) and tail suspension test (TST) models were used in experimental rats. The results of the tests prove the antidepressive potential of the methanol extract of this plant. The researchers indicate that the mechanism of this activity has not yet been understood and its explanation requires further in-depth studies [26].

3.6. Anti-Inflammatory Activity

A. lividus and *A. tricolor* extracts possess anti-inflammatory activity and can reduce pro-inflammatory cytokine gene expression. An increased amount of proinflammatory cytokines, such as IL-1, IL-6, and TNF was observed [24]. In 2021, information on bioactive peptides with anti-inflammatory activity from germinated amaranth released by in vitro gastrointestinal digestion was described in the scientific literature for the first time [27].

3.7. Antimicrobial and Antiviral Effect

A new antimicrobial peptide with strong activity against *E. coli* was found in the medicinal plant *Amaranthus tricolor.* This peptide was selected after analysis of the protein fraction from *A. tricolor* and characterized as being highly antimicrobial [28]. The antimicrobial activity of ethanolic and aqueous extracts of *Amaranthus caudatus* was also examined in a study by Jimoh and colleagues [29]. *Streptococcus pyogenes, Staphylococcus aureus, Bacillus subtilis, Streptococcus pneumoniae, Escherichia coli,* and *Pseudomonas aeruginosa* were tested in this study. The used strains of fungi were: *Candida albicans, Penicillium chrysogenum*, *Candida glabrata*, and *Penicillium aurantiogriseum*. The ethanolic extract of amaranth showed stronger antimicrobial activity than the aqueous extract. The extracts also showed antifungal activity with an MIC in the range of 0.675 to 10 mg/mL [29]. A new application of amaranth seed oil (apolar fraction from *Amaranthus cruentus* L. seeds extract) as an agent against *Candida albicans* was examined by De Vita and colleagues. Amaranth oil in combination with an antifungal drug named terbinafine possesses synergic fungistatic and fungicidal activity and can be a potentially important ingredient of antifungal formulations [30]. In the next study, stem and seed methanol extracts of *A. lividus* and *A. hybridus* were examined as antimicrobial factors. In vitro susceptibility of five pathogenic bacteria (*E. coli, P. aeruginosa, B. subtilis, S. typhi, S. aureus*) was confirmed in the disk diffusion assay [16]. There have also been recent reports of the antiviral activity of amaranth. Chang and colleagues investigated the antiviral properties of betacyanin fractions from leaves of red spinach, *Amaranthus dubius* [31]. Betacyanin fractions from *A. dubius* inhibited DENV-2 in vitro. Betacyanin fractions exhibited antiviral activity against DENV-2 after virus adsorption to the host cells in a dose-dependent manner. For betacyanin fractions from red spinach, the IC50 value was 14.62 μg mL^{-1}, with an SI of 28.51. The researchers point out that the mechanism of infectivity inhibition by the betacyanins must be confirmed by rigorous scientific studies [31]. In other experimental work, the antimicrobial activity of *A. tricolor* crude extract against *S. aureus* was assessed by disk diffusion, minimum inhibitory concentration (MIC) determinations, and growth curves. The researchers of the experiment proved that the extract has antibacterial activity and the mechanism of this activity was connected with cell membrane depolarization, reduction in intracellular pH, decrease in bacterial protein content, DNA cleavage, and leakage of cytoplasm. The plant extract has the potential to be a good food preservative that improves meat quality [32]. The major biological effects of amaranth are summarized in **Table 1**.

Table 1. Key biological effects of amaranth.

Activity	Active Agent	References
Astringent	Saponins, protoalkaloids and betacyans	[5][8]
For skin problems	Naphthalene, squalene, sulfonates of *Amaranthus* spp.	[6]
Hypolipidemic, antihyperglycemic	Methanol extract of *A. viridis* leaves Methanol extract of *Amaranthus* spp. Proteins from *A. cruentus* squalene Leaves aqueous extracts	[19] [20] [21] [9] [23]
Action against microorganisms	*A. tricolor* isolated peptide Ethanolic, aqueous extract of *A. caudatus* Seed oil from *A. cruentus* Methanol extract of *A. lividus* and *A. hybridus* Betacyanins isolated from *A. dubius* *A. tricolor* crude extract	[28] [29] [30] [16] [31] [32]
Neuroprotective or antidepressant	*A. lividus, A. tricolor* extracts *A. lividus* and *A. tricolor* leaves methanol extract *A. spinosus* methanol extract	[24] [25] [26]
Anti-inflammatory	*A. lividus* and *A. tricolor* extracts Bioactive peptides	[24] [27]
Antioxidant	Whole plant extract Seed extract Phenolic compounds Betaxanthins, betalains Seed or stem methanol extract of *A. hybridus* AHP-H-1, AHP-H-2 polysaccharides from *A. hybridus* Different extracts of *A. viridis* Phenolic compounds *A. caudatus*	[10] [13] [14] [15] [16] [17] [18] [3]
Anticancer	Water extract of *A. lividus* Water extract of *A. hybridus*	[16]

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