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BIOACTIVE COMPOUNDS AND PHARMACOGNOSTIC POTENTIAL OF *Tetragonia tetragonioides*

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In the recent years, due to the increasing resistance of pathogens to synthetic antimicrobial drugs, the use of highly active compounds from plants, which have proven their effectiveness in traditional medicine practices, is increased. Extracts of medicinal plants often contain a unique species — specific combination of active ingredients that have a synergistic therapeutic effect. Therefore, the analysis of the biochemical composition of cultivated plants and the range of their potential biotechnological application is an urgent task.

Aim. To summarize the information on the potential of the xerophytic plant *Tetragonia tetragonioides* as a source of functional food ingredients and biologically active substances that increase nonspecific organism resistance and contribute to the prevention and treatment of various diseases.

Results. *T. tetragonioides* is a salt-tolerant and heat-resistant plant containing valuable nutrients and biologically active substances, a significant amount of vitamins, minerals, and dietary fibers. The high level of antioxidant compounds, especially flavonoids and carotenoids, helps to reduce the risk of degenerative pathologies developing associated with excessive oxidative stress. The unique complex of biologically active substances in *T. tetragonioides*, which includes 6-methoxyflavonols, predominantly derivatives of 6-methoxykaempferol, as well as megastigmanes and their glucosides, lignanamide, provides significant antioxidant, anti-inflammatory, antitumor, and antimicrobial activity and may be beneficial for the prevention of chronic diseases and age-related health problems. The effectiveness of *T. tetragonioides* has been demonstrated in animal models in the treatment of metabolic disorders such as obesity, hyperlipidemia, and hyperuricemia.

Conclusions. *T. tetragonioides*, containing a specific complex of biologically active compounds, primarily 6-methoxyflavonols, may be a promising raw material for obtaining effective medications for the treatment and prevention of various chronic diseases and metabolic disorders.

Key words: *Tetragonia tetragonioides*,nutritional and biochemical status, antioxidants, therapeutic activity, anti-inflammatory activity.

Tetragonia tetragonioides (Pallas) Kuntze, commonly known as New Zealand spinach, is a naturally occurring species in Eastern Asia, Australia, and New Zealand, from where it was introduced to countries in Western Europe, America, and Africa. *T. tetragonioides* belongs to the Aizoaceae family and has succulent, fleshy, toothed, and triangular-shaped leaves. They are located on a highly branched stem, approximately 50–60 cm long, which spreads along the ground. This plant thrives well in both tropical and temperate climates, in various natural environments ranging from sandy coastlines to forested areas [1]. However, wild plants are rarely found in regions far from the sea. Only in the last century *T. tetragonioides* has been cultivated in small quantities as an annual food crop. In the areas of natural growth, the local population has long consumed *T. tetragonioides* greens and used them to treat many diseases. In some countries, it is used raw as a salad vegetable that is vaguely similar in taste and texture to garden spinach

Spinacia oleracea L. (Amaranthaceae). Unlike S. *oleracea*, which grows poorly in the summer, *T. tetragonioides* produces good yields throughout the summer until late fall [2] because it is a high-temperature, drought-tolerant, daylight-neutral crop [3]. Because of its salinity tolerance and ability to extract salt from saline soils, New Zealand spinach is recommended for cultivation in arid regions and for use in saline field reclamation [4–6]. This review analyzes the information on the biochemical composition of *T. tetragonioides* and the prospects for its use in pharmacology.

Nutritional Properties and Biochemical Composition of *T. tetragonioides*

T. tetragonioides is a low-calorie product (14 kcal/100 g of leaves [7]) with a fairly rich composition of mineral elements and vitamins, which is highly valued in dietary nutrition. Table 1 shows the content of major nutrients in the leaves of *T. tetragonioides*.

The leaves of *T. tetragonioides* contain a small amount of protein and virtually no fat compared to the carbohydrates (Table 1). Although the protein content of *T. tetragonioides* is lower than that of legumes, it can be an additional source of amino acids in a meat-free diet. According to Jaworska and Kmiecik [9], the protein content in the leaves of *T. tetragonioides* was slightly different and amounted to 27.5–30.6 g/100 g dry weight, depending on the season, planting and harvesting time, and the total amount of amino acids was 24.25 g/100 g dry weight [10], with aspartic and glutamic acids accounting for 2.67 g and 3.36 g, respectively. *T. tetragonioides*, like all green leafy vegetables, contains dietary fiber, which helps reduce gastrointestinal problems and the risk of cardiovascular disease [11]. Table 2 shows the content of major mineral elements in the leaves of *T. tetragonioides* vs. *S. oleracea*.

Table 1

Content of major nutrients in the leaves of *T. tetragonioides*

The main nutrients substances	Nutrient content, g/100 g of fresh weight	Nutrient content, g/100 g of dry weight [8]
Protein	1.33	18.25
Carbohydrates	3.69	50.65
Fiber	1.02	13.94
Fat	0.3	4.15

The mineral content of New Zealand spinach (Table 2) is similar to that of other leafy vegetables such as *S. oleracea* and *Brassica oleracea* var. sabellica (kale) [6] and, in the case of *T. tetragonioides*, between 5 and 10% of the human daily requirement per 100 g of leaves. At the same time, the content of manganese, which is a vital nutrient in very small quantities (the daily requirement for an adult male is 2.3 mg), provides more than a quarter of the daily human requirement for this microelement.

As an enzyme cofactor, Mn is involved in several biological processes, including macronutrient metabolism, bone formation and the maintenance of the body's reproductive functions. It is an important cofactor for dozens of proteins and enzymes that carry out redox reactions of intracellular metabolism [15]. Manganese superoxide dismutase (MnSOD) is involved in the free radical defence system of eukaryotic cells as a major mitochondrial antioxidant [16].

Like other leafy vegetables, *T. tetragonioides* is low in calories and fat per calorie and high in dietary fibre, vitamins C and B6, vitamin A, carotenoids and vitamin K. Table 3 shows the content of vitamins and other biochemicals in the leaves of *T. tetragonioides* vs. *S. oleracea*.

Table 2

Content of major mineral elements in the leaves of *T. tetragonioides* vs. *S. oleracea*

Main mineral elements	Content of mineral elements (mg/100 g of fresh weight)	
	T. tetragonioides	*S. oleracea*
Potassium, K	378	646
Phosphorus, P	24	47
Calcium, Ca	107	225
Magnesium, Mg	45	73
Sodium, Na	87	27
Iron, Fe	4.2	4.6
Manganese, Mn	0.526 (25% DV) [12]	0.897 (43% DV) [13]

Note: other indicators are cited in [14]. %DV — % of the daily value.

The content of vitamin K is particularly high in leafy vegetables because they are photosynthetic tissues and phylloquinone (vitamin K) is involved in photosynthesis [20], where it participates in the electron transfer chain in photosystem I. Consumption of 100 g of *T. tetragonioides* provides almost 3 times the daily requirement of vitamin K. The classical role of vitamin K is as an anti-haemorrhagic factor, necessary for the synthesis of proteins in the liver that ensure normal blood clotting. Vitamin K consists of many related forms of structurally similar fat-soluble substances derived from 2-methyl-1,4-naphthoquinone. The biochemical pathways of vitamin K metabolism include its interaction with protein receptors and its involvement in the synthesis of protein structures by modifying certain glutamic acid residues in procoagulant proteins and converting them into γ-carboxylglutamic acid residues (Gla-residues) [21]. Fourteen Gla-proteins have now been identified in humans, occupying key positions in cardiovascular regulation, blood coagulation, bone metabolism, and energy metabolism and cognitive functions. Due to their two free carboxyl groups, Gla-radicals are involved in calcium binding and play an important role in the biological activity of all known Gla-proteins, enabling calcium-vitamin D interactions. The only generally recognized health consequence of vitamin K deficiency is bleeding due to impaired blood coagulation, which results from decreased γ-carboxylation of procoagulant proteins. At the same time, consumption of vitamin K-enriched foods is prohibited in thrombosis and during anticoagulant treatment [21].

T. tetragonioides also contains B vitamins, a class of water-soluble vitamins that play an important role in cellular metabolism. Each B vitamin either is a cofactor (usually a coenzyme) for key enzymes or is a precursor necessary for their formation [22]. Thiamine (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3, vitamin PP, nicotinic acid),

Table 3

Content of vitamins and other biochemicals in the leaves of *T. tetragonioides* vs. *S. oleracea*

Vitamins and other biochemicals	Content of vitamins and other biochemicals (mg/100 g of fresh weight)	
	T. tetragonioides	*S. oleracea*
β-carotene	3.98 [17]	3.15 [18]
Lutein	5.35 [17]	5.22 [18]
Violaxanthin	1.97 [17]	2.66 [18]
Neoxanthin	1.55 [17]	1.53 [18]
Flavonoids	402 [8]	370 [19]
Vitamin A, RAE	1.086 (136.7% DV) [12]	0.469 (59% DV) [13]
Thiamine (B1)	0.03 (3% DV) [12]	0.078 (7% DV) [13]
Riboflavin (B2)	0.107 (9% DV) [12]	0.189 (16% DV) [13]
Pantothenic acid (B5)	0.256 (5% DV) [12]	0.065 (1.27% DV) [13]
Niacin (B3)	0.39 (3% DV) [12]	0.724 (5% DV) [13]
Vitamin B6	0.237 (18% DV) [12]	0.195 (14.8% DV) [13]
Vitamin K	0.292 (278% DV) [12]	0.483 (460% DV) [13]
Vitamin C	16 (19% DV) [12]	28 (34% DV) [13]
Vitamin E	1.23 (8% DV) [12]	2 (13% DV) [13]
Soluble oxalates	311	405
Oxalates	391	654

Note: other indicators are cited in [14]. RAE — Retinol activity equivalent; % DV — % of the daily value.

vitamin B5 and vitamin B6 (the common name for three substances: pyridoxine, pyridoxal, and pyridoxamine) have been found in *T. tetragonioides* (Table 3). Insufficient amounts of these vitamins in the body can provoke a number of serious diseases, including nervous system diseases, digestive problems, and even cardiovascular diseases [8, 11, 22].

T. tetragonioides leaves are also rich in vitamin A. The content of this vitamin in 100 g of leaf mass exceeds the daily human requirement by about 1.4 times (Table 3). The essential fat-soluble vitamin A has many functions: it is necessary for maintaining the immune system and for vision, especially for night (twilight) vision, which depends entirely on the presence of this vitamin. A group of chemically related organic compounds that includes retinol, retinal, retinoic acid, and several provitamins — carotenoids, especially β-carotene, exerts vitamin A activity. Retinal is part of the visual pigment of the retina, where it combines with the protein opsin to form rhodopsin, a light-absorbing molecule necessary for both twilight and color vision [23]. Vitamin A deficiency results in various lesions of mucous membranes and skin, impaired vision, impaired corneal wetting, decreased immune function and growth retardation.

Vitamin A provitamins — carotenoids are present in the composition of *T. tetragonioides* leaves in a total amount of 12.85 mg/100 g crude weight [17]. These include β-carotene and xanthophylls, which are effective antioxidants — preventing the formation of oxygen radicals or scavenging reactive oxygen species [24].

Significant antioxidant activity is also inherent in water-soluble vitamin C (ascorbic acid) and fat-soluble vitamin E.

Thus, New Zealand spinach contains a large amount of bioactive compounds and nutrients, including essential minerals and vitamins, as well as compounds that have strong antioxidant activity. As a result, consumption of *T. tetragonioides* can help strengthen the immune system to resist infection.

In addition to valuable dietary constituents and antioxidants, *T. tetragonioides* can accumulate undesirable substances such as oxalates (salts of oxalic acid), which reduce calcium absorption and contribute to the formation of kidney stones [14]. Oxalates in the form of potassium and sodium salts are considered water soluble, whereas calcium, magnesium and zinc salts are considered insoluble. The content of water-soluble oxalates in *T. tetragonioides* was 80% of the total oxalate content (Table 3). The amount of oxalates can be reduced by pre-treating the leaves with steam.

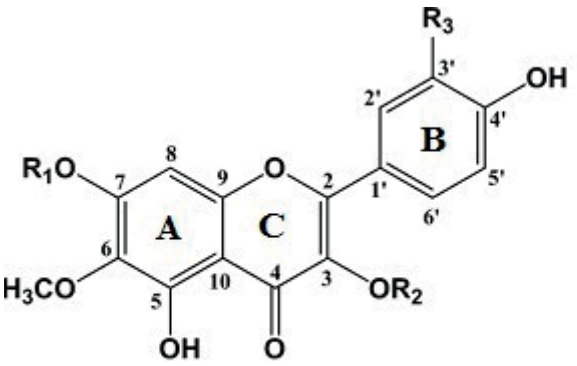
Non-enzymatic antioxidant substances of *T. tetragonioides*

T. tetragonioides can accumulate non-enzymatic antioxidant substances such as L-ascorbic acid, various flavonoids and lipophilic carotenoids [8, 17, 25, 26], which are used in clinical practice and for the prevention of many diseases, including cardiovascular diseases. Among the bioactive compounds with antioxidant activity, flavonoids (Table 3) have the highest content in relation to 100 g raw weight of *T. tetragonioides*. These secondary metabolites are potent antioxidants and play an important role in neutralising oxygen radicals, protecting cells from oxidative damage and reducing the risk of oxidative stress associated with various chronic diseases and other disorders that occur with age [27]. They have anti-inflammatory, antimicrobial and antitumour properties of various types, due to their antioxidant nature [28] or their ability to influence enzyme systems involved in the immune response.

A unique complex of bioactive compounds, 6-methoxyflavonols, was isolated from the aerial part of *T. tetragonioides* by chromatographic method and its chemical structure was determined by infrared spectroscopy, FAB mass spectroscopy and NMR [25, 29, 30]. The figure shows the structural formulas of the obtained 6-methoxyflavonols. They are believed to be the major bioactive components of *T. tetragonioides*. Quantitative analysis by HPLC chromatography showed that most of the compounds in the 6-methoxyflavonol complex are 6-methoxykaempferol derivatives [25].

Active oxygen species (ROS) and free oxygen radicals are major drivers of inflammatory processes associated with various chronic and degenerative diseases [27, 31]. Therefore, the suppression of ROS may be important for the prevention and treatment of various pathologies caused or accompanied by an increase in free radical oxidation processes.

The antioxidant capacity of 6-methoxyflavonols extracted from *T. tetragonioides* was evaluated in DPPH and ABTS tests, which determined the ability of substances to neutralise the stable free radical 1,1-diphenyl-2-picrylhydrazyl (DPPH) and the cationic radical 2,2′-azino-bis(3-ethylbenzothiozoline-6-sulfonic acid) (ABTS) (Table 4).



	R_1	R_2	R_3
1	6-caf-glc	glc (1→2) glc	H
2	6-fer-glc	glc (1→2) glc	H
3	glc	glc (1→2) glc	H
4	H	glc (1→2) glc	OH
5	H	H	OH
6	H	H	H
7	glc	H	H
8	6-fer-glc	H	H

glc: *β*-D-glucopyranosyl
glc (1→2)glc: *β*-D-glucopyranosyl(1→2)-*β*-D-glucopyranosyl
6-caf-glc: (6-(*E*)-caffeoyl)-*β*-D-glucopyranosyl
6-fer-glc: (6-(*E*)-feruloyl)-*β*-D-glucopyranosyl

Structural formulas of 6-methoxyflavonols isolated from the aerial parts of *Tetragonia tetragonioides* [25]:
1 — 6-methoxykaempferol 3-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-7-*O*-(6‴-(*E*)-caffeoyl)- β-D-glucopyranoside
2 — 6-methoxykaempferol 3-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-(6‴ ′-(*E*)-feruloyl)-7-*O*-β-D-glucopyranoside
3 — 6-methoxykaempferol 3-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-7-*O*-β-D-glucopyranoside
4 — 6-methoxyquercetin 3-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside
5 — 6-methoxyquercetin
6 — 6-methoxykaempferol
7 — 6-methoxykaempferol 7-*O*-β-D-glucopyranoside
8 — 6-methoxykaempferol 7-*O*-(6‴ ′-(*E*)-feruloyl)-β-D-glucopyranoside

Significant activity in the deactivation of DPPH and ABTS radicals was found in 6-methoxyquercetin and 6-methoxykaempferol and its derivatives (1, 8 — in DPPH test; 7 — in ABTS test) (Table 4). At the same time, the highest potential for radical scavenging was observed in 6-methoxyquercetin and quercetin itself [25]. Correlations between the chemical structure of flavonols and their antiradical activity have been experimentally confirmed [32, 33]. There is a direct correlation between the antioxidant capacity of flavonols and the number of phenolic -OH groups and their location in their molecules [34]. The presence of a hydroxyl group in the flavonol structure at the C-3 position of the B ring represents the best target for radical attack, while the presence of an OH group at the neighbouring C-4 carbon atom (catechol structure) facilitates the detachment of a hydrogen atom [35]. Hydrogen bonds are formed between adjacent hydroxyls of the B ring, so substances with such fragments in their structure are characterised by low oxidative potential and relatively easy formation of radicals [36, 37]. Thus, the most effective radical scavengers are flavonols with a catechol structure in the B ring (quercetin and its derivatives) [25]. The main structural features of flavonols also determine their antioxidant activity as chelators of transition metal ions (iron and copper), preventing the formation of oxidants and highly reactive hydroxyl radicals that can act, for example, as initiators of lipid peroxidation or lipoxygenase reactions [38]. There is a lot of convincing evidence that the activation of lipid peroxidation is a universal pathogenetic factor responsible for the onset and development of a wide range of diseases [34, 39, 40].

Like all natural substances, flavonoids, including flavonols, can undergo various structural modifications that affect their antioxidant activity. In general, glycoside

Table 4

Antiradical activity of 6-methoxyflavonols from *T. tetragonioides* in DPPH and ABTS assays [25]

	1	2	3	4	5	6	7	8
DPPH IC_{50} (μM)	22.7	64.7	> 100	64.1	15.4	31.0	92.3	23.3
ABTS IC_{50} (μM)	> 250	176.6	> 250	208.8	13.7	21.1	31.6	123.7

Notes: 1–8 are 6-methoxyflavonols isolated from the aerial part of *T. tetragonioides* (Figure). Kaempferol and quercetin were used as "positive" controls. The IC_{50} value indicates the sample concentration required for 50% scavenging of DPPH or ABTS radicals. IC_{50} for kaempferol was 16.3 and 10.5 in DPPH and ABTS tests, respectively; IC_{50} for quercetin was 14.5 and 8.7 in DPPH and ABTS tests, respectively [25].

forms showed lower antiradical activity than aglycones in DPPH and ABTS assays. In addition, flavonols with a methoxy group at the C-6 position showed lower radical scavenging activity in DPPH and ABTS assays than those without [25]. It should be noted that various structural modifications affect the physicochemical properties of flavonoids, and this is not exclusive to flavonols. Conjugations with saccharides, i.e. glycosylation reactions, make the molecule more hydrophilic. On the other hand, methylation of free hydroxyl fragments in a flavonol molecule increases its lipophilicity [41]. The glycosidic forms of methoxylated flavonols extracted from *T. tetragonioides* combine hydrophilic and lipophilic structural functions and, although they reduce their antioxidant potential, increase their ability to penetrate membranes and stabilise membranes as well. In this case, they can act as structural antioxidants: by penetrating the hydrophobic region of membranes, flavonol molecules significantly reduce lipid mobility, which in turn reduces the efficiency of the interaction between peroxide radicals and new lipid molecules. The bioavailability of flavonoids is known to be generally low due to their rapid metabolic conversion in the intestine and liver. Methylation of free hydroxyls in the flavonol molecules can increase their resistance to metabolic transformations and contribute to improving their bioavailability [41].

The antioxidant activity of flavonoids is not only due to direct suppression of singlet oxygen and chelation of metal ions of variable valence [34, 42, 43]. They are also able to inhibit free radical generating enzymes such as xanthine oxidase and nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), inducible nitric oxide synthase (iNOS) and cyclooxygenase COX-2 [34, 42, 43], as well as to model the intracellular levels of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-px), etc.

The 6-methoxyflavonols extracted from the aerial part of *T. tetragonioides* inhibited the expression of tumour necrosis factor-α (TNF-α), interleukins IL-6, IL-1β, iNOS and COX-2 and reduced the formation of prostaglandins PGE2 and NO in lipopolysaccharide-induced RAW 264.7 macrophages [25]. Different degrees of inhibition were observed, with flavonol aglycones (6-methoxyquercetin, 6-methoxykaempferol, kaempferol and quercetin) showing higher activity than glycosides. PGE2 and NO are typical inflammatory mediators associated with various chronic diseases [44, 45]. NO is synthesised with the participation of iNOS, while PGE2 is synthesised with the participation of COX-2 [46, 47]. The cytokines IL-6, IL-1β and TNF-α are produced by macrophages and play a crucial role in stimulating and triggering the inflammatory process [45]. In this context, inhibition of pro-inflammatory mediators and cytokines plays an important role in regulating the immune system, and inhibition of iNOS and COX-2 is essential for controlling the immune response.

Using mass spectrometry and NMR, 20 additional compounds of different structures were identified in *T. tetragonioides*: 15 phenolic compounds, one of which was identified for the first time; one acyl-galactopyranosyl-glycerol; four megastigmans and their glucosides [26]. As previously shown, megastigmans and their glucosides exhibit weak DPPH radical scavenging activity. On the other hand, megastigman derivatives inhibited NO formation in rat hepatic stellate cells and RAW 264.7 macrophage cells [48, 49]. The phenolic compounds extracted from *T. tetragonioides*, including 4-hydroxybenzoic acid derivatives, phenylpropanoids, lignans and kaempferol glucoside, have been repeatedly shown to have varying degrees of antiradical activity [50, 51]. The compound first identified in *T. tetragonioides* was found to belong to the lignanamides. Various lignanamides have been experimentally shown to have potent antioxidant, anti-inflammatory, neuroprotective, anticancer and antihyperlipidemic properties *in vitro*, in cell culture and *in vivo* [52–54]. These lignanamides are thought to have significant potential for the prevention and treatment of certain chronic diseases.

Choi et al. determined the planar structure of a new compound from *T. tetragonioides* as N-2,3-dihydroxy-3-(3,4-dihydroxyphenol)-tyramine and found a catechol structure in its composition [26]. The presence of this important fragment in the molecule, which is directly involved in scavenging free radicals [50], suggested the potent antiradical activity of the new compound. In general, most of the identified phenolic compounds, especially lignanamide, may make an additional contribution to the overall antioxidant activity of *T. tetragonioides*. However, further studies such as circular dichroism analysis or X-ray crystallography are required to elucidate the true stereochemistry of the hydroxyl groups at the C-7 and C-8 positions in its molecule.

Another group of potent antioxidants in *T. tetragonioides* are carotenoids, known as effective quenchers of singlet oxygen ($^1O_2$)

and scavengers of ROS [55–57]. As highly lipophilic molecules, carotenoids are likely to be particularly effective scavengers of ROS in hydrophobic areas of cell membranes and lipoproteins, reducing the risk of oxidation of membrane structures [58]. β-carotene is a precursor of vitamin A (retinol) [57]. However, the main function of it and other carotenoids in all non-photosynthetic organisms is (photo)protection. Able to inhibit the accumulation of free radicals, β-carotene has an immunostimulatory and adaptogenic effect, protecting immune system cells from damage. The proliferative capacity of T cells is stimulated by β-carotene [59], especially in humans and animals suffering from oxidative stress due to malnutrition, disease, and old age. Carotenoids can also affect the humoral mechanisms of immunity — the synthesis and secretion of inflammatory cytokine markers [60, 61].

The ability of carotenoids to act as a protective agent against ROS has been observed in ocular disorders. Xanthophylls, such as lutein and zeaxanthin, are present in the lens of the eye and macular area of the retina (yellow spot). It is believed that their main function is to protect against high-energy ultraviolet radiation focused in the foveal region [57] and to reduce the risk of cataracts and age-related macular degeneration of the fundus [62]. The antioxidant activity of these xanthophylls is of particular importance due to the fact that biochemical processes occurring inside photoreceptors (phototransduction and oxidative phosphorylation) are important sources of ROS [63].

Due to the ability to quench singlet oxygen, carotenoids can perform a protective function in photosensitive disorders associated with the skin. It has been suggested that carotenoids (especially β-carotene and astaxanthin) can act as effective scavengers of the excited triplet states of endogenous photosensitizers, such as protoporphyrin, which accumulates in the blood and skin of patients with hereditary erythropoietic protoporphyria [64].

Although vitamin C is present in relatively small amounts in *T. tetragonioides* (Table 3), the contribution of L-ascorbic acid to the overall antioxidant effect of *T. tetragonioides* should be considered. Being water soluble, ascorbic acid easily penetrates all tissues; many reactions involving it are reversible; it actively interacts with other antioxidants and vitamins in the body [65, 66]. Ascorbic acid is an immediate-action antioxidant that directly absorbs free radicals generated during cellular metabolism [67]. Together with its metabolite dehydroascorbic acid, it forms a potent redox system that transports hydrogen ions. The mechanisms of antioxidant action of ascorbic acid include donation of hydrogen atoms to lipid radicals, quenching of singlet oxygen and removal of molecular oxygen, and regeneration of α-tocopherol from tocopheroxyl radicals [67, 68]. The stimulatory effect of vitamin C on the activity of cytochrome P-450, a key enzyme of hydroxylation and peroxidation, has been demonstrated [66]. Ascorbic acid can regulate the activity of antioxidant enzymes (GSH-px and CAT) [69] and reduce lipid peroxidation, thereby preventing oxidative stress [65, 66]. This vitamin is essential for growth and development, helps accelerate metabolic processes, increases the stability of the nervous system, and improves the condition of the skin, joints and gums [66, 70]. It strengthens the human immune system, has a positive effect on its antimicrobial activity and natural killer cell activity, lymphocyte proliferation and chemotaxis. Some cells of the immune system require vitamin C to perform their functions, in particular phagocytes and T cells [71].

The content of vitamin E (mainly α-tocopherol) in the leaves of *T. tetragonioides* is low, amounting to only 8% of the daily requirement per 100 g of leaves. α-tocopherol is a highly active antioxidant that acts in hydrophobic environments [72]. It inhibits lipid peroxidation and scavenges lipid peroxyl radicals, preventing the spread of free radical-mediated chain reactions, thereby effectively protecting biological membranes and lipoproteins from oxidation [73]. Vitamin E also protects polyunsaturated fatty acids present in membrane phospholipids and plasma lipoproteins through its peroxyl radical scavenging activity [74]. When interacting with lipid peroxyl radicals, vitamin E reduces them to hydroperoxides and, converting itself to tocopheroxyl radicals, which can be further oxidised to tocopheryl quinones [75] and excreted by the kidneys, or to the α-tocopherol radical, the restoration of which restores antioxidant properties with the participation of ascorbic acid [76]. By participating in reactions with polyunsaturated fatty acids (mainly in the arachidonic acid cascade), vitamin E prevents the formation of prostaglandins, which cause platelet aggregation and reduce inflammation [77, 78].

The effectivennes of vitamins can be significantly enhanced by combining them with certain biologically active substances. For example, the activity of lipid-soluble vitamin E in deactivating radicals in biological membranes increases synergistically in

combination with water-soluble vitamin C. The synergistic effect of hydrophobic α-tocopherol in combination with hydrophilic ascorbic acid and hydrophobic β-carotene has been observed in protection against nitroxyl radicals (RNS) [79]. The combination of two lipid-soluble antioxidants, β-carotene and α-tocopherol, inhibited lipid peroxidation more than the sum of the effects of the individual antioxidants [80]. The combined effect of α-tocopherol and zeaxanthin provided better protection against photosensitized lipid peroxidation mediated by $^1O_2$ and free radicals than the individual effect of each of these substances [81]. Thus, despite low content of vitamins C and E in the biomass of *T. tetragonioides*, their antioxidant effect may be quite high due to synergistic interactions between them and carotenoids.

Given the high vitamin K content in *T. tetragonioides*, its role (reduced form of vitamin K — hydroquinone) in protecting cells against oxidative damage by directly scavenging oxygen radicals in lipid membranes and reducing intracellular ROS levels by modulating the expression of antioxidant enzymes should be noted [21]. Polyunsaturated fatty acids in membrane phospholipids can be oxidized by ROS or by the Fenton reaction or by the activity of iron-containing redox enzymes. Oxidation leads to the accumulation of phospholipid hydroperoxides in cell membranes, which can cause ferroptosis. Ferroptosis is a form of programmed cell death characterized by the accumulation of iron and lipid hydroperoxides in cells [82, 83]. Vitamin K effectively inhibits lipid peroxidation and indirectly prevents ferroptosis. Vitamin K also has an anti-inflammatory effect by reducing the production of pro-inflammatory cytokines [84], which is a key factor in several chronic diseases and age-related disorders.

T. tetragonioides for treating and preventing various chronic and age-related diseases associated with oxidative stress

The presence of 6-methoxyflavonols in *T. tetragonioides*, mainly 6-methoxykaempferol derivatives [25], has been shown to be useful in the treatment and prevention of various chronic diseases and age-related disorders associated with oxidative stress. The pharmacological properties of *T. tetragonioides* have long been recognised and used in alternative medicine in some countries. For example, in Oriental medicine *T. tetragonioides* is actively used to treat gastric hypersecretion, dyspepsia, gastric ulcers and gastritis, and even gastric cancer [85–87]. The effectiveness of the protective effects of *T. tetragonioides* against various diseases has been demonstrated in *in vitro* and *in vivo* experiments.

In particular, numerous preclinical studies have shown that kaempferol and some of its glycosides present in the leaves of *T. tetragonioides* have a wide pharmacological spectrum of activity, including antioxidant, anti-inflammatory, antimicrobial, antitumour and neuroprotective effects [88]. Kaempferol has also been shown to have a high anti-diabetic potential — due to its antioxidant activity it improves glucose absorption [89, 90]. In a study of the effect of five types of flavonols on the levels of triglycerides (TG), cholesterol and low-density lipoprotein (LDL) in blood serum after administration to mice fed a high-fat diet and affected by diabetes, the most significant reduction in levels was found with those compounds containing kaempferol [91]. In addition, the antiadipogenic effect of kaempferol has been shown on pre-adipocyte cells of 3T3-L1 mice [91].

In this context, the consumption of *T. tetragonioides* with a significant content of 6-methoxykaempferol derivatives by diabetic mice improved blood circulation, reduced inflammation and blood lipids, inhibited fat synthesis and reduced plasma uric acid levels, showing anti-obesity, hyperlipidemic and hyperuricemic effects [92]. The beneficial effect of T. tetragonioides on lipid metabolism in rats was confirmed in studies modelling testosterone and progesterone levels. Consumption of *T. tetragonioides* by rats for four weeks resulted in a decrease in total cholesterol, TG and LDL in blood serum without a decrease in hormone levels [93]. Since complications in lipid metabolism due to a decrease in testosterone can lead to cardiovascular and cerebrovascular disease [94], the use of *T. tetragonioides* may serve as an adjunct to reduce the risk of developing these pathologies.

Encouraging results have been obtained in trials of *T. tetragonioides* preparations for the correction of metabolic disorders that may occur with age-related changes in hormonal status. The addition of *T. tetragonioides* extract to the diet of ovariectomised rats fed a high-fat diet reduced insulin resistance and improved glucose absorption [95]. Pancreatic β-cells are known to be particularly sensitive to oxidative stress, which can lead to the dysfunctional conditions characteristic of

diabetes [34]. Consumption of *T. tetragonioides* prevented a decrease in b-cell mass and even led to an increase, which in turn increased insulin secretion. It is believed that an increase in cell mass of pancreatic islets as a result of the use of the plant extract is associated with increased proliferation of b-cells and inhibition of apoptosis due to a decrease in the expression of inflammatory cytokines [95]. *T. tetragonioides* has also been shown to reduce the symptoms of depression associated with fluctuations in estrogen levels. The antidepressant activity of *T. tetragonioides* was mediated by increasing serum serotonin levels and regulating serotonin reuptake activity [96].

The introduction of *T. tetragonioides* also had a positive effect on the gut microbiome, as it contains a significant amount of vitamins, minerals (Table 2, 3), pectin polysaccharides and polyphenolic compounds [8], which promote the development of beneficial microbes in the gut and reduce the number of harmful bacteria. Dysbiosis of the gut microbiota leads to systemic chronic inflammation, which in turn can lead to neuroinflammation, cerebral oedema and ultimately neuronal dysfunction [97–99]. Neuroinflammation, increased oxidative stress in brain cells and insulin resistance in the brain are implicated in the neurotoxic accumulation of amyloid [100–102] and phosphorylation of tau-protein leading to the development of Alzheimer's disease [103, 104]. There is some experimental evidence that the use of *T. tetragonioides*, having a positive effect on the gut microbiota, may help to improve memory deficits and alleviate the symptoms of dementia. An analysis of the microbiota in rats injected with β-amyloid into the hippocampus to induce Alzheimer's disease and fed a high-fat diet to exacerbate insulin resistance showed that consumption of *T. tetragonioides* reduced the number of Desulfovibrionales, Enterobacteriales, Erysipelotrichales and Clostridiales and increased the number of Lactobacillales and Bacteroidales [105]. In addition, the inclusion of *T. tetragonioides* in the diet of amyloid rats led to a reduction in the expression of inflammatory cytokines, reduced insulin resistance in the brain and improved the transmission of insulin signals in the hippocampus, as well as inhibiting the phosphorylation of tau-proteins and reducing their content [105].

Positive results regarding the antitumour properties of *T. tetragonioides* were obtained in experiments on ICR mice inoculated with Sarcoma 180, which was a preliminary step towards the development of effective antitumour agents using *T. tetragonioides* [106].

Thus, *T. tetragonioides*, which is a source of mineral elements and various biologically active substances, can serve as a valuable addition to a balanced diet for maintaining good health and may also be a promising tool for the treatment and prevention of various chronic diseases and metabolic disorders.

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БІОАКТИВНІ СПОЛУКИ ТА ФАРМАКОГНОСТИЧНИЙ ПОТЕНЦІАЛ *Tetragonia tetragonioides*

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За останні роки у зв'язку зі зростаючою резистентністю патогенів до синтетичних антимікробних препаратів збільшується застосування високоактивних рослинних сполук, що довели свою ефективність у практиках народної медицини. Екстракти лікарських рослин часто містять унікальну видоспецифічну комбінацію активних речовин, що мають синергічний терапевтичний ефект. Тому аналіз біохімічного складу рослин, що вводяться в культуру, і діапазону їхнього можливого біотехнологічного застосування, є актуальним.

Мета. Узагальнити відомості щодо потенціалу ксерофітної рослини *Tetragonia tetragonioides* як джерела функціональних харчових інгредієнтів і біологічно активних речовин, які підвищують неспецифічну стійкість організму і сприяють профілактиці та лікуванню різних захворювань.

Результати. *T. tetragonioides* — сольостійка і термовитривала рослина, що містить цінні поживні і біологічно-активні речовини, значну кількість вітамінів, мінеральних елементів, харчові волокна. Високий рівень антиоксидантних сполук, зокрема флавоноїдів та каротиноїдів, сприяє зниженню ризику розвитку дегенеративних патологій, пов'язаних з надмірним окислювальним стресом. Унікальний комплекс біологічно-активних речовин *T. tetragonioides*, що містить 6-метоксифлавоноли, переважно похідні 6-метоксикемпферолу, а також мегастигмани та їхні глюкозиди, лігнанамід забезпечує значну антиоксидантну, протизапальну, протипухлинну та протимікробну активність і може бути корисним для профілактики хронічних захворювань і вікових проблем зі здоров'ям. Ефективність *T. tetragonioides* продемонстрована на моделях тварин у лікуванні метаболічних порушень таких, як ожиріння, гіперліпідемія та гіперурикемія.

Висновки. *T. tetragonioides*, що містить специфічний комплекс біологічно активних сполук, насамперед 6-метоксифлавонолів, може бути перспективною сировиною для одержання ефективних лікарських препаратів для лікування і профілактики різних хронічних захворювань і метаболічних порушень.

Ключові слова: *Tetragonia tetragonioides*, поживний та біохімічний статус, антиоксиданти, терапевтична активність, протизапальна активність.