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Review

POSSIBILITIES OF PLANT PREPARATIONS USE FOR COLLAGEN STRUCTURE AND METABOLISM DISTURBANCES CORRECTION: MODERN STATE OF PROBLEM

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The review summarizes information on possibilities of plant preparations use for collagen structure and metabolism disturbances correction. Biologically active compounds of plant origin can both stimulate and inhibit the biosynthesis of various types collagens, accelerate or slower down their catabolism, regulate the activity of enzymes involved in the collagen's metabolism. Most of the studied compounds realize their effects simultaneously by several mechanisms. Among them, the most common are the direct influence of the substance on the processes of collagen genes expression and indirect influence via TGF-beta1- pathway. In addition, a fairly common are effects on collagen synthesis by changing organism's pools of free amino acids (as the starting compounds for this protein synthesis) and by regulation of hydroxylases (performing collagen post-translational modifications and crosslinking). Besides TGF-beta1 others cytokines can also be involved in the processes of collagen metabolism regulation by compounds of plant origin. In particular, this is characteristic of triterpenes and phytoestrogens. Such a variety of methods for collagens metabolism regulation creates a wide range of possibilities for developing new preparations based on extracts or pure plant compounds able to correct connective tissue collagen structure and metabolic disorders with minimal adverse effects. Fundamentally different possibilities for the influence of plant organisms on collagens are opened with the use of genetically modified plants. Recombinant collagens allow to obtain proteins with new programmed features, making it possible to synthesize proteins with predetermined properties for medical use.

Keywords: plant preparations; collagen structure; collagen metabolism; disturbances correction; recombinant collagens.

Introduction

Among human conventional chemical exposures an important role belongs to modern medicines, whose use in various combinations is increasing year by year. The problem is that, along with their curative activities, these compounds also have wide spectra of adverse effects [1]. Such effects belong to the top 10 leading causes of death and illness in developed countries [2].

The severity of medicines negative effects on the organism largely depends on genotype, age, sex, race, pathology, drug category, route of administration, and drug–drug interactions. Undesirable influences of whole drug combinations may differ from the separate drug combination components side effects [3]. In this case, it is both possible to increase the negative effects of the components with combined administration, and their weakening. There are also cases of the emergence of fundamentally new adverse reactions when combining medicines.

The more serious is the disease, the higher is the probability of using a drugs combination with a different spectrum of side effects, which can aggravate the state of patients. Therefore, it is quite understandable, that pharmacologists strive to find among the preparations of plant origin, compounds that can cause a mild pharmaceutical effect without rude disturbing the metabolic processes in the cell [4].

This is especially important for agents able to correct connective tissue collagen structure and metabolic disorders, which accompanying many systemic diseases such as diabetes, neoplastic processes, cardiovascular and autoimmune diseases [5].

Unfortunately reports concentrating on the effects of plants-derived compounds on collagen structure and metabolic disorders are very scanty [6, 7]. Basically, such studies in the last half century have been focused on ascertaining the fact of the presence of a certain activity in one or another dosage form based on plant materials.

The second large group of publications is works devoted to little-studied endemics of Africa, South America and Asia biological activities. Such works are often carried out by local scientists from developing countries in laboratories whose material base does not allow for more in-depth studies of these plant compounds effects on the structure and function of various types of collagens. Their research is mainly limited to isolating the total fraction of biologically active substances from representatives of the local flora and testing their medicinal properties. In isolated cases, it is possible to identify individual compounds responsible for a certain type of biological activity [6–8].

The small number, fragmentation and lack of consistency in the study of herbal preparations effects on collagen structure and functions did not allow obtaining a complete picture of the available information in this area of research to date.

The aim of the present study was to summarize all the accumulated information and to evaluate possibilities of herbal preparations and their phytochemical constituents for collagen structure and metabolic disorders treatment.

Herbal preparations for collagen anabolism regulation

The greatest amount of research is devoted to the ability of herbal preparations to regulate collagen biosynthesis.

Many phytochemicals demonstrated positive activity at collagen synthesis stimulation [9]. A number of attempts were made to identify the active constituents responsible for stimulation of enhanced collagen production with simultaneous identification of chemical structures responsible for this activity [10].

Metabolism of collagens is complex process and requires understanding of multiple interactions with several agents. It was shown that *Allium sativum*, *Aloe vera*, *Centella asiatica*, and *Hippophae rhamnoides* are characterized by the best activity among herbal monopreparations [10]. The active ingredients obtained from the plant materials have been analyzed for the presence of alkaloids, carbohydrates, glycosides, terpenoids, diterpenes, sesquiturpenes and phytosterols, phenolic compounds and multiple kinds of tannins, proteins, flavonoids, saponins, lignins, alkaloids and essential oils. Exact structure activity relationships are not yet understood. Extracts from *Achillea biebersteinii*, *Achillea kellalensis* and *Punica granatum*, *Adhatodavasica*, *Alkanna tinctoria*, *Annona squamosa*, *Arnica Montana* and *Artemisia absinthium*, *Bauhinia purpurea*, *Bulbine frutescens* and *Bulbinenatalensis*, *Butea monosperma*, *Calotropis gigantea*, *Capparis zeylanica*, *Cassia occidentalis*, curcumin from *Curcuma longa*, *Desmodiumgangeticum*, *Elaeisguineensis*, *Elephantopusscaber*, *Eucheuma cottonii*, *Ficus racemosa*, *Gynura procumbens*, *Heliotropium indicum*, *Hyptissuaveolens*, *Indigofera asphalathoides*, *Jasminum sambac*, *Kalanchoe pinnata*, *Leonotisnepetaefolia*, *Martynia annua*, *Moringa oleifera*, *Nigella sativa* caused increased DNA production and total collagen synthesis. However, in all these cases individual specific chemical entities having such activity have not been found. Enhanced collagen synthesis in all these cases probably was a result of synchronized action of multiple active ingredients present in the phytoextracts [10].

Interesting data was obtained in experiments with *Aronia melanocarpa* extracts and *Oenanthe javanica* extracts [11]. High performance liquid chromatography (HPLC) analysis data allowed to determine main active ingredients – chlorogenic acid and rutin. Active compounds of *Aronia melanocarpa* extracts significantly increased collagens type I and III biosynthesis with simultaneous significant decreasing levels of matrix metalloproteinase MMP-1 and 3. Chlorogenic acid protected keratinocytes and fibroblasts from negative exogenic factors damage via scavenging reactive oxygen species (ROS) including superoxide anion and hydroxyl radicals. Rutin protected this cell via enhancing ROS scavenging activity via inhibiting cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). Researchers supposed that both compounds could act by reducing ROS-induced DNA damage and superoxide anion production, elevating antioxidant enzyme expressions in collagen-synthesizing cells and inhibition of matrix metalloproteinases activity, resulting in suppression of collagen degradation and of extracellular matrix destruction.

Olea europaea leaf extract (Linefade complex) containing 1.6% oleanolic acid and 0.4% of other compounds (maslinic acids, oleuropein, oleuropeoside, ligustroside and hydroxytyrosol) [12] induced collagen IV synthesis *in vitro* and *ex vivo*. This lipidic mixture realized its activity via stimulation of collagen IV biosynthesis. *Hydnophytum formicarum* extract influences on collagen density and biosynthesis, stimulates fibroblast activities [13].

Bambara groundnut (*Vigna subterranea*) extracts, containing different flavonoids, phenols, phenolic glycosides, saponins, tannins, xanthones, alkaloids and terpenoids saponins [14] stimulated

collagen biosynthesis by human dermal fibroblasts possibly due to these compounds. Its effect of collagen stimulation might be caused by decreasing collagenase activity of a metalloproteinase enzymatic complex.

The formula herbal extract (PH) mixed with *Equisetum arvense* (Equisetaceae), *Achillea millefolium* (Asteraceae), *Echinacea purpurea* (Asteraceae) and *Hyssopus officinalis* (Lamiaceae) containing such phenolic compounds as chlorogenic acid, caffeic acid, luteolin and apigenin, also caused increase in collagen synthesis on L929 mouse fibroblasts cell line [15].

Glycine max seeds extract and fresh soymilk fractions also demonstrate collagen stimulating effect [15]. Pycnogenol is a French maritime pine bark extract produced from the outer bark of *Pinus pinaster Ait. subsp. atlantica*. It has strong antioxidant, anti-inflammatory and vasodilator activities, antithrombotic effects and collagen stabilizing properties [16]. Aloe vera increases collagen formation and inhibiting collagenase [17]. *Labisia pumila* extract promotes skin collagen synthesis [18]. Preparations from *Eucommia ulmoides Oliv* (Eucommiaceae) bark and leaves as soon as *Eleutherococcus senticosus Maxim (Acanthopanax senticosus Harms)* bark of the root and the stem promote collagen synthesis [19]. Chinese medicinal herbs including DuhuoJisheng decoction (DHJST), BuyangHuanwu decoction (HYBWT), ShentongZhuyu decoction (STZYT), TaohongSiwu decoction (THSWT), Yanghe decoction (YHT) and TongduHuoxue decoction (TDHXT) cause collagen synthesis enhancement [20]. The overproduction of insoluble collagen and decreased degradation of collagen occur as a result of exposure to *Areca* nut extracts via stimulation of the *transforming growth factor* TGF-β pathway of the cell signaling [21].

Herbal preparations for collagen catabolism regulation

A few smaller numbers of publications are devoted to herbal preparations that have a retroactive effect. Collagen catabolism regulation was demonstrated with extracts from grapes, berries and especially in the dried roots of *Polygonum cuspidatum-Sieb. et Zucc* [22].

Red sage (*Salvia miltiorrhiza Bunge*), or Danshen in Chinese, has long been used in combination with other herbal medicines for the treatment of skeletal diseases in traditional Chinese medicine (TCM) [23]. So far, more than 100 individual compounds have been extracted from this plant and tested in different *in vivo* and *in vitro* experiments (animal models and biochemical assays). Test items showed anti-resorptive and bone formation-stimulating effects targeting different pathways in the bone remodeling cycle (the activation of osteoblasts, the modulation of osteoclastogenesis, and the inhibition of collagen degradation) [23].

Silymarin (standardized mixture of flavonolignanes) was found to cause reduction of collagen synthesis [24].

The extracts of pomegranate peels and seeds can decrease the level of TGF-β1 and inhibit collagen synthesis [25].

In addition to direct study of collagen metabolism indices, the attention of scientists was also drawn to collagenases and hydroxylases regulating its metabolism. There are several publications devoted to herbal preparations effects on these enzymes.

Thus, *Aloe vera* preparations demonstrate ability to inhibit collagenases activities [17]. Persimmon leaf *(Diospyros kaki folium)* extracts also demonstrate such ability with simultaneous activation of elastase [26]. Areca nut extracts cause disruption of the equilibrium between matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMP) [27].

Collagen crosslinking was studied in C57BL/6 mice [28]. Six groups of young and adult mice received vitamin C, vitamin E, vitamins C and E, blueberry, green tea extract (GTE), or no treatment for a period of 14 weeks. Collagen glycation remained unchanged by the treatment. However, GTE or vitamins C and E (combined) blocked collagen crosslinking at mice 10 months of age ($p < 0.05$, adult group). Green tea extract also blocked fluorescent products at 385 and 440 nm ($p = 0.052$ and $p < 0.05$, respectively) and tended to decrease skin pentosidine levels. These results suggest that green tea is able to delay collagen crosslinking by an antioxidant mechanism that is in part duplicated by the combination of vitamin Cand E.

Herbal preparations for collagen – cell interactions regulation

Several publications are devoted to the influence of herbal preparations on various cell-signalling molecules interaction with collagen fibrils. Cocoa preparations inhibited epinephrine-collagen and adenine dinucleotide (ADP)-collagen induced primary hemostasis [29]. Higenamine (benzylisoquinoline alkaloid isolated from *Aconiti*

tuber) also inhibits ability of collagen to induce platelet aggregation [30]. The same activity has aged garlic extract [31]. In oriental countries, some medicinal plants have been claimed for uses to improve circulation, induce fibrinolysis or prevent thrombosis. Some of them act as collagen-receptor antagonists [32].

Experiments on cell cultures have been demonstrated that *Smilax glabra* Roxb (SGR) suppresses collagen induced adhesion and migration of PC3 and LNCaP prostate cancer cells by oppression of Beta 1 integrin expression [33].

SGR has been used as a traditional Chinese medicine for brucellosis and syphilis. Its water extracts (in doses 100 μg/mL for PC3 and 50 μg/mL for LNCaP) attenuates interaction between collagen and PC3 and LNCaP cells. PC3 and LNCaP cells (pretreated with *Smilax glabra* water extracts) and those cells that were not treated were loaded to the upper side of a Transwell chamber and incubated in a CO_2 incubator. Investigated extract did not inhibit the PC3 and LNCaP cells migration to the serum-coated area. However, the migration of PC3 and LNCaP cells to the collagen-coated bottom area was dose dependently attenuated by *Smilax glabra* water extract treatments. It attenuated direct interactions between collagen and prostate cancer cells, significantly inhibited collagen-dependent PC3 and LNCaP cell adhesion, gen-dependent PC3 and LNCaP cell adhesion. Among this *Smilax glabra* water extract regulates expression of α2β1 integrin, which is a known receptor for collagen in PC3 and LNCaP cells. It was demonstrated that integrin-dependent signaling could be effectively inhibited by *Smilax glabra* water extract to slow PC3 and LNCaP cells adhesion to collagen-rich extracellular matrix regions. Further investigations allowed to determine 5-O-caffeoylquinic acid as a single functional anti-adhesive component of *Smilax glabra* water extract.

The similar effect was previously found in experiments with water extract of *Gleditsia sinensis* Thorn [34]. This extract also slowed down the collagen-based migration of PC3 prostate cancer cells by oppression of $\alpha_2\beta_1$-integrin expression. Using the Boyden chamber migration assay, it was shown that non-toxic levels of *Gleditsia sinensis water extract* could not attenuate the PC3 migration to the bottom area coated with serum but significantly inhibited PC3 cell migration to the collagen-coated bottom area. It also significantly attenuated collagen against adhesion. Researchers noted that the expression of α_2-integrin but not that of β_1-integrin was significantly inhibited by the administration of *Gleditsia sinensis water extract*, leading to the inhibition of focal adhesion kinase (FAK) phosphorylation. *In vivo* experiments on nude mice demonstrated that, oral administration of this extract (25 mg/kg/day) significantly inhibited the size of a PC3 cell-xenografted tumor.

Herbal pure substances effects on collagen

As for the biological effects of pure substances of plant origin and their mechanisms of action on the collagen metabolism, number of such publications is much smaller and they are very scattered. The most investigated among these compounds are vitamins.

For example, it was demonstrated that vitamin C served as a cofactor in the synthesis of collagen [35]. Ascorbic acid also markedly stimulates collagen synthesis in dependently to its cofactor roles for hydroxylation of lysine and proline [36]. Human fibroblasts grown in the absence of ascorbate produced 30% less collagen [37]. This protein was under-hydroxylated and its degradation was increased from 16% (basal level) to 49% due to disturbed triple-helical conformation causing it to be susceptible to intracellular degradation. The enzyme-linked immunosorbent assay (ELISA) tests showed that both types I and III collagens synthesis were regulated by ascorbic acid.

According to other scientists' data L-ascorbic acid stimulates procollagen synthesis in cultured human skin fibroblasts without influence on intracellular degradation of newly synthesized procollagen [38, 39]. Levels of mRNA for pro alpha 1(I), pro alpha 2(I), and pro alpha 1(III), as soon as levels of procollagen functional mRNA are increased in the presence of ascorbic acid. Ascorbic acid obviously can control the expression of three different procollagen genes, located on separate chromosomes (translational level of procollagen synthesis regulation). At post-translation level it promotes hydroxyproline formation and cross-linking with hydroxylisine. Authors noted that the control point at the level of gene transcription or mRNA degradation also could not be excluded.

Among this ascorbic acidhas been shown to stimulate collagen synthesis through induction of lipid peroxidation leading to increased transcription of the collagen genes via transforming growth factor-beta and fibroblast growth factor mediated mechanism [40]. Vitamin C stimulating influence on collagen synthesis can be realized due to inhibiting of extracellular signal-regulated kinase [41]. Formation of collagen triple helices is also regulated

by ascorbic acid via induction of the synthesis of osteoclast differentiation factor – receptor activator of NF-κB (RANK) ligand (RANKL)/osteoprotegerin (OPG) [42]. Recent data on vitamin C involvement in cell signaling and collagen gene expression open new perspectives for its pharmacological use [43].

Alpha-tocopherol (50 μM) prevents the stimulation of collagen gene expression [44]. L-ascorbic acid and Trolox (a water-soluble vitamin E) regulate matrix metalloproteinase (collagenase) MMP-1 functioning [45].

Vitamin E prevents collagen oxidation and degradation [46]. It significantly inhibits renal collagen deposition and reduces hydroxyproline content [47]. The mechanism of its action is mediated by TGF-β1. Transforming growth factor-β1 (TGF-β1) transduces its signal by binding to TGF-β type 1 receptor kinase or activin-like kinase (ALK5) receptor and increase the transcription of collagen via Smad2 and Smad3.

Several genes that modulate the expression of extracellular proteins (tropomyosin, α_1-collagen, MMP-1, MMP-19, connective tissue growth factor) are regulated by tocopherols [48]. Several mechanisms may underlie tocopherol-dependent gene regulation:

– protein kinase C-mediated (due to its deactivation by alpha-tocopherol),

– by direct involvement of pregnane X receptor PXR/retinoid X receptor RXR,

– antioxidant responsive element and transforming growth factor beta responsive element (TGF-beta-RE)-mediated.

But the central signaling mechanism remains unclear.

Tocotrienols, members of the vitamin E family, which exist in four different isoforms (α, β, γ, and δ tocotrienol) modulate collagens (type I and III) and collagenases synthesis (MMP-1), as well as their genes expression in human skin fibroblasts [49, 50]. Tocotrienols supplementation down-regulates the expression of TGF-δ, fibronectin and collagen type IV in rats [51].

Oral administration of the antioxidant mixture of vitamin C, vitamin E, pycnogenol, and evening primrose oil influence on collagen metabolism through inhibition of collagen-degrading matrix metalloproteinases activity or through enhancement of procollagen synthesis [52].

Nicotinamide (vitamin B_3) cause changes in amino acids content of bone collagen [53]. Such effect could be realized both directly (on the level of gene expression) and indirectly via influence on free amino acids pools [54].

Flavonoids, alkaloids, saponins and phenolic compounds are active constituents present in different herbs facilitating collagen synthesis and fibrils formation [8, 9]. Such activity demonstrates vitamin P (vegetable polyphenol) [55].

Polyphenols from Persimmon leaf regulate collagen synthesis and collagenases activities [26]. Such plant polyphenols as gallic acid, elaeocarpusin, pedunculagin, and ellagitannin enhance collagen production and inhibit collagenase and elastase activities in the fibroblasts [56].

Phytoestrogens stimulate bone formation, increase levels of alkaline phosphatase, osteocalcin, osteopontin, and α_1(I) collagen, suppress the rate of bone resorption and enhance the rate of bone formation [57].

The effects of genistein (soy isoflavone phytoestrogen) on collagen and DNA biosynthesis (measured by the 5-[^{3}H]proline and the [^{3}H]thymidine incorporation assays) were examined in normal human dermal fibroblasts (CRL-1474) [58]. At 10 μM, genistein had protective effect on collagen biosynthesis in fibroblasts, while at 100 μM it induced inhibition of this process. The protective effect of genistein on collagen biosynthesis was not related to modulation of prolidase activity or the expression of the beta1-integrin receptor, focal adhesion kinase FAK, proto-oncogene, non-receptor tyrosine kinase Src or growth factor receptor-bound protein Grb2. The mechanism of genistein effect on collagen biosynthesis in these experiments may be due to prevention of disturbances in the insulin-like growth factor IGF-I receptor-mediated, extracellular signal-regulated kinases ERK1/ERK2-associated signaling pathway.

Triterpenes from *Centella asiatica* can modulate collagen biosynthesis avoiding slower scarring or faster, hyperthrophic scarring and cheloids [59]. Ginsenoside Rg3 (steroid glycoside and triterpene saponin) at concentrations 50 or 100 μg/ml inhibits keloid fibroblast proliferation, angiogenesis and collagen synthesis *in vitro* via the TGF-β/Smad and ERK signaling pathways [60].

Component of licorice 18α-glycyrrhetinic acid down-regulates expression of type I and III collagen via TGF-B1/Smad signaling pathway in human and rat hepatic stellate cells due to down-regulation of Smad3, up-regulation of Smad7, and inhibition of DNA binding activities of specificity protein SP-1, activator protein AP-1 and nuclear factor kappa B NF-κB [61]. Glycosides (madecas-

sosides, asiaticosides) are among the main active components facilitating collagen synthesis and fibrils formation [8, 9]. Asiaticosides can inhibit *transforming growth factor* TGF-β expression, collagen synthesis, effectively up-regulate the expression of Smad7 protein [62].

Another heterocyclic compounds such as chlorogenic acid and its derivatives regulated collagen biosynthesis [11, 33]. 5-O-caffeoylquinic acid can inhibit collagen induced adhesion and migration of cells via beta 1 integrin expression inhibiting [33].

Lignans and iridoid glycosides from *Eucommia ulmoides* bark, *Eucommia ulmoides* leaves, and Siberian ginseng also can regulate collagen synthesis [18]. Other lignin – phyllanthin – isolated from the plant *Phyllanthus amarus*, inhibit collagen synthesis by down-regulating *transforming growth factor* TGF signaling pathway via ALK5, Smad-2 and -3 inhibition [63]. Lignans from the bark of *Eucommia ulmoides* inhibit mRNA and protein expression of collagen type I (Col I), collagen type III (Col III), collagen type IV (Col IV) in mesangial cells [64].

Cinnamophilin (from *Cinnamomum philippinense*) inhibited collagenases MMP-1 and MMP-13 expressions in IL-1β-treated chondrocytes simultaneously by two mechanisms (NF-κb or ERK/p38 MAPK inhibition and/or p-c-Jun pathway repressing) [65]. Licarin E regulates MMP-1 expression by inactivating mitogen-activated protein kinases (MAPKS) and increases type-1 procollagen expression by stimulating transforming growth factor β (TGFβ)/Smad signaling [66]. Flavonolignan silymarin was found to inhibit collagen synthesis at the level of DNA/RNA-mediated effects [24]. Silymarin may be a natural multi-functional and multi-target drug.

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a phytoalexin contained in a variety of plants. It significantly stimulates the expression of collagen type II at the mRNA [67].

Alkaloids from areca nut are the most important biologically for collagen metabolism regulation whilst tannin may have a synergistic role. These chemicals appear to interfere with the molecular processes of deposition and/or degradation of extracellular matrix molecules such as collagen [27, 68]. *In vitro* studies on human fibroblasts with chemically purified arecoline established its ability to increase collagen formation that is also demonstrable histologically in human fibrosis tissues. Increased collagen synthesis could be a result of not only expression of collagen genes, but also of disruption of the equilibrium between matrix metalloproteinases and their tissue inhibitors [27].

Curcumin (diferuloylmethane) from *Curcuma longa* can reduce the expression of collagen IV [69]. Curcumin inhibits the IL-1β-induced activation of NF-κB and suppresses IκBα phosphorylation and p65/RelA nuclear translocation. It causes inhibition of matrix metalloproteinase MMP-13 expression and stimulation of type II collagen expression via NF-κB – mediated mechanism [70].

Alkaloid capsaicin(8-methyl-*N*-vanillyl-6-nonenamide), an active component of plants belonging to the genus *Capsicum*, significantly influences on the molecular stability, self-assembly, and fibril stability of type I collagen. It can suppress collagen fibril formation, increase of collagen fibers stability and protects them from enzymatic degradation [71].

Different fatty acids (especially unsaturated and hydroxylized) have been shown to act as stimulators of collagen synthesis and inhibitors of collagen degrading matrix metalloproteinase-1 and matrix metalloproteinase-3 [12].

Collagens from genetically modified plants

Fundamentally different possibilities for the influence of plant organisms on collagens are opened with the use of genetically modified plants [72].

Currently, several plant systems are known to express collagen type I genes [73–75]. These genes were successfully transduced into such well-studied and long-used in genetic engineering plants as maize (*Zea mays*) and tobacco plants(*Nicotiana tabacum*).

It became possible not only to accurately reproduce the primary structure of collagen type I molecule both α and β strands, but also to achieve their post-translational self-assembly into triple helixes of collagen microfibrils [76]. These collagens had thermostability, resistance to protease activity up to 39 °C, abilities to cellular adhesion, binding and interaction with different types of cells similar to native collagen [77, 78].

In vivo experiments demonstrated that collagen type I synthesized by a tobacco recombinant system significantly better interacts with living tissues than collagens isolated from animal sources [79].

Recombinant collagens allow to obtain proteins with new programmed features, making it possible to create proteins with predetermined properties, with a certain number of sites responsible for cell adhesion or nucleation centers for hy-

droxyapatite crystals formation to regulate the ossification of collagen implants.

Taking into account collagen genes polymorphism not only with pathologies but also in norm [80, 81] different genes from the same collagen type I superfamily transcription rates regulation (as it was previously demonstrated for osteogenesis imperfecta [82, 83]) opens new possibilities in the creation of medical agents directly stimulating wound healing and new bones accelerated formation.

Conclusions

Thus, biologically active compounds of plant origin can both stimulate and inhibit the biosynthesis of various types collagens, accelerate or slower down their catabolism, regulate the activity of enzymes involved in the collagen's metabolism. Most of the studied compounds realize their effects simultaneously by several mechanisms. Among them, the most common are the direct influence of the substance on the processes of collagen genes expression and indirect influence via TGF-β1-pathway. In addition, a fairly common are effects on collagen synthesis by changing organism's pools of free amino acids (as the starting compounds for this protein synthesis) and by regulation of hydroxylases (performing collagen post-translational modifications and crosslinking). Besides TGF-β1 and others cytokines can be involved in the processes of collagen metabolism regulation by compounds of plant origin. In particular, this is characteristic of triterpenes and phytoestrogens. Such a variety of methods for collagens metabolism regulation creates a wide range of possibilities for developing new preparations based on extracts or pure plant compounds able to correct connective tissue collagen structure and metabolic disorders with minimal adverse effects.

Fundamentally different possibilities for the influence of plant organisms on collagens are opened with the use of genetically modified plants. Recombinant collagens allow to obtain proteins with new programmed features, making it possible to synthesize proteins with predetermined properties for medical use.

Interests disclosure

Larysa Bondarenko is the member of the Editorial Council of *Innovative Biosystems and Bioengineering* and was not involved in the editorial evaluation or decision to accept this article for publication. The other authors have no conflicts of interest to declare.

References

[1] Zazzara MB, Palmer K, Vetrano DL, Carfм A, Onder G. Adverse drug reactions in older adults: a narrative review of the literature. Eur Geriatr Med. 2021;12(3):463-73. DOI: 10.1007/s41999-021-00481-9

[2] Cacabelos R, Naidoo V, Corzo L, Cacabelos N, Carril JC. Genophenotypic factors and pharmacogenomics in adverse drug reactions. Int J Mol Sci. 2021;22(24):13302. DOI: 10.3390/ijms222413302

[3] Elliott WJ, Bistrika EA. Perindopril arginine and amlodipine besylate for hypertension: a safety evaluation. Expert Opin Drug Saf. 2018;17(2):207-16. DOI: 10.1080/14740338.2018.1397129

[4] Hasnain A, Naqvi SAH, Ayesha SI, Khalid F, Ellahi M, Iqbal S, et al. Plants in vitro propagation with its applications in food, pharmaceuticals and cosmetic industries; current scenario and future approaches. Front Plant Sci. 2022;13:1009395. DOI: 10.3389/fpls.2022.1009395

[5] Bondarenko LB. Structure and metabolism of collagens in various pathologies. Ukr Biokhim Zh. 1998;70(3):12-23.

[6] Kavitha O, Thampan RV. Factors influencing collagen biosynthesis. J Cell Biochem. 2008;104(4):1150-60. DOI: 10.1002/jcb.21728

[7] Ren J, Yang M, Xu F, Chen J, Ma S. Acceleration of wound healing activity with syringic acid in streptozotocin induced diabetic rats. Life Sci. 2019;233:116728. DOI: 10.1016/j.lfs.2019.116728

[8] Golembiovska OI, Galkin AY, Besarab AB. Development and validation of a dissolution test for ursodeoxycholic acid and taurine from combined formulation. Sci Study Res Chem Chem Eng Biotechnol Food Industry. 2019;20(3):377-94.

[9] Bahramsoltani R, Farzaei MH, Rahimi R. Medicinal plants and their natural components as future drugs for the treatment of burn wounds: an integrative review. Arch Dermatol Res. 2014;306(7):601-17. DOI: 10.1007/s00403-014-1474-6

[10] Ghosh PK, Gaba A. Phyto-extracts in wound healing. J Pharm Pharm Sci. 2013;16(5):760-820. DOI: 10.18433/j3831v

[11] Her Y, Lee TK, Kim JD, Kim B, Sim H, Lee JC, et al. Topical application of Aronia melanocarpa extract rich in chlorogenic acid and rutin reduces UVB-induced skin damage via attenuating collagen disruption in mice. Molecules. 2020;25(19):4577. DOI: 10.3390/molecules25194577

[12] Majewski GP, Singh S, Bojanowski K. Olive leaf-derived PPAR agonist complex induces collagen IV synthesis in human skin models. Int J Cosmet Sci. 2021;43(6):662-76. DOI: 10.1111/ics.12742

[13] Ananda N, Ariawan D, Juniantito V. Effects of the Hydnophytumformicarum plant extract on collagen density, angiogenesis, wound length, and re-epithelialization in wound healing: Experimental study on rats. Dent Med Probl. 2022;59(1):67-73. DOI: 10.17219/dmp/140208

[14] Chutoprapat R, Malilas W, Rakkaew R, Udompong S, Boonpisuttinant K. Collagen biosynthesis stimulation and anti-melanogenesis of bambara groundnut (Vigna subterranea) extracts. Pharm Biol. 2020;58(1):1023-31. DOI: 10.1080/13880209.2020.1822419

[15] Waqas MK, Akhtar N, Mustafa R, Jamshaid M, Khan HM, Murtaza G. Dermatological and cosmeceutical benefits of Glycine max (soybean) and its active components. Acta Pol Pharm. 2015;72(1):3-11.

[16] Gulati OP. Pycnogenol in chronic venous insufficiency and related venous disorders. Phytother Res. 2014;28(3):348-62. DOI: 10.1002/ptr.5019

[17] Ahmadi A. Potential prevention: Aloe vera mouthwash may reduce radiation-induced oral mucositis in head and neck cancer patients. Chin J Integr Med. 2012;18(8):635-40. DOI: 10.1007/s11655-012-1183-y

[18] Chua LS, Lee SY, Abdullah N, Sarmidi MR. Review on Labisia pumila (Kacip Fatimah): bioactive phytochemicals and skin collagen synthesis promoting herb. Fitoterapia. 2012 Dec;83(8):1322-35. DOI: 10.1016/j.fitote.2012.04.002

[19] Deyama T, Nishibe S, Nakazawa Y. Constituents and pharmacological effects of Eucommia and Siberian ginseng. Acta Pharmacol Sin. 2001 Dec;22(12):1057-70.

[20] Lin XJ, Chen CY. Advances on study of treatment of lumbar disk herniation by Chinese medicinal herbs. Zhongguo Zhong Yao Za Zhi. 2007 Feb;32(3):186-91.

[21] Rajalalitha P, Vali S. Molecular pathogenesis of oral submucous fibrosis — a collagen metabolic disorder. J Oral Pathol Med. 2005 Jul;34(6):321-8. DOI: 10.1111/j.1600-0714.2005.00325.x

[22] Han G, Xia J, Gao J, Inagaki Y, Tang W, Kokudo N. Anti-tumor effects and cellular mechanisms of resveratrol. Drug Discov Ther. 2015 Feb;9(1):1-12. DOI: 10.5582/ddt.2015.01007.

[23] Guo Y, Li Y, Xue L, Severino RP, Gao S, Niu J, et al. Salvia miltiorrhiza: an ancient Chinese herbal medicine as a source for anti-osteoporotic drugs. J Ethnopharmacol. 2014;155(3):1401-16. DOI: 10.1016/j.jep.2014.07.058

[24] Saller R, Melzer J, Reichling J, Brignoli R, Meier R. An updated systematic review of the pharmacology of silymarin. Forsch Komplementmed. 2007 Apr;14(2):70-80. DOI: 10.1159/000100581

[25] Wei XL, Fang RT, Yang YH, Bi XY, Ren GX, Luo AL, et al. Protective effects of extracts from Pomegranate peels and seeds on liver fibrosis induced by carbon tetrachloride in rats. BMC Complement Altern Med. 2015 Oct 27;15(1):389. DOI: 10.1186/s12906-015-0916-9

[26] An BJ, Kwak JH, Park JM, Lee JY, Park TS, Lee JT, et al. Inhibition of enzyme activities and the antiwrinkle effect of polyphenol isolated from the persimmon leaf (Diospyros kaki folium) on human skin. Dermatol Surg. 2005;31(7 Pt 2):848-54. DOI: 10.1111/j.1524-4725.2005.31730

[27] James A, Gunasekaran N, Krishnan R, Arunachalam P, Mahalingam R. Anti-fibrotic activity of licorice extract in comparison with colchicine on areca nut-induced fibroblasts: An in vitro study. J Oral Maxillofac Pathol. 2022 Apr-Jun;26(2):173-8. DOI: 10.4103/jomfp.jomfp_110_21

[28] Rutter K, Sell DR, Fraser N, Obrenovich M, Zito M, Starke-Reed P, et al. Green tea extract suppresses the age-related increase in collagen crosslinking and fluorescent products in C57BL/6 mice. Int J Vitam Nutr Res. 2003 Nov;73(6):453-60. DOI: 10.1024/0300-9831.73.6.453

[29] Pearson DA, Holt RR, Rein D, Paglieroni T, Schmitz HH, Keen CL. Flavanols and platelet reactivity. Clin Dev Immunol. 2005;12(1):1-9. DOI: 10.1080/10446670410001722140

[30] Zhou SJ, Du GY. Effects of higenamine on the cardio-circulatory system. Zhongguo Zhong Yao Za Zhi. 2003;28(10):910-3.

[31] Ahmed T, Wang CK. black garlic and its bioactive compounds on human health diseases: a review. Molecules. 2021;26(16):5028. DOI: 10.3390/molecules26165028

[32] Teng CM, Ko FN. Antiplatelet agents isolated from medicinal plants. Res Commun Mol Pathol Pharmacol. 1998 Dec;102(3):211-25.

[33] Kwon OY, Ryu S, Choi JK, Lee SH. Smilax glabra Roxb. inhibits collagen induced adhesion and migration of PC3 and LNCaP prostate cancer cells through the inhibition of beta 1 integrin expression. Molecules. 2020;25(13):3006. DOI: 10.3390/molecules25133006

[34] RyuS, Park KM, Lee SH. Gleditsia sinensis thorn attenuates the collagen-based migration of PC3 prostate cancer cells through the suppression of α2β1 integrin expression. Int J Mol Sci. 2016;17(3):328. DOI: 10.3390/ijms17030328

[35] Gallie DR. Increasing vitamin C content in plant foods to improve their nutritional value-successes and challenges. Nutrients. 2013;5(9):3424-46. DOI: 10.3390/nu5093424

[36] Holmes DF, Lu Y, Starborg T, Kadler KE. Chapter three - Collagen fibril assembly and function. In: Current topics in developmental biology. Vol. 130. Elsevier; 2018. p. 107-42. DOI: 10.1016/bs.ctdb.2018.02.004

[37] Berg RA, Steinmann B, Rennard SI, Crystal RG. Ascorbate deficiency results in decreased collagen production: under-hydroxylation of proline leads to increased intracellular degradation. Arch Biochem Biophys. 1983 Oct 15;226(2):681-6. DOI: 10.1016/0003-9861(83)90338-7

[38] Bai R, Chang Y, Saleem A, Wu F, Tian L, Zhang S, et al. Ascorbic acid can promote the generation and expansion of neuroepithelial-like stem cells derived from hiPS/ES cells under chemically defined conditions through promoting collagen synthesis. Stem Cell Res Ther. 2021;12(1):48. DOI: 10.1186/s13287-020-02115-6

[39] Gohar O, Weiss T, Wineman E, Kessler E. Ascorbic acid promotes procollagen C-proteinase enhancer 1 expression, secretion, and cell membrane localization. Anat Rec (Hoboken). 2020 Jun;303(6):1670-9. DOI: 10.1002/ar.24182

[40] Geesin JC, Hendricks LJ, Gordon JS, Berg RA. Modulation ofcollagensynthesisby growth factors: the role of ascorbate-stimulated lipid peroxidation. Arch Biochem Biophys. 1991;289(1):6-11. DOI: 10.1016/0003-9861(91)90434-k

[41] Park HJ, Ock SM, Kim HJ, Park HJ, Lee YB, Choi JM, et al. Vitamin C attenuates ERK signalling to inhibit the regulation of collagen production by LL-37 in human dermal fibroblasts. Exp Dermatol. 2010 Aug;19(8):e258-64. DOI: 10.1111/j.1600-0625.2010.01070.x

[42] Otsuka E, Kato Y, Hirose S, Hagiwara H. Role of ascorbic acid in the osteoclast formation: induction of osteoclast differentiation factor with formation of the extracellular collagen matrix. Endocrinology. 2000 Aug;141(8):3006-11. DOI: 10.1210/endo.141.8.7597

[43] De Tullio MC. Beyond the antioxidant: the double life of vitamin C. In: Stanger O, editor. Water soluble vitamins. Subcellular biochemistry. Vol 56. Dordrecht: Springer; 2012. p. 49-65. DOI: 10.1007/978-94-007-2199-9_4

[44] Chojkier M, Houglum K, Solis-Herruzo J, Brenner DA. Stimulation of collagen gene expression by ascorbic acid in cultured human fibroblasts. A role for lipid peroxidation? J Biol Chem. 1989 Oct 5;264(28):16957-62. DOI: 10.1016/S0021-9258(19)84800-7

[45] Yin L, Morita A, Tsuji T. Alterations of extracellular matrix induced by tobacco smoke extract. Arch Dermatol Res. 2000 Apr;292(4):188-94. DOI: 10.1007/s004030050476

[46] Tiku ML, Shah R, Allison GT. Evidence linking chondrocyte lipid peroxidation to cartilage matrix protein degradation. Possible role in cartilage aging and the pathogenesis of osteoarthritis. J Biol Chem. 2000 Jun 30;275(26):20069-76. DOI: 10.1074/jbc.M907604199

[47] Wang QL, Yuan JL, Tao YY, Zhang Y, Liu P, Liu CH. Fuzheng Huayu recipe and vitamin E reverse renal interstitial fibrosis through counteracting TGF-beta1-induced epithelial-to-mesenchymal transition. J Ethnopharmacol. 2010 Feb 17;127(3):631-40. DOI: 10.1016/j.jep.2009.12.011

[48] Azzi A, Gysin R, Kempná P, Munteanu A, Villacorta L, Visarius T, Zingg JM. Regulation of gene expression by alpha-tocopherol. Biol Chem. 2004 Jul;385(7):585-91. DOI: 10.1515/BC.2004.072

[49] Makpol S, Azura Jam F, Anum Mohd Yusof Y, Zurinah Wan Ngah W. Modulation of collagen synthesis and its gene expression in human skin fibroblasts by tocotrienol-rich fraction. Arch Med Sci. 2011 Oct;7(5):889-95. DOI: 10.5114/aoms.2011.25567

[50] Makpol S, Zainuddin A, Chua KH, Yusof YA, Ngah WZ. Gamma-tocotrienol modulation of senescence-associated gene expression prevents cellular aging in human diploid fibroblasts. Clinics (Sao Paulo). 2012;67(2):135-43. DOI: 10.6061/clinics/2012(02)08

[51] Siddiqui S, Ahsan H, Khan MR, Siddiqui WA. Protective effects of tocotrienols against lipid-induced nephropathy in experimental type-2 diabetic rats by modulation in TGF-β expression. Toxicol Appl Pharmacol. 2013 Dec 1;273(2):314-24. DOI: 10.1016/j.taap.2013.09.004

[52] Cho HS, Lee MH, Lee JW, No KO, Park SK, Lee HS, et al. Anti-wrinkling effects of the mixture of vitamin C, vitamin E, pycnogenol and evening primrose oil, and molecular mechanisms on hairless mouse skin caused by chronic ultraviolet B irradiation. Photodermatol Photoimmunol Photomed. 2007 Oct;23(5):155-62. DOI: 10.1111/j.1600-0781.2007.00298.x

[53] Guzyk MM, Sergiichuk IuT, Dyakun KO, Yanitska LV, Kuchmerovska TM. Effect of nicotinamide on amino acids content in bone collagen depending on biological availability of vitamins in diabetic rats. Ukr Biochem J. 2014 Jul-Aug;86(4):138-49. DOI: 10.15407/ubj86.04.138

[54] Kuchmerovska T, Shymanskyy I, Bondarenko L, Klimenko A. Effects of nicotinamide supplementation on liver and serum contents of amino acids in diabetic rats. Eur J Med Res. 2008;13(6):275-80.

[55] Choi SJ, Lee SN, Kim K, Joo da H, Shin S, Lee J, et al. Biological effects of rutin on skin aging. Int J Mol Med. 2016 Jul;38(1):357-63. DOI: 10.3892/ijmm.2016.2604

[56] Działo M, Mierziak J, Korzun U, Preisner M, Szopa J, Kulma A. The potential of plant phenolics in prevention and therapy of skin disorders. Int J Mol Sci. 2016 Feb 18;17(2):160. DOI: 10.3390/ijms17020160

[57] Chiang SS, Pan TM. Beneficial effects of phytoestrogens and their metabolites produced by intestinal microflora on bone health. Appl Microbiol Biotechnol. 2013;97(4):1489-500. DOI: 10.1007/s00253-012-4675-y

[58] Sienkiewicz P, Surazyński A, Pałka J, Miltyk W. Nutritional concentration of genistein protects human dermal fibroblasts from oxidative stress-induced collagen biosynthesis inhibition through IGF-I receptor-mediated signaling. Acta Pol Pharm. 2008 Mar-Apr;65(2):203-11.

[59] Belcaro G, Maquart FX, Scoccianti M, Dugall M, Hosoi M, Cesarone MR, et al. TECA (Titrated Extract of Centella Asiatica): new microcirculatory, biomolecular, and vascular application in preventive and clinical medicine. A status paper. Panminerva Med. 2011 Sep;53(3 Suppl 1):105-18.

[60] Tang M, Bian W, Cheng L, Zhang L, Jin R, Wang W, et al. Ginsenoside Rg3 inhibits keloid fibroblast proliferation, angiogenesis and collagen synthesis in vitro via the TGF-β/Smad and ERK signaling pathways. Int J Mol Med. 2018 Mar;41(3):1487-99. DOI: 10.3892/ijmm.2018.3362

[61] Zong L, Qu Y, Xu MY, Dong YW, Lu LG. 18α-glycyrrhetinic acid down-regulates expression of type I and III collagen via TGF-B1/Smad signaling pathway in human and rat hepatic stellate cells. Int J Med Sci. 2012;9(5):370-9. DOI: 10.7150/ijms.4395

[62] Hou SQ, Fang M, Chen SS, Cong XP, Zhang DD, Li XM. Biochemical regulatory mechanism of asiaticoside in preventing and treating stent restenosis. Zhongguo Zhong Yao Za Zhi. 2014 Apr;39(8):1479-84.

[63] Krithika R, Jyothilakshmi V, Prashantha K, Verma RJ. Mechanism of protective effect of phyllanthin against carbon tetrachloride-induced hepatotoxicity and experimental liver fibrosis in mice. Toxicol Mech Methods. 2015;25(9):708-17. DOI: 10.3109/15376516.2015.1077361

[64] Li ZY, Deng XL, Huang WH, Li L, Li H, Jing X, et al. Lignans from the bark of Eucommia ulmoides inhibited Ang II-stimulated extracellular matrix biosynthesis in mesangial cells. Chin Med. 2014 Feb 14;9(1):8. DOI: 10.1186/1749-8546-9-8

[65] Lu YC, Hsiao G, Lin KH, Hsieh MS, Jayakumar T, Wu TS, et al. Cinnamophilin isolated from Cinnamomum philippinense protects against collagen degradation in human chondrocytes. Phytother Res. 2013 Jun;27(6):892-9. DOI: 10.1002/ptr.4812

[66] Kwon YY, Kim D, Kim J, Hwang JK. Effects of licarin E on expression of matrix metalloproteinase-1 and type-1 procollagen in UVB-irradiated human skin fibroblasts. Phytother Res. 2011 Dec;25(12):1891-4. DOI: 10.1002/ptr.3521

[67] Maepa M, Razwinani M, Motaung S. Effects of resveratrol on collagen type II protein in the superficial and middle zone chondrocytes of porcine articular cartilage. J Ethnopharmacol. 2016 Feb 3;178:25-33. DOI: 10.1016/j.jep.2015.11.047

[68] Yuwanati M, Ramadoss R, Kudo Y, Ramani P, Senthil Murugan M. Prevalence of oral submucous fibrosis among areca nut chewers: A systematic review and meta-analysis. Oral Dis. 2022 May 3. DOI: 10.1111/odi.14235

[69] Lu M, Tao L, Mei W, Luo R, Fu X, Wang L, et al. Effect of curcumin on the expression of p-STAT3 and IκB in db/db mice. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2014 Jun;39(6):591-7. DOI: 10.11817/j.issn.1672-7347.2014.06.008

[70] Wang J, Ma J, Gu JH, Wang FY, Shang XS, Tao HR, et al. Regulation of type II collagen, matrix metalloproteinase-13 and cell proliferation by interleukin-1β is mediated by curcumin via inhibition of NF-κB signaling in rat chondrocytes. Mol Med Rep. 2017 Aug;16(2):1837-45. DOI: 10.3892/mmr.2017.6771

[71] Perumal S, Dubey K, Badhwar R, George KJ, Sharma RK, Bagler G, et al. Capsaicin inhibits collagen fibril formation and increases the stability of collagen fibers. Eur Biophys J. 2015 Feb;44(1-2):69-76. DOI: 10.1007/s00249-014-1002-9

[72] Davison-Kotler E, Marshall WS, García-Gareta E. Sources of collagen for biomaterials in skin wound healing. Bioengineering (Basel). 2019 Jun 30;6(3):56. DOI: 10.3390/bioengineering6030056

[73] Perret S, Merle C, Bernocco S, Berland P, Garrone R, Hulmes DJ, et al. Unhydroxylated triple helical collagen I produced in transgenic plants provides new clues on the role of hydroxyproline in collagen folding and fibril formation. J Biol Chem. 2001 Nov 23;276(47):43693-8. DOI: 10.1074/jbc.M105507200

[74] Setina CM, Haase JP, Glatz CE. Process integration for recovery of recombinant collagen type I α1 from corn seed. Biotechnol Prog. 2016 Jan-Feb;32(1):98-107. DOI: 10.1002/btpr.2191

[75] Xu X, Gan Q, Clough RC, Pappu KM, Howard JA, Baez JA, et al. Hydroxylation of recombinant human collagen type I alpha 1 in transgenic maize co-expressed with a recombinant human prolyl 4-hydroxylase. BMC Biotechnol. 2011 Jun 24;11(1):69. DOI: 10.1186/1472-6750-11-69

[76] Stein H, Wilensky M, Tsafrir Y, Rosenthal M, Amir R, Avraham T, et al. Production of bioactive, post-translationally modified, heterotrimeric, human recombinant type-I collagen in transgenic tobacco. Biomacromolecules. 2009 Sep 14;10(9):2640-5. DOI: 10.1021/bm900571b

[77] Yan J, Hu K, Xiao Y, Zhang F, Han L, Pan S, et al. Preparation of recombinant human-like collagen/fibroin scaffold and its promoting effect on vascular cells biocompatibility. J Bioact Compat Polym. 2018;33(4):416-25. DOI: 10.1177/0883911518769680

[78] Li J, Zhang YP, Kirsner RS. Angiogenesis in wound repair: angiogenic growth factors and the extracellular matrix. Microsc Res Tech. 2003 Jan 1;60(1):107-14. DOI: 10.1002/jemt.10249

[79] Shilo S, Roth S, Amzel T, Harel-Adar T, Tamir E, Grynspan F, et al. Cutaneous wound healing after treatment with plant-derived human recombinant collagen flowable gel. Tissue Eng Part A. 2013 Jul;19(13-14):1519-26. DOI: 10.1089/ten.TEA.2012.0345

[80] Inamasu J, Guiot BH, Sachs DC. Ossification of the posterior longitudinal ligament: an update on its biology, epidemiology, and natural history. Neurosurgery. 2006 Jun;58(6):1027-39. DOI: 10.1227/01.NEU.0000215867.87770.73

[81] Lee B, D'Alessio M, Vissing H, Ramirez F, Steinmann B, Superti-Furga A. Characterization of a large deletion associated with a polymorphic block of repeated dinucleotides in the type III procollagen gene (COL3A1) of a patient with Ehlers-Danlos syndrome type IV. Am J Hum Genet. 1991 Mar;48(3):511-7.

[82] Wirtz MK, Rao VH, Glanville RW, Labhard ME, Pretorius PJ, de Vries WN, et al. A cysteine for glycine substitution at position 175 in an alpha 1 (I) chain of type I collagen produces a clinically heterogeneous form of osteogenesis imperfecta. Connect Tissue Res. 1993;29(1):1-11. DOI: 10.3109/03008209309061961

[83] Volodina TT, Korotkevich NV, Romanyuk SI, Galkin OY, Kolybo DV, Komisarenko SV. Implementation of dietary supplements with effect of dezintoxication and improvement of osteogenesis and metabolism. Sci Innov. 2017;13(6):39-50. DOI: 10.15407/scin13.06.041

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МОЖЛИВОСТІ ВИКОРИСТАННЯ РОСЛИННИХ ПРЕПАРАТІВ ДЛЯ КОРЕКЦІЇ СТРУКТУРИ КОЛАГЕНУ ТА ПОРУШЕНЬ МЕТАБОЛІЗМУ: СУЧАСНИЙ СТАН ПРОБЛЕМИ

В огляді узагальнено інформацію про можливості використання рослинних препаратів для корекції порушень структури та метаболізму колагену. Біологічно активні сполуки рослинного походження здатні як стимулювати, так і пригнічувати біосинтез різних типів колагенів, прискорювати або сповільнювати їх катаболізм, регулювати активність ферментів, що беруть участь у метаболізмі колагенів. Більшість досліджених сполук реалізують свою дію одночасно за кількома механізмами. Серед них найбільш поширеними є: прямий вплив речовини на процеси експресії генів колагену та непрямий – через TGF-beta1-шлях. Крім того, досить поширеною є регуляція синтезу колагену через зміну запасів вільних амінокислот в організмі (як вихідних сполук для синтезу цього білка) і через регуляцію гідроксилаз (що виконують посттрансляційні модифікації колагену та його зшивання). Крім того, TGF-beta1 та інші цитокіни можуть бути залучені до участі у процесах регуляції метаболізму колагену сполуками рослинного походження. Зокрема, цей механізм є характерним для тритерпенів і фітоестрогенів. Така різноманітність методів регуляції метаболізму колагенів створює широкі можливості для розробки нових препаратів на основі екстрактів або чистих рослинних сполук, здатних коригувати структуру колагену сполучної тканини та метаболічні порушення з мінімальними побічними ефектами. Принципово інші можливості впливу рослинних організмів на колагени відкриваються з використанням генетично модифікованих рослин. Рекомбінантні колагени дають змогу отримувати білки з новими запрограмованими властивостями, що уможливлює синтез білків із заздалегідь заданими властивостями для медичних потреб.

Ключові слова: рослинні препарати; структура колагену; метаболізм колагену; корекція порушень; рекомбінантні колагени.