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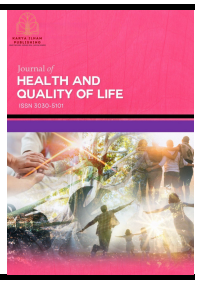

Using Medicinal Plants to Perform the Epigenetic Regulation of Gene Expression

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ABSTRACT

Phytochemical substances contained in medicinal plants are able to reverse epigenetic changes, actively regulate gene expression, prevent oncogenesis, as well as prevent diseases through epigenetic modifications. The purpose of the study was to perform the analysis of scientific literature on the effect of biologically active plant substances on epigenetic regulation of gene expression in various diseases. A systematic analysis of publications was carried out in order to identify the main directions of pharmacology of biologically active plant substances with an emphasis on epigenetic regulation. Biologically active plant substances affect DNA methylation, histone acetylation, etc., modulating the course of hereditary, viral, autoimmune diseases. Epigenetic studies of biologically active plant substances as gene expression regulators may be of interest as an explanation for the anti-tumor, anti-inflammatory, and metabolic and hereditary disorders effects of plants, as well as for identifying new plants that are promising for these purposes.

1. Introduction

Epigenetic regulation is the most important adaptive mechanism for controlling DNA gene expression, which allows changing the implementation of the biological program and functions of the body, tissues, and cells depending on external and internal conditions, needs, and stages of development. Thus, the system of epigenetic modifications is a complex of mechanisms aimed at regulating the genome, but not affecting its structure. Epigenetic molecular targets of phytotherapy in cells. Phytotherapy can regulate histone methylation, histone acetylation and DNA methylation, histone ubiquitination and phosphorylation, histone ubiquitination and phosphorylation [1].

Epigenetics and its section nutrigenomics (the science of the effect of human nutrition on gene expression) is now a rapidly developing branch of modern genetics, in addition to the traditional model of genetics. Epigenetic factors are extremely diverse – these are any exogenous influences – electromagnetic, infectious, medicinal, everything related to lifestyle, nutrition, thoughts, any kind

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of human activity. This emphasizes a person's personal responsibility to their every thought and action as factors of sanoepigenesis.

2. Plants and Epigenetics

Biologically active substances of plants are currently one of the intensively studied epigenetic factors. The molecular foundations of epigenetics at the transcription stage are represented by the methylation of cytosine bases of DNA, at the post-transcriptional stage - by the modification of histones, the effect on microRNAs (small non-coding RNAs).

The most important and stable mechanisms of epigenetic regulation include cytosine nucleotide methylation. These are permanent epigenetic labels transmitted to daughter cells, a scenario of cellular life. Shorter-term marks include acetylation of histone proteins, they can be compared with less significant edits to the cellular scenario. DNA methylation at the 5-cytosine position has the effect of reducing gene expression, occurs with the participation of DNA methyltransferases and S-adenosyl methionine (SAM) (a methyl group donor), and can occur “spontaneously" without the participation of enzymes. It has been shown that even minor changes in the degree of DNA methylation can significantly alter the level of genetic expression [2].

Methylation causes cellular differentiation, specificity of cell structure and function, and suppresses the expression of genes, the inclusion of which is impractical and harmful to a given cell at a given time. DNA methylation can only be removed in extremely extreme circumstances for the body. It is noted that under conditions of stress, accompanied by increased synthesis of adrenaline, the body consumes methyl groups for the process of methylation of norepinephrine with the formation of adrenaline. This explains why excessive stress increases the risk of the manifestation and progression of hereditary diseases. B vitamins folic acid and cyanocobalamin are donors of methyl groups, effectively contributing to the methylation of genes. Phytotherapy products that provide the necessary synthesis of vitamins of this group by the normal intestinal microflora indirectly contribute to the stabilization of the genome.

Carcinogenesis is associated with a violation of methylation. Over the past 15-20 years, it has been found that methylation in cancer cells changes significantly compared to normal cells, and total genome demethylation is accompanied by demethylation of proto-oncogenes, increased activity of methyltransferase, and local hypermethylation of CpG (cytosine-guanine) islands (for example, in the area of tumor suppressor genes of tumor growth, thereby blocking the activity of these suppressor genes [3].

In many DNA viruses, DNA methylation is necessary to ensure their replication. Many viruses (adenoviruses, herpesviruses, papillomaviruses, etc.), when infected, are able to stimulate an increase in the expression level of DNA methyltransferases of the host cell [4]. But on the other hand, DNA methylation suppresses the expression of endogenous retroviral genes and other "harmful" DNA regions that have been incorporated into the host genome over time.

Impaired DNA methylation is associated with the onset and development of hereditary diseases, in particular, homocysteinemia. Less stable mechanisms of epigenetic regulation include posttranslational histone modifications that attract decoding proteins that build complexes of other proteins on the nucleosome. Many biologically active substances of medicinal plants contain methyl groups, such as anthocyanins peonidine, malvidin, petunidine, beet betaine (trimethylglycine), licorice saponin, and glycyrrhizic acid, which contains seven methyl groups.

Plant substances have also shown their effect on histone modifications – methylation, lysine methylation, acetylation, etc. The use of phytotherapy, among other things, can suppress the transcription of active genes and eliminate the manifestations of hereditary diseases. Our colleagues

have positive experience in the treatment of Duchenne myodystrophy, cystic fibrosis, ichthyosis, neurofibromatosis, and tuberous sclerosis with long-term clinical remission [2]. Gordeev, PhD, M.V. demonstrated the effectiveness of silicon concentrator plants in neurofibromatosis. Prolonged (at least 12 months) administration of a decoction of nettle, horsetail, knotweed, and pickleberry significantly reduced the volume and number of multiple cutaneous neurofibromas in a patient with type I neurofibromatosis.

Some plants that affect the regulation of gene expression are also being studied as a means for the prevention and treatment of tumors. In tumors, abnormal hypermethylation of tumor suppressor genes (nuclear receptors, cell cycle regulators, apoptosis inducers, etc.), abnormal histone modification and microRNA modifications often occur, which ultimately contributes to the development of cancer [5]. Cytostatics azanucleosides are known to eliminate hypermethylation of suppressor genes. Due to the myelosuppressive effect of these cytostatics and their activity only in the c-phase of the cell cycle, they have limited use. This makes it urgent to search for other inhibitors of DNA hypermethylation. The properties of the yellow turmeric pigment curcumin have been studied for their effect on the inhibition of methyltransferase-1 in acute myeloid leukemia cells for the purpose of tumor suppression activation promoter genes. Thus, curcumin acts as a powerful hypomethylating agent, suppressing the expression of acute myeloid leukemia genes both in vivo and in the laboratory by blocking the catalytic thiolate C1226 methyltransferase-1. Curcumin inhibits the JNK signaling pathway and plays a role in the epigenetic regulation of prostate cancer cells by suppressing H3K4me3 [6].

Oleanolic acid (found in olive oil, American laconose, etc.) and its more active derivatives are of interest. After treating gastric cancer cells with MKN-45 oleanolic acid, the increased IL-1b-induced DNA demethylase activity in MKN-45 cells was suppressed [7].

Garlic diallyl sulfide and its active metabolite S-allyl mercaptocysteine are converted into the final metabolite allyl mercaptan and other substances. All of these listed substances are histone deacetylase (HDAC) inhibitors, induce histone acetylation, and are capable of activating epigenetically suppressed genes in cancer cells, which leads to cell cycle arrest and apoptosis [8].

Some plant components are capable of intercalation (reversible incorporation of a molecule) into DNA as a DNA ligand. This applies to the vegetable benzophenanthridine alkaloid of large celandine and various types of macleay, sanguinarine [9]. The intercalation of sanguinarine in DNA was judged, in particular, by the removal of supercoiling from negatively supercoiled covalently ringed double-stranded phage DNA molecules, complete relaxation of the ring, and then the appearance of right supercoiling with an increase in the number of sanguinarine molecules in complexes with phage DNA. According to the researchers, sanguinarine modifies the DNA double helix and therefore inhibits enzymatic reactions that depend on the DNA structure. Similar data have now been obtained for other benzophenanthridine alkaloids. The results are discussed in connection with the high malignotoxic potential of benzophenanthridine alkaloids and the preparations "ukrain" and "sanguiritrin" obtained on their basis. Let's explain that DNA intercalators are used in chemotherapy as agents that inhibit DNA replication in fast-growing cancer cells, for example, doxorubicin (adriamycin) and daunorubicin (both used to treat Hodgkin's disease), and dactinomycin (used to treat nephroblastoma, Ewing's sarcoma and rhabdomyosarcoma).

Baikal skullcap flavone glycoside baykalin suppresses the development of liver tumors caused by type 2 diabetes mellitus in vitro and in vivo, regulates the METTL3/HKDC1/JAK2/STAT1/caspase-3 pathway in liver cancer cells when exposed to high glucose concentrations, significantly reduces the epigenetic modification (DNA 5mC and RNA m6A) of HKDC1 in tumors of HepG2, mainly affecting the m6A (2854) RNA region [10].

Epigenetic mechanisms such as DNA methylation, histone modifications, and gene regulation by non-coding RNAs are important factors influencing the pathogenesis of autoimmune diseases [11] and inflammatory processes in general.

Plant polyphenolic compounds can regulate epigenetic factors responsible for oxidation and thiol-mediated signaling of modulation, which is one of the mechanisms of antioxidant action of polyphenols. Polyphenols have also been shown to be involved in DNA methylation (inhibition of DNA methyltransferase-1), histone modification, and post-transcriptional regulation of microRNAs. As mentioned above, curcumin, genistein, and quercitin have been studied as histone deacetylase inhibitors, genistein as histone acetyltransferase activator, and resveratrol as SIRT (silent information regulator) activators, and SIRT-genistein inhibitors. These substances regulate the expression of pro- and anti-inflammatory genes [12].

Polyphenols are also effective in the treatment of autoimmune diseases, as they promote the production of T-suppressors. Flavonol fisetin (pentoxifylline) inhibits the transcription of NF-kB target genes, including TNF-alpha and IL-6 cytokine synthesis genes in THP-1 cells and monocytes in type 1 diabetes mellitus, a systemic inflammatory disease with an autoimmune attack directed primarily at glycated proteins of the microcirculatory wall [13].

3. Conclusion

Recently, much attention has been paid to the study of the role of small non-coding RNAs (miRNAs) in the regulation of genetic activity. microRNAs can alter the stability and translation of mRNAs by complementary binding to the 3'-untranslated region of the mRNA. Proanthocyanidins of grape seed extract and cocoa extract, isolated epigallocatechin gallate of green tea affect the expression of microRNAs in G2 hepatoma cells with preserved reactions of glucuronidation, sulfonation and methylation [14]. To date, more than 15,000 microRNAs are known, and it is believed that these tiny molecules can regulate about 30% of all cellular transcription, regulating the synthesis of receptors for insulin, cholesterol, triglycerides, and others involved in differentiation and development. Therefore, the recommendation to enrich the daily diet with dishes and drinks containing plant pigments of colored berries and fruits is our mandatory recommendation for most patients. Epigenetic studies of biologically active substances of plants as correctors of gene expression may be of interest as an explanation of antitumor, anti-inflammatory, metabolic disorders and hereditary disorders of plant effectors, and also allow us to identify new promising plants for these purposes.

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