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Bacterial Violacein: Properties, Biosynthesis and Application Prospects

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Abstract—This review discusses the properties of violacein, a chromogenic secondary metabolite of bacteria with a wide range of biological activity, as well as the issues of its microbial synthesis and prospects for application. Violacein-synthesizing bacteria have been isolated from various sources, including the rhizosphere of cultivated plants, soils, marshes, sea coasts, ponds, and glacier melt waters. The study of the antibacterial, antimycotic, insecticidal, and antitumor properties of violacein makes it an extremely promising biologically active compound and causes a steadily increasing interest in both the compound itself and in the group of bacteria that produce it, in terms of the development of new drugs and veterinary drugs, as well as plant protection products. The purpose of this review is to attempt to summarize the considerable amount of data on this compound, especially regarding its antimicrobial and anticancer properties.

Keywords: secondary metabolites, pigments, violacein, antimicrobial activity, cytotoxicity, insecticides, biotechnological significance

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INTRODUCTION

Bacteria of many genera, including the most studied *Chromobacterium* [1–3], *Janthobacterium* [4–6], *Iodobacter*, and *Collimonas* [7, 8] as well as some representatives of such genera as *Alteromonas* and *Pseudomonas* [9–11], are capable of synthesizing the violet pigment violacein ([3-[1,2-dihydro-(5-Hydroxy-*1H*-indol-3-yl)2-oxo-*3H*-pyrrol-3-ylidene]-1,3-dihydro-*2H*-indol-2-one]) (Fig. 1) with an extremely broad spectrum of biological activities [12–15].

The interest of researchers in violacein and the microorganisms synthesizing this compound is steadily growing. A search in the databases about violacein provides links to more than 5500 publications, while the query "*C. violaceum*" provides more than 15 000 publications in the period from 2012 to 2022 [NCBI PubMed https://pubmed.ncbi.nlm.nih.gov/. Accessed 20 Jan 2021].

At the same time, there are relatively few works in Russian scientific journals in this area. In this regard, this review is devoted to the general characteristics of this compound, the pathways of its biosynthesis, some properties, and its prospects for use.

Violacein biosynthesis. The biosynthesis of violacein is carried out by the expression of the *vio* operon with the participation of five genes *vioA*, *vioB*, *vioC*, *vioD*, and *vioE* read in one direction, which provide the condensation of two molecules of L-tryptophan, which is a universal metabolite of a number of secondary metabolic pathways in microorganisms [17] that leads to the formation of a pigment molecule (Fig. 1, Table 1). The priority in the discovery of the violacein biosynthesis pathway belongs to Pemberton and coauthors [16].

The biosynthesis of violacein begins with the formation of the autoinducer N-hexanoyl-L-homoserine lactone (C_6-AHL), which is the main quorum sensing signal. With an increase in the cell population density due to the catalytic conversion of fatty acids or S-adenosylmethionine with the participation of synthase, which is under the control of the *CviI* gene, C_6-AHL is produced and, forming a protein-ligand complex with the CviR receptor protein, changes its configuration, which makes it possible to bind to DNA. Formed complex triggers quorum-dependent transcription of target genes of the *vioABEDC* operon by binding to its promoter site [19–21] (Fig. 2).

The gene product, VioA, flavin-dependent tryptophan 2-monooxygenase, catalyzes the oxidative transformation of L-tryptophan into indole-3-pyruvate imine (IPA) in a process coupled with the reduction of flavin adenine dinucleotide (FAD) [22, 23].

At the next stage, two IPA molecules are converted with the participation of the heme-containing synthase encoded by *vioB* into a short-lived dimer [24–26], which, with the participation of the VioE enzyme, is further converted into protodeoxyviolaceic acid. The indole ring of protodeoxyviolaceic acid in the fifth

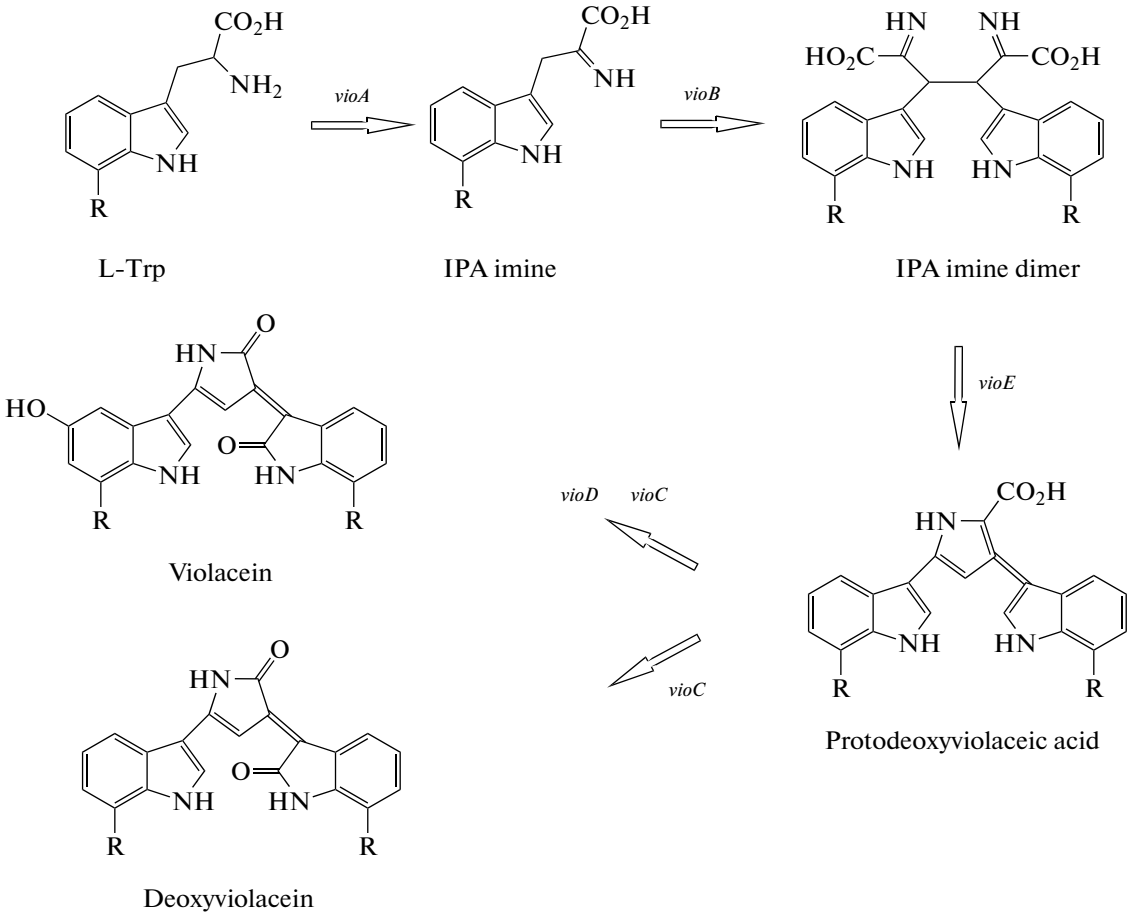

Fig. 1. Bacterial violacein biosynthetic pathways.

position is hydroxylated with the participation of VioD monooxygenase to form proviolacein. The final stage of biosynthesis consists in the formation of violacein from proviolacein under the control of flavin-dependent monooxygenase VioC. Detailed characteristics of the biosynthetic pathway are presented in *MetaCyc* database: https://biocyc.org/META/NEW-IMAGE-?object=PWY-7040.

Violacein is produced by a wide range of bacteria that inhabit almost all types of natural ecosystems: from sea waters to agricultural soils and glaciers. In this regard, it seems rather difficult to give an unambiguous definition of the biological role of violacein. For example, as for a number of other bacterial pigments, its role may be to protect the cell from ultraviolet radiation [27]. At the same time, it was shown that *Chromobacterium violaceum* synthesizes violacein as a competitive agent in intermicrobial interactions. The same idea is suggested by the fact that violacein producers are mainly species with an attached lifestyle and, therefore, are easy prey for predators [28].

Table 1. The genes of the *vio* operon [18]

Gene	Designation	Function	Molecular mass	Size (b.p.)	PDB number
vioA	CV_RS16140	Flavin-dependent tryptophan 2-monooxygenase	48	1257	5G3S
vioB	CV_RS16135	Iminophenyl-pyruvate dimer synthase	111	2997	–
vioC	CV_RS16130	FAD-dependent monooxygenase	48	1290	2WBO
vioD	CV_RS16125	Flavin-dependent monooxygenase	42	1122	3C4A
vioE	CV_RS16120	Isomerase responsible for the conversion of flavanones into isoflavones	22	576	2ZF3

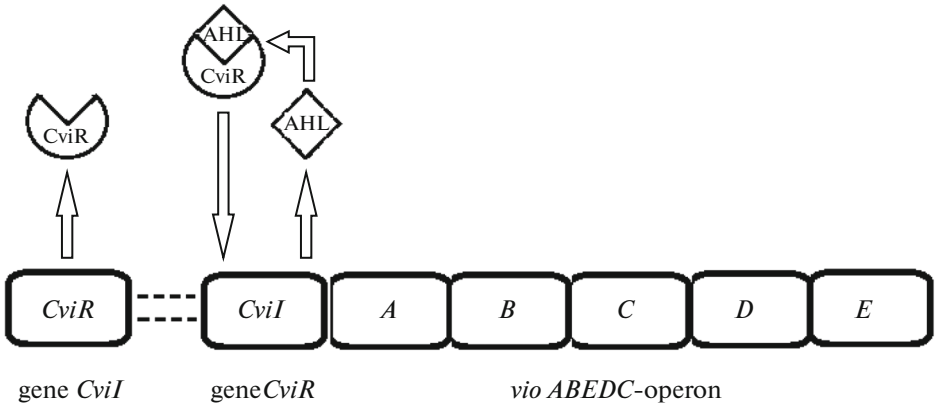

Fig. 2. Quorum-dependent synthesis of violacein in *C. violaceum* [21].

In 2003, whole genome sequencing of *C. violaceum* was published [29]. The analysis of the genome led to the conclusion that the very high degree of adaptability and versatility of *C. violaceum* is due to the large and complex genome of the bacterium, which includes a significant proportion of open reading frames (ORFs) that are specifically associated with the ability of the organism to interact and respond to the environment. The complexity of the genome may be of great practical importance due to the fact that the bacterium is an important potential source of biotechnologically useful genes, in particular those involved in the biosynthesis of violacein.

The biological effects of violacein. The antibacterial properties of violacein were one of the first features that researchers paid attention to [30–34]. Thus, the work of Baricz and co-authors [35] demonstrated the antimicrobial effect of the culture fluid extract of the bacterium *Janthinobacterium lividum* – ROICE173, which was isolated in the Antarctic, against 200 multidrug-resistant bacterial strains of natural and clinical origins. The extract showed a bactericidal effect in relation to 40% of the strains, a bacteriostatic effect in relation to 12% of the strains, while 48% of the studied strains were not affected by violacein. It should be noted that a significant inhibitory effect was noted in relation to such microorganisms as staphylococci, enterococci, and enterobacteria.

The antimicrobial properties of violacein are exhaustively described in the review [36]. In particular, one of the clinically significant strains that has recently attracted the most attention is *Staphylococcus aureus*, in part due to its status as a multidrug-resistant pathogen. Several research teams [37–39] found that violacein is able to suppress the growth of *S. aureus* at concentrations from 5.7 to 15 mg/L, or approximately 17 to 43 μmol/L.

Violacein is a hydrophobic compound with a lipophilicity coefficient of 3.34 [40], which raises the question of how it can enter the environment and affect other organisms. To a certain extent, this can be explained by works describing transport systems for violacein. The mechanism of violacein delivery to suppress the vital activities of bacteria and potential competitors using outer membrane vesicles (OMVs) has been described in detail in the work of Batista and co-authors [41]. OMVs of the bacteria *C. violaceum* have been found to be a long-distance delivery vehicle for violacein to kill competitors. The release of OMV in *C. violaceum* is a quorum-sensing (QS)-regulated process required for interbacterial competition using antimicrobial compound delivery. At the same time, violacein induces OMV biogenesis for its own delivery and promotes biofilm formation. OMVs without violacein are harmless to bacteria. The formation of vesicles is due to the accumulation of phospholipids in the outer membrane and is regulated by the phospholipid transporter VacJ/Yrb. At low cell density, the OMV release rate decreases due to increased expression of the VacJ/Yrb system. It was noted that the expression of VacJ/Yrb decreases at the early stages of host infection, which stimulates vesiculation and, accordingly, adaptation to environmental conditions. Thus, the two-component "quorum sensing" CviI/CviR system activates violacein production.

Violacein-containing vesicles are structural component of the biofilm and play the role of protecting the population of violacein-synthesizing bacteria from protozoa, which was discovered and described by Matz and co-authors [42]. The authors showed that violacein suppresses the activity of flagellates, ciliates and amoebae. In experiments with the nematode *Caenorhabditis elegans*, it was found that violacein disrupts the functioning of the IIS signaling pathway, including insulin-like growth factor, which mediates cell apoptosis [43]. In the same work, it was shown that apoptosis in the nematode was also induced by the presence of *E. coli* in the intestine of the host, in which the genes for violacein synthesis were expressed. In conclusion, the authors, comparing their results with data from other studies on the toxic effects of violacein on mammalian and protozoan cells, make an assump-

tion about the presence of a common molecular apoptosis-like mechanism of cell death in distantly related eukaryotic systems as a target for the toxic effects of violacein.

Some molecular mechanisms of the action of violacein on protozoa are presented in [44], whose results of which showed that violacein disrupts the functions of chaperones in the malarial plasmodium *Plasmodium falciparum*, which leads to disruption of the protein structure, proteosomal degradation, and impaired the development of the parasite.

Violacein also has a negative effect on fungal cultures [45]. Being an alkaloid in its chemical structure, violacein, like many other alkaloids, has a very wide range of physiological activities. The antibacterial activity of violacein, which allows violacein-synthesizing bacteria to compete well, has already been mentioned. At the same time, it was shown that violacein can have a stimulating and regulating effect on the microbial community of the gastrointestinal tract in multicellular organisms. Pauer and co-authors [46], when evaluating the effects of different doses of violacein (50 and 500 μg/mL) administered orally to rats for a month found that low doses of violacein were associated with greater taxonomic diversity of the intestinal microbiota compared with the control group and high doses of violacein. The group treated with a low dose of violacein was dominated by representatives of the classes *Bacilli* and *Clostridia* due to a decrease in the competitiveness of other groups of bacteria, including *Proteobacteria*.

In experiments with laboratory mice and rats, significant immunomodulatory, anti-inflammatory and analgesic effects of violacein obtained from a strain of *Chromobacterium violaceum* were demonstrated [47]. The authors suggested that the effect is due to the fact that violacein at doses of 10, 20, and 40 mg/kg of body weight is able to inhibit the synthesis/release of inflammatory mediators.

Verinaud and co-authors [48] showed in experiments with mice subjected to acute or chronic inflammation that intraperitoneal administration of 3.5 mg/kg body weight of violacein to mice led to the suppression of cytokine production (in acute inflammation) and had a stimulatory effect on regulatory T-cells (in chronic inflammation), which largely smoothed the inflammatory effect.

Based on conflicting data on the effect of violacein on the expression of tumor necrosis factor (TNF-α), (Alshatwi and co-authors reported about the induction of tumor necrosis factor expression in MCF-7 breast cancer cell culture [49], while Ferreira and co-authors [50] found no induction in endomythocin-affected rat gastric mucosa cells.), Venegas and co-authors [51] found that violacein has a direct effect on macrophage cells. First of all, using the Raw 264.7 mouse macrophage cell line, the authors showed that violacenin does not affect the dynamics of nitric oxide release by macrophages. They further found that violacein directly increased the level of the immune response by inducing the expression of pro-inflammatory cytokines in Raw 264.7 and ANA-1 cells by activating the TLR signaling pathway. Using the human embryonic kidney cell line HEK-293 in the work, the authors found that at a concentration of 15 μmol/L violacein activates hTLR8 tol-like receptors, whose function is to activate the cellular immune response by recognizing the molecular structures of pathogens and triggering the signaling cascade that leads to the synthesis of cytokines and other inflammation-associated molecules. The expression of genes involved in the inflammatory response and signaling system, chemotaxis, as well as changes in the expression level of genes associated with the regulation of cell proliferation were revealed. In this work, evidence that violacein can bind to hTLR8 similarly to imidazoquinoline compounds was obtained. Low-molecular-weight imidazoquinoline compounds are TLR8 receptor agonists and exhibit antiviral and anticancer properties. The evidence suggests that violacein has the potential to be used in future immunotherapy strategies. The TLR8 receptor is involved in recognition of single-stranded RNA (ssRNA) and initiates an immune response that can be mediated through two different mechanisms involving different adapter proteins, namely MyD88 or TRIF.

A considerable amount of information has been accumulated regarding the anticancer activity of violacein. A number of studies have shown that violacein is able to induce apoptosis in various types of cancer cells, including leukemia cell lines. The authors of [52] used nontumor (CHO-K1 and MRC-5) and tumor (HeLa) cell lines to evaluate the effect of violacein as an oxidizing agent. Despite the fact that a relationship between the appearance of oxidative stress biomarkers in response to cell treatment with violacein (3 and 5 μm) and the induction of apoptosis was not revealed, the authors nevertheless concluded that violacein causes hyperpolarization of mitochondrial membranes, thereby causing cell death. The greatest effect was observed for the MRC-5 and HeLa lines.

In [53], the molecular mechanisms of the action of violacein on melanoma cells have been described: violacein causes a significant decrease in the expression of histone deacetylase 6, an activator of melanoma cell proliferation. In addition, violacein inhibition of signaling pathways (receptor tyrosine kinase AXL and kinase AKT) responsible for avoiding apoptosis was found. AXL overexpression is characteristic of many types of cancerous tumors. These molecular events cause the inhibition of autophagy and, consequently, the death of melanoma cells as a result of apoptosis.

Despite significant advances in the study of the mechanisms of anticancer activity of violacein, many aspects remain unexplored. For example, in a recent study [54], the mechanisms of the effect of violacein

on hepatocellular carcinoma cells were established. This study showed for the first time that violacein inhibits the proliferation of Huh7 and Hep3B hepatocarcinoma cell lines. The antiproliferative effect of violacein was associated with cell cycle arrest at the sub-G1 interphase stage and the induction of apoptotic cell death. Violacein altered the mitochondrial membrane potential (MMP), increased the generation of reactive oxygen species (ROS), activated the caspase cascade, and increased p53 and p21 levels. The p21 protein is an intracellular inhibitor of cyclin-dependent kinase. The dynamics of p21, depending on the intracellular localization of the protein, correlates with the aggressiveness of the tumor and its ability to metastasize. The p53 protein induces apoptosis, programmed cell death. The p53 protein occurs in the cytoplasm in a latent state. Its activation occurs not only in response to DNA damage, but can also be the result of many other processes occurring in the cell, including the activation of oncogenes, hypoxia, nutritional deficiency, aging, etc. When activated, the p53 protein is capable of independently initiating two programs: 1, temporary arrest of the cell cycle in the G1 phase by the p21W AFI protein, which inhibits cyclin-dependent kinases; and 2, stimulation of apoptosis by activating the *Bax* or *Bid* genes, proapoptotic genes of the Bcl-2 family, and/or activating the formation of free oxygen species, which promote the release of cytochrome from mitochondria. Violacein inhibited the proliferation and formation of Huh7 hepatocarcinoma tumor cells and Hep3B hepatoma cancer stem cells and reduced the expression of key cancer stem cell markers including CD133, Sox2, Oct4, and Nanog by inhibiting the transducer and transcription activator-3 (STAT3)/AKT/ERK signal pathways.

Studies have also shown that violacein increases the level of negative regulators of cell cycle progression p53, p27, and p21 [55] and induces reactive oxygen species mediated apoptosis in colon cancer cells as an example [56]. Based on the results obtained by Melo [57], which showed that HL60 promyelocytic leukemia cells respond to violacein with both increased cell death and a decrease in cell proliferation, Ferreira and co-authors [50] revealed the mechanism of this action by demonstrating that violacein activates the tumor necrosis factor (**TNF**) signal. Since this effect was specific for these cells (the authors did not find a similar effect in U937 or K562 cell lines), it was concluded that violacein is a representative of a novel class of cytotoxic drugs that mediate apoptosis by specifically activating signal transduction of the TNF 1 receptor. In HL60 cells, exposure to violacein resulted in phosphorylation of p38 MAP kinase, upregulation of the NF-κB pathway, and activation of caspase.

The p38 MAP kinase plays a major role in multiple signaling pathways that are involved in the initiation and maintenance of chronic long-term inflammation in human disease. MAP kinase p38 activates a number of pro-inflammatory cytokines. This activation leads to the accumulation and release of additional pro-inflammatory cytokines. Oxidative stress is the strongest specific stress that activates p38 MAPK. Abnormal activity (above or below physiological) of p38 MAPK causes pathological stresses in several tissues, including neurons, bones, lungs, cardiac and skeletal muscles, erythrocytes, and fetal tissues. The protein product of the RAS proto-oncogene can increase the activity of p38 MAPK and thereby cause excessive activity of the transcription factor NF-κB. This transcription factor is usually regulated by intracellular pathways that integrate signals from the surrounding tissue and the immune system. In turn, these signals coordinate cell survival and death. Dysregulation of NF-κB activity can activate genes that cause cancer cell survival and can also activate genes that promote cancer cell metastasis to other tissues. Thus, it is believed that inhibitors directed against p38a/p MAPK are effective in reducing various parameters of inflammation in cells and tissues.

The high potential of violacein as an anticancer agent was shown in the work of Mehta and co-authors [58], using cancer cell lines U87 (glioblastoma), A549 (lung tissue), and MCF7 (mammary gland). Treatment of U87, A549 and MCF7 cells with violacein at a concentration of 1 μm resulted in a decrease in cell proliferation of all 3 cell lines within 5 days. In the same cell lines, the level of expression of several intracellular signaling proteins was analyzed upon exposure to violacein at various concentrations. In violacein-treated U87, A549, and MCF7 cell lines, survival proteins and pro-apoptotic proteins Akt and PARP were investigated. As a result, a significant increase in the level of cleaved PARP was found in U87 brain tumor cells treated with violacein at a concentration of 500 nM, as well as in A549 lung cancer cells treated with 1 μM violacein. The same dose of violacein significantly increased the level of p-44/42 MAPK in U87 cell line, but no changes were noted in the expression of the pro-apoptotic Akt protein. As well, violacein did not change the level of expression of pS6 ribosomal protein. These observations indicate that violacein does not affect the signaling network of translational control, but inhibits the migration of brain tumor cells, probably as a result of the destruction of subcellular domain structures of the actin filament network, including lamellipodia and filopodia, which leads to a change in the cell phenotype, disrupting their mobility. The fact that violacein has various mechanisms of action on cells is also confirmed by the data of Queiroz and co-authors [59], who found that violacein showed selective cytotoxicity for HL60 and TF1 cell lines, but the pathways leading to cell death differed for these two cell lines.

As previously mentioned [50], in HL60 cells, exposure to violacein resulted in p38 MAP kinase phosphorylation, upregulation of the NF-κB pathway, and caspase activation. In TF1 cells, the canonical apoptotic pathway is not realized [59]. In this case, the

death of leukemic cells was not mediated by apoptosis and/or autophagy, since the dynamics of biomarkers of both types of cell death did not change under the influence of violacein. Using kinome profiling based on peptide arrays, the authors obtained a picture of cellular kinase activity, according to which the pro-apoptotic activity of violacein is actually carried out by inhibition of calpain and DAPK1 and activation of PKA, AKT, and PDK, followed by structural changes caused by endoplasmic reticulum stress and destruction of the Golgi apparatus, which leads to cell death. The results of this study strongly suggest that violacein induces kinome reprogramming, thus overcoming death signal dysfunctions in internally resistant human leukemia cells. Violacein was able to bypass the natural resistance of TF1 cells by activating kinases that promote endoplasmic reticulum stress [59]. The anticancer activities of violacein and prodigiosin, which is close to it in properties, are described in the review [36].

Despite the great attention of researchers around the world to violacein, there are no unambiguous conclusions about the mechanisms of its action at the moment. However, the fact that violacein has a cytotoxic effect on a wide variety of organisms and cells points to the likely existence of a common target or pathway. The study of the effect of violacein and similar compounds (bisindoles) at the genetic level in model eukaryotic organisms such as *C. elegans* will help elucidate its mechanism of action and assess its promise and potential as a clinical therapeutic agent.

Violacein production. Due to the possibility and prospects of using violacein as an anticarcinogenic agent, the issue of microbial synthesis of violacein on a scale sufficient for its commercial use is of considerable interest. These issues are associated both to the selection of producer strains and, no less important, to the cultivation conditions.

Already in early reports, the need to optimize the composition of the culture medium and cultivation conditions for the optimal yield of violacein was emphasized. Mendes and co-authors [60] used the so-called response surface methodology to determine the optimal cultivation parameters for the *C. violaceum* strain. It was shown that the presence of tryptone and yeast extract in the culture medium positively correlated with biomass yield and violacein content, while the presence of glucose negatively correlated with violacein production.

The influence on microbial culture productivity of such parameters as temperature, lighting, pH value, and the presence of vitamins was also studied. In particular, it was shown that for the strain *C. violaceum* BB-78, the presence of methionine in the cultivation medium was a critical factor for biosynthesis [61].

Using the methods of a multifactorial experiment, the authors of [62] determined the optimal content of the main components in the culture medium: meat broth, tryptophan, potassium nitrate, pH value, volume of medium and inoculum. As a result, they obtained a yield of 1.62 g/L of crude violacein, which significantly exceeded the previously known levels.

At the same time, when selecting a producer, it is necessary to take the fact into account that a significant part of the known natural producers of violacein are pathogenic for humans. *C. violaceum* [63, 64] and *Janthinobacterium lividum* [65] are assigned to pathogenicity class II. In this regard, the attention of researchers was directed both to the selection of natural nonpathogenic producer strains and, more promisingly, to the possibility of creating safe genetically engineered constructs for the production of violacein. For example, in [66], the procedures for cultivating the yeast *Yarrowia lipolytica* carrying the pYaliA1-*vioDCBAE* plasmid, optimizing the biosynthesis process, and isolating and purifying violacein have been described in detail. Cloning of genes for the synthesis of violacein in yeast has opened the prospect of effectively scaling up the laboratory process for the production of this compound. Tong and co-authors [67] used the Golden Gate assembly method to create a library of violacein-producing strains of the yeast *Yarrowia lipolytica*, where each gene in the violacein synthesis pathway was controlled by three different promoters with different transcription strengths. The results showed that strong expression of VioB, VioC, and VioD contributed to the production of violacein with minimal by-production of deoxyviolacein. Optimization of the composition of the medium and cultivation conditions made it possible to achieve a violacein yield of 70.04 mg/L. According to the authors, the developed cloning protocols make it possible to gain access, among other things, to the intermediate products of the violacein biosynthesis pathway and the use of *Y. lipolytica* as an industrially significant producer for biosynthesis.

Fang and co-authors [68] reconstructed the metabolic pathway of violacein biosynthesis in *E. coli* directly from glucose. They combined the violacein synthesis pathway gene cluster with a modified tryptophan pathway and obtained a high yield of the finished product. The use of recombinant *E. coli* B2/pED + pVio under batch cultivation in a 5-L bioreactor and glucose as a carbon source made it possible to obtain crude violacein with a yield of 1.75 g L^{-1} and a productivity of 36 mg L^{-1} h^{-1}.

The creation of genetically engineered constructs using various approaches for microbial synthesis of secondary metabolites, biologically active compounds is attracting more and more attention of researchers. The breakthroughs in the field of genomics and the development of systems biology over the past decade have made it possible to develop methods for modifying the so-called microbial chassis, the working platform of the microorganism-producer, on the basis of which novel microbial metabolic pathways may be

created both for the purpose of fundamental research and practical use (for development biotechnological, pharmaceutical, biomedical, and other areas) [69]. Wei Liu and co-authors [70] expressed a heterologous pathway for the synthesis of β-carotene and violacein. Typically, a heterologous metabolic pathway is constructed by genetically engineering the chassis and optimizing the exogenous pathway. Often this is a trial and error method. The authors used a combinatorial method based on recombinase (named SCRaMbLE-in) to simultaneously solve both problems. The method includes an in vitro set of recombinases for rapid prototyping and diversification of gene expression at the pathway level, and an in vivo genome shuffling system for integrating the assembled pathways into a synthetic yeast genome while combinatorially inducing massive genomic rearrangements in the host chassis. As a result, β-carotene and violacein biosynthetic pathways in the yeast producer were successfully assembled, diversified, and integrated. The authors describe this method as fast, efficient, and versatile for accelerating the cycle of manipulations in engineering biology.

Often the low yield of the product, as well as the relatively limited range of natural compounds, is due, among other things, to their complex chemical structure and, accordingly, the complex genetic organization of biosynthesis pathways. The authors of [71], based on successfully used genetic manipulations [72–74], believe that the integration of synthetic biology with synthetic chemistry allows access to a much more diverse range of active compounds that have no direct analogs in nature, and this should accelerate the discovery of novel therapeutic preparations. Thus, taking the fact into account that the VioA enzyme has a broad substrate specificity with respect to tryptophan analogs, the authors, using a crude cell extract and halogenated tryptophan derivatives, ultimately obtained 26 new violacein or deoxyviolacein analogs with high levels of biological activity.

The use of the latest technological advances in the field of writing and editing the genome, simulating the process of natural evolution at the genomic level, the methodologies of structural rearrangements, and the prospects of such approaches have been reflected in a number of interesting works [36, 75, 76].

CONCLUSIONS

This review considers some areas of research in the field of studying bisindole violacein produced by bacteria. The unique characteristics of violacein have attracted the attention of many research groups. The prospect of this compound for use in medicine, veterinary medicine, and agriculture is undeniable.

A wide range of biological activity, including antimicrobial, anti-inflammatory, immunostimulating, anticancer and other properties, is expected to make violacein and its derivatives an object of clinical research. The existing difficulties associated with the production of violacein, such as low productivity of strains, high cost of the product, must be overcome with the development of synthetic biology and chemistry, which already allow the development of effective protocols and novel producer strains, which will eventually lead to the possibility of obtaining biologically active compounds, including violacein, in amounts necessary for in-depth study and practical application.

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflicts of interest. This article does not contain any studies involving animals or human participants performed by any of the authors.

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