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Review Article

Therapeutic Potential of Bacterial Pigments as Antimicrobial Agents A Review Article

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ABSTRACT

Bacterial pigments make a good substitute for synthetic pigments because of their important characteristics. Since bacterial pigments present a wealth of potential applications, they are also one of the burgeoning fields of study. Previous studies exposed the enormous significance of bacterial secondary metabolites and pigments in particular. Because of their extraordinary antibacterial, anticancer, cytotoxic, and antioxidant characteristics, the therapeutic nature of the bacterial pigments is revealed in the therapy for various diseases. Bacterial pigments are generally selected because of their ease of scaling up, straightforward, and crose-effectiveness in terms of time. Most bacterial pigments are safe for human consumption, making them useful in a variety of industries, including the pharmaceutical industry. Currently, cancer and many other bacterial illnesses are treated using bacterial pigments instead of traditional therapy. Because of the importance of bacterial pigments, it was thought necessary to thoroughly review recent advancements in the literature on the therapeutic potential of bacterial pigments.

Keywords: Bacterial pigments, antimicrobial agents, Prodigiosin, Pyocyanin, Staphyloxanthin

INTRODUCTION

Natural dyes have drawn more attention due to their biodegradability, making them more environmentally friendly. Natural dyes have been used for coloring purposes since the first known civilizations of humans (Kant, 2012). For its powerful antioxidant properties, carotenoid has developed a reputation among researchers. Bacterial carotenoid offers a compelling advantage that may be leveraged as a viable alternative in a period where chemical or plant-derived carotenoids are predominant (Ram *et al.,* 2020). Currently, the pharmaceutical sector utilizes bacterial pigments as an alternative to traditional medicines for treating bacterial infections and cancer. They are becoming increasingly popular due to their affordable prices, biodegradability, lack of carcinogens, and environmental advantages (Agarwal *et al.,* 2023). Fig. (1). Show the important applications of bacterial pigments.

Bacterial pigment synthesis is presently among the rising topics of study, demonstrating the potential for an assortment of commercial applications (Venil *et al.,* 2009). Most of the production of bacterial pigments is present in the research and development phase.

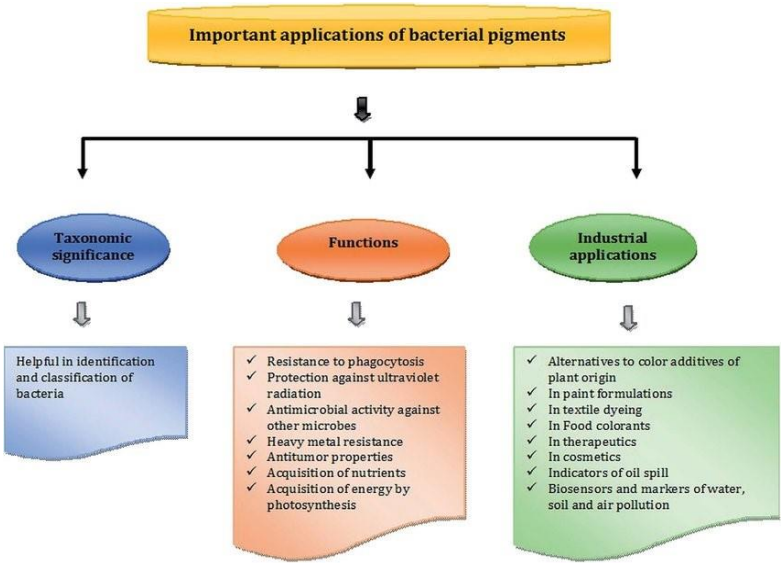

Fig. 1: The important applications of bacterial pigments. (Venil *et al.*, 2014)

Consequently, research on bacterial pigments ought to be prioritized in particular in the search for a cheap and adequate growing medium that might lower costs while increasing its application for industrial production (Ahmed *et al.,* 2012). Biosynthesis of numerous industrially vital pigments, such as zeaxanthin, lutein, carotenoids, etc., are able to introduce using contemporary genetic engineering techniques into microorganisms that either do not naturally produce them or only produce a tiny amount of them (Usmani *et al.,* 2020). Scientists have been able to adapt certain microorganisms, like yeast and *E. coli*, for large-scale synthesis of carotenoids because of recent developments in genetic engineering. For instance, tunable intragenic regions incorporated into an engineered *E. coli* to express the genes *crtY* and *crtZ* which encode for the enzyme's lycopene β -cyclase and β -carotene-hydroxylase, respectively and to synthesize zeaxanthin from lycopene via two fusion protein-mediated substrate channels (Li *et al.,* 2015). Numerous studies have demonstrated the use of pigments such as staphyloxanthin, prodigiosin and pyocyanin against a wide range of microorganisms as alternatives to antibiotics (Alshamaa and Issam, 2017; Al-Kazaz *et al.,* 2014; Qasim, 2019; Dhaif and Al-Attar, 2021).

Given the possible pharmacological potential of bacterial pigments, it was thought important to illustrate the recent advancer of some of these pigments and showtheir biological and antimicrobial power, such as prodigiosin, pyocyanin, and staphyloxanthin.

Prodigiosin

Prodigiosin is a red tripyrrole bacterial pigment that is generally released as a secondary metabolite by the human pathogen *Serratia marcescens* during the bacterial idiophase (Williams, 1973; Ali *et al.,* 2007). Two important intermediates, 2-methyl3-n-amylpyrrole (MAP) and 4-methoxy-2, b2'-bipyrrole-5-carbaldehyde (MBC), are produced jointly by the prodigiosin biosynthesising gene cluster (pig cluster) of 20 kb and a bifurcated pathway. PigC then condenses MBC to produce prodigiosin (Williamson *et al.,* 2005). Prodigiosin is made up of three pyrrole rings. A, B, and C. A bipyrrole unit connects the A and B rings, whereas a dipyrrin connects the B and C rings (Jolicoeur and Lubell, 2008). A methylene bridge connects the monopyrrole moiety (C ring) to the methoxy bipyrrole moiety (A and B rings) (Garneau-Tsodikova *et al.,* 2006) as show in Fig. (2).

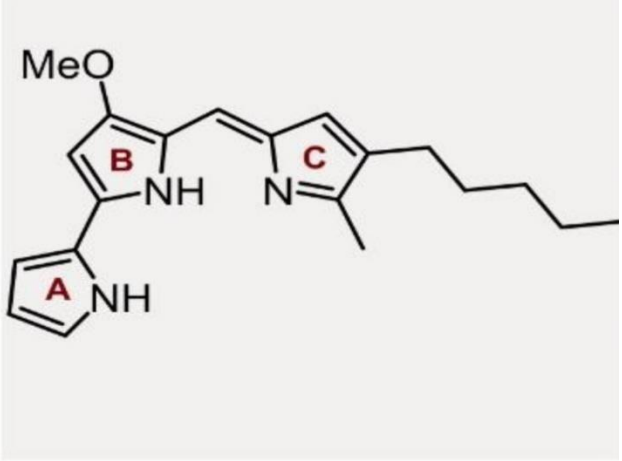

Fig. 2: Prodigiosin structure (A, B and C rings) (Lazic *et al.,* 2022)

Prodigiosin's antibacterial effectiveness was previously linked to 3 mechanisms: Bacterial DNA breakage, cell cycle suppression, and pH regulation (Kamble and Hiwarale, 2012). Suryawanshi, *et al.,* (2017) claimed that prodigiosin is a hydrophobic stressor capable of a chaotropic mechanism action used to disrupt the plasma membrane of rivaling microorganisms. Other hypothesized processes include phototoxicity (Wang *et al.,* 2013) and the production of reactive oxygen species (ROS) (Darshan and Manonmani, 2016). Moreover, prodigiosin has been shown to stimulate the synthesis of autolysins in the process of expanding *Bacillus subtilis* and other *Bacillus* species. Nonetheless, it is probable that the observed antibacterial function of prodigiosin affects bacterial physiology in a variety of ways, including cell growth, respiration, and outer membrane integrity. It may also have a pleiotropic effect on these processes (Danevčič *et al.,* 2016).

Prodigiosin as an Antimicrobial Agent

Before the pre-penicillin age, the antimicrobial activity of prodigiosin and its strong antiprotozoan, antifungal and antibacterial special effects were described. The structure defined with a single tripyrrole is considered accountable for its pharmacological characteristics as antimicrobial, anti-oxidant, anti-cancer and immunosuppressant (Casullo de Araújo *et al.,* 2010) and primarily used as a

naturally formed dye for olephins and textiles (Gulani *et al.,* 2012). The antimicrobial activity of prodigiosin is associated with plasma membrane damage (Suryawanshi *et al.,* 2014).

Prodigiosin exhibits a hydrophobic characteristic, indicating that it may carry out antimicrobial activity via chaotropic mediated stress. Conversely, soluble chaotrops can decrease water activity and introduce additional stress to the cell. Prodigiosin is not soluble enough to accomplish this. Furthermore, stress mediated by chaotropicity will result in differences in the cells on various surfaces and in various locations. Therefore, this type of performance could cause of prodigiosin's inability to maintain the pH slope of the bacterium and its inhibition of the proton pump. There is evidence that prodigiosin primarily targets the plasma membrane in microbial cell, serving as a substitute for cytosolic enzyme systems (Francisco *et al.,* 2007). Gulani *et al.* (2012) mentioned that the heading of evaluating factors influence the *Serratia marcescens* prodigiosin producing while considering the substance's anti-oxidant, antimicrobial, and dyeing properties.

Antibacterial Activity

In many researches, a wide variety of antimicrobial activity is based on the prodigiosin system. Minimal inhibitory concentrations were between 10 and 100 μg / ml against both Gram -ve and Gram +ve bacteria (Lee and Zhang, 2015). An additional study done by Priya *et al.* (2013) found that prodigiosin produced by *S. marcescens* CMST 07 isolated from an estuary had an antimicrobial effect against *Alteromonas sp., P. aeruginosa*, *B. subtilis*, and *Gallionella sp.* that were sensitive to it. Altered experiments have demonstrated that prodigiosin inhibits the growth of a wide variety of Gram +ve bacteria (*Staphylococcus spp., Bacillus spp.,* etc.) in addition to Gram -ve bacteria (*Escherichia coli, Salmonella enterica,* etc.) (Danevčič *et al.,* 2016). Previous research has indicated that prodigiosin has a positive antibacterial impact on the ability stop the target enzymes that inhibit cell growth like topoisomerase IV and DNA gyrase (Berlanga *et al.,* 2000). In 2015, Darshan and Manonmani published a paper in which they described prodigiosin as a suggestion that affects the function of biological membranes, due to its hydrophobic properties. Prodigiosin reaches the cytoplasm of the bacterial cells and then affects the integrity of the membrane by reducing the layer of lipopolysaccharide at higher concentrations *B. cereus* as well as *E. coli.* Prodigiosin may substitute naturally produced pigments with synthetic dyes for likely utilization in the food sector as noted by Dozie-Nwachukwu *et al.,* (2017). The concern about prodigiosin as a drug is evident from several reports in the literature of various domains involved in the measurement to the review of its complications and encapsulation for both drug delivery in order to improve its efficacy. Additionally, in the most recently sequenced cluster, prodigiosin resistance genes have not been clearly identified, which is a valuable indicator for potential additional prodigiosin developments towards more effective antibiotics. However, prodigiosin's effects must be protected during the strains' development, because in contrast to other susceptible strains from the same genus, mutant strains that are unable to produce prodigiosin remain resistant to its action (Borić *et al.,* 2011).

Pyocyanin

Pyocyanin is a blue redox-active secondary metabolite that belongs to the phenazines, a wide family of tricyclic chemicals. They are secreted during the late stationary phase and serve as a regulator. The medium has a distinct blue hue. It may be easily separated from culture media because it dissolves in chloroform. Pyocyanin is a chemical compound that may undergo a complicated series of oxidation-reduction reactions (Ran *et al.,* 2003). The discovery of the phenazine nucleus as a natural product was made possible by understanding the structure of pyocyanin. There are two possible states

of pyocyanin: oxidized and reduced. The latter is unstable and reacts rapidly with molecular oxygen (Hassett *et al.,* 1992). Fig. (3) show the structure of pyocyanin.

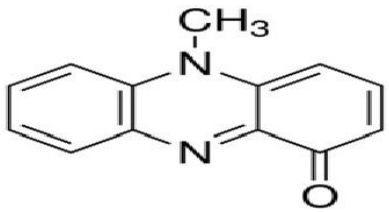

Fig. 3: The structure of pyocyanin. (Rani and Azmi, 2019)

Pyocyanin is an example of a secondary metabolite with antibacterial properties and the ability to coordinate the response of microbial populations to environmental changes. After investigating the process by which pyocyanin restricts bacterial growth, it was discovered that pyocyanin interacts with the respiratory chain of the cell membrane to stop the bacterial cells from carrying out their active metabolic transport function (Baron *et al.,* 1989). Pyocyanin affects pharmacologically in a variety of ways in both eukaryotic and prokaryotic cells (Vukomanovic *et al.,* 1997) as well as having antibacterial, fungal, and protozoal activities (Karpagam *et al.,* 2013). Together, pyochelin and pyocyanin create reactive oxygen species that harm and consequently cause resistance (Audenaert *et al.,* 2002).

Antibacterial Activity of Pyocyanin

According to Saha *et al.* (2008), the formation of the water-soluble secondary metabolite pyocyanin was responsible for roughly 90 and 95 percent of the *P. aeruginosa* strains antimicrobial inhibitions. It provides that pathogenic microbe such as *Klebsiella pneumoniae, E. coli,* and *Salmonella paratyphi* are inhibited. Pyocyanin derived from *P. aeruginosa* 4B strain showed antibiotic activity in opposition to a variety of pathogens and food deterioration microorganisms, including *Listeria monocytogenes* and *Bacillus cereus*. Secondary metabolites and enzymes such as haemolysin and hydrolytic enzymes were important in their antibacterial properties (Fontoura *et al.,* 2009). Pyocyanin from *P. aeruginosa* DSO-129 shows antibacterial activity against species such as *Micrococcus luteus, Staphylococcus aureus, Staph. epidermidis, Saccharomyces cerevisiae,* and *Bacillus subtilis* (Rahman *et al.,* 2009). Another study found that pyocyanin had antibacterial activity directed against diverse bacteria; the pigment generated by the strain was found to be extremely efficient in opposition to pathogens such as *Streptococcus pneumoniae, Acinetobacter, E. coli,* and *Staph. aureus* (Sweden, 2010). *P. aeruginosa* pyocyanin has antibacterial action against competing microorganisms, including *E. coli* that produces indole (Hassett *et al.,* 1992). Sudhakar *et al.* (2013) also found that pyocyanin from *P. aeruginosa* SU1 effectively against *E. coli, Staph. aureus, Proteus sp., Klebsiella sp.,* and *Pseudomonas sp.* the highest efficacy was shown toward *E. coli, Proteus sp., S. aureus,* and *Klebsiella sp.,* with resistance observed against *Pseudomonas spp.*

Staphyloxanthin

Staphylococcus aureus produce the secondary metabolite staphyloxanthin, a yellow pigment staphyloxanthin as a secondary metabolite. It is believed to have antibacterial activity against bacteria (Kamble *et al.,* 2022). The golden color of the colonies in growing conditions gave *Staph. aureus* its name (the Latin word aureus means "golden") (Valliammai *et al.,* 2021). According to recent research, staphyloxanthin, a carotenoid pigment, is critical for *Staph. aureus'* capacity to withstand neutrophil death (Xue *et al.,* 2019). The evidence suggests that staphyloxanthin plays a key role in encouraging bacterial invasion (Yehia *et al.,* 2022). The biosynthesis of the pigment is controlled by an operon that

contains five genes called crtOPQMN (Elmesseri *et al.,* 2022). A σ^B-dependent promoter upstream of *crtO* and a terminator downstream of *crtN* drive the operon's transcription. An operon called crtOPQMN which is controlled by *SigB* contains the genes involved in pigment production (Gao *et al.,* 2017). The rsbUVWsigB system and the crtOPQMN operon have been shown to be crucial for *Staph. aureus* pigmentation by investigations (Abbas *et al.,* 2022). Other genes besides these can also control the generation of pigments. *S. aureus* is protected from the destruction caused by reactive oxygen species (ROS) by the pigments that give it its golden color (Paul *et al.,* 2021). The carotenoid pigment staphyloxanthin has several conjugated double bonds, which enable it to absorb more energy from ROS. Certain bacterial carotenoids, such as those generated by *S. aureus*, have been shown to be able to defend against these defensive molecules, according to reports (Xue *et al.,* 2019).

Biosynthesis of Staphyloxanthin

The biosynthesis of staphyloxanthin includes many steps in the presence of unique enzymes to accelerate and convert molecules. These steps are: At the dehydrosqualene synthase, *CrtM* catalyzes the process by which two molecules of farnesyl diphosphate condense yield dehydrosqualene (4,4′-diapophytoene), which is the initial step in the production of staphyloxanthin. Then, dehydrosqualene desaturase *CrtN* dehydrogenate dehydrosqualene to produce 4,4′-diaponeurosporene, a yellow primary intermediate. After that, the terminal methyl group of 4,4′-diaponeurosporene is oxidized by *CrtP*, which is most likely a mixed-function oxidase, to produce 4,4′-diaponeurosporenic acid. Followed by glycosyltransferase *CrtQ* produces glycosyl 4,4′-diponeurosporenoate as a byproduct of esterifying glucose at the C1′ position with 4,4′-diaponeurosporenic acid's carboxyl group. This substance was the main product in the clone expressing CrtPQMN (Ni *et al.,* 2020). In the last step, staphyloxanthin is produced due to the acyltransferase *CrtO* esterifying glucose at the C6″ position with the carboxyl group of 12-methyltetradecanoic acid. The crucial enzymes for the production of staphyloxanthin are *CrtM* and *CrtN* (Yang *et al.,* 2020). The Biosynthesis pathway of staphyloxanthin is illustrated in Fig. (4).

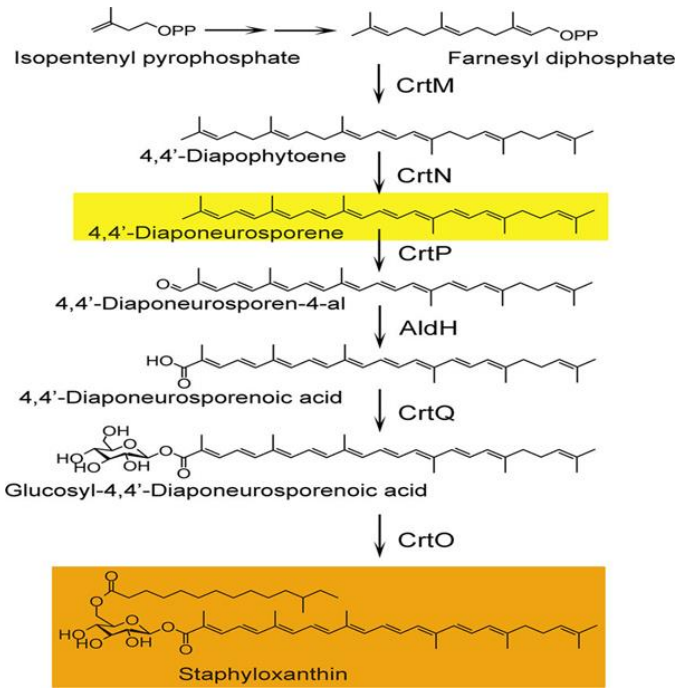

Fig. 4: Biosynthesis pathway of staphyloxanthin. (Gao *et al.,* 2017)

Early enzymatic stages in the synthesis of STX resemble those in the cholesterol biosynthesis. It was found that the cholesterol biosynthesis inhibitor phosphonosulfonates (bisphosphonates and similar) can bind to *CrtM* and block it by binding to it, increasing the susceptibility of non- pigmented bacteria to neutrophil killing and innate immune clearance in a mouse infection model (Zhang and Cheng, 2022). It was discovered that naftifine and NP 16 (Gao *et al.,* 2017) could both inhibit *Staph. aureus CrtN* competitively to block the biosynthesis of carotenoid pigment, which in turn reduces the virulence of these *Staph. aureus* isolates and increases their susceptibility to innate immune clearance (Xue *et al.,* 2019; Ford *et al.,* 2021).

Biological Activities of the Staphyloxanthin

Microbial cells generate biological pigments known as microbial pigments (Sánchez-Muñoz *et al.,* 2020). A microbial pigment called staphyloxanthin has been shown to play a significant role in the pathophysiology of *Staph. aureus* through interactions with host immune systems and the expression of pro-inflammatory or cytotoxic properties (Yehia *et al.,* 2022). However, the discovery of microbial pigments is attributable to carotenoid pigments, which play a variety of crucial biological roles in a variety of living things (Ashokkumar *et al.,* 2022). Staphyloxanthin, is a golden carotenoid pigment (Xue *et al.,* 2019). Because of their wide range of bioactive properties, bacterial carotenoid pigments supply a potential path for applied biomedical studies (Venil *et al.,* 2013). Staphyloxanthin is a form of apocarotenoid triterpenoid pigment generated by *Staph. aureus* (Dzib-Cauich *et al.,* 2020). Apocarotenoids, like carotenoids, have been shown to be biologically active compounds with potent antioxidant and anticancer activities. Apocarotenoids, according to Sharoni *et al.* (2012) may be seen as biological substances having multifunctional, as opposed to monofunctional, activity (Simkin, 2021). As a result, they may help prevent cancer and other degenerative disorders (Bhatt and Patel, 2020). Among the most significant *S. aureus* virulence factors is the staphyloxanthin pigment (Elmesseri *et al.,* 2022). Results by Kamble *et al.* (2022), suggest that staphyloxanthin, which was derived from the *Staphylococcus gallinarum* strain, had strong anticancer, antibacterial, and antioxidant, DNA damage-protecting properties, which could be connected to the pigment's high antioxidant capacity.

Antioxidant Activity

DNA, proteins, and lipids are just a few of the biological substances that reactive oxygen species (ROS) may disrupt. Carotenoid pigments have antioxidant properties that help combat ROS. The carotenoid staphyloxanthin clearly has the most antioxidant effects. In general, almost all carotenoids have antioxidant properties. Common carotenoid pigments have alternating single and double bonds along their carbon backbone (Zia-Ul-Haq, 2021). By receiving extra energy from ROS, these alternating bonds transform the carotenoid molecule into a powerful antioxidant (Maslova *et al.,* 2021). Investigations led to the DPPH free radical technique being used to demonstrate the C30 carotenoids' capacity to scavenge free radicals and their antioxidant properties (Kim *et al.,* 2019).

CONCLUSION

The use of bacterial pigments against different types of bacteria that cause many infections is important in the field of alternatives to antibiotics, especially since researchers around the world are interested because of the spread of bacterial strains that are resistant to many antibiotics, which are difficult to treat and may lead to serious consequences. Until now, there has been no sufficient interest in treatment alternatives, as in the case of antibiotics. Therefore, it is not possible to dispense with antibiotics in treating infections, but on the other hand, the effectiveness of alternatives, including bacterial pigments, has been proven in many studies, so it is possible to combine them with antibiotics,

that is, in a mixture, and this may contribute to reducing the emergence of resistance and also the side effects when it decreases the concentration of the antibiotic used with bacterial pigments.

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الامكانيات العلاجية للصبغات البكتيرية كعوامل مضادة للميكروبات

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الملخص

تعتبر الأصباغ البكتيرية بديلاً جيدًا للأصباغ الاصطناعية نظرًا لخصائصها المهمة. وبما أن الأصباغ البكتيرية تقدم ثروة من التطبيقات المحتملة، فهي أيضًا واحدة من مجالات الدراسة المزدهرة. كشفت الدراسات السابقة عن الأهمية الهائلة لمركبات الايض الثانوية للبكتريا والصبغات على وجه الخصوص. تم الكشف عن الطبيعة العلاجية للصبغات البكتيرية في علاج مجموعة من الأمراض وذلك بسبب خصائصها غير العادية المضادة للبكتيريا، والمضادة للسرطان، والسامة للخلايا، والمضادة للأكسدة، وقد تم اختيار الأصباغ البكتيرية بشكل عام وذلك نظرًا لسهولة توسيع نطاقها، وطرق استخراج الصبغات المباشرة، وفعالية التكلفة من حيث الوقت، وغالبية الأصباغ البكتيرية آمنة للاستهلاك البشري، مما يجعلها مفيدة في مجموعة متنوعة من الصناعات، بما في ذلك صناعة الأدوية. حاليًا، يتم علاج السرطان والعديد من الأمراض البكتيرية الأخرى باستخدام الصبغات البكتيرية بدلاً من العلاج التقليدي. بسبب أهمية الأصباغ البكتيرية، فقد كان من الضروري إجراء مراجعة شاملة للدراسات المتعلقة بالإمكانات العلاجية للأصباغ البكتيرية.

الكلمات الدالة: الصبغات البكتيرية, العوامل المضادة للميكروبات، برودجيوسين، بايوسيانين، ستافلوزانثين.