

Pigments-Producing Bacteria as a Different Sources of Pharmaceuticals Therapeutics

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ABSTRACT

Pigment is a substance that is frequently used in industries and comes in a broad range of color, some of which are water soluble. The pigment created by a no. of non-toxic microorganisms make them eco-friendly. Pigmented bacteria are a remarkable category of microorganisms that produce vibrant pigments to aid in their survival, communication and ecological niches. These bacteria produce pigment with astonishing diversity, ranging from yellow, orange, red, purple, blue, and brown. Pigments have antioxidant, antiviral, antibacterial, and anticancer properties among others. Bacteria that produce pigment have become a promising source of bioactive substances that may have anticancer effects. Bacterial pigments, which include melanin, prodigiosin, violacein, and carotenoids have a variety of pharmacological properties, including the ability to modulate oxidative stress, induce apoptosis, and have anti-proliferative effect. They are desirable prospect for therapeutic development due to their distinct modes of action. Disrupted cell function is the cause of the malignant process. This results in genetic instability because of the accumulation of many genetic and epigenetic alterations inside the cell, which manifest as chromosomal or molecular abnormalities. In addition, a sophisticated super cellular communication network is created by interactions between tumour and other cell types.

Keywords- Colors, Pigments, Antioxidant, Anticancer, Prodigiosin, Carotenoids.

INTRODUCTION OF BACTERIAL PIGMENT

A class of highly coloured chemicals known as pigments is used to colour other materials. Pigments with a large range of colours, some of which dissolve in water. Microbial pigments are the natural pigments that are taken from microorganisms. Microorganisms that produce pigments are found in all biological niches, including soil, rhizospheres sand, woodland sand, desert sand, marine samples, and fresh water [1]. Microorganisms used to produce pigments must meet a number of requirements, one of which is the ability to use a variety of spectrums. sources of carbon and nitrogen, resistance to temperature and pH changes, high concentration of minerals, moderate growth conditions, fair colour output, low toxicity or pathogenicity, and easy cell mass separation [2]. There are two different types of pigments, plants and micro-organisms.

One of a product's most crucial visual attributes is its colour. Colours affect acceptability and give a desired quality to something that can be sold. Since ancient times, colour have been used to help create a variety of items, both to enhance their look and compensate for colour loss that occurs naturally during processing. Colours have now become very useful sensory evaluation tool for product quality. Artificial synthetic colours are used extensively in number of industries, such as food, cosmetics, textiles,

and pharmaceuticals. As a result, several synthetic hues are no longer permitted for use because of their toxicological problems. Because of the negative effects of synthetic dyes, natural pigments have been the focus of much research [3].

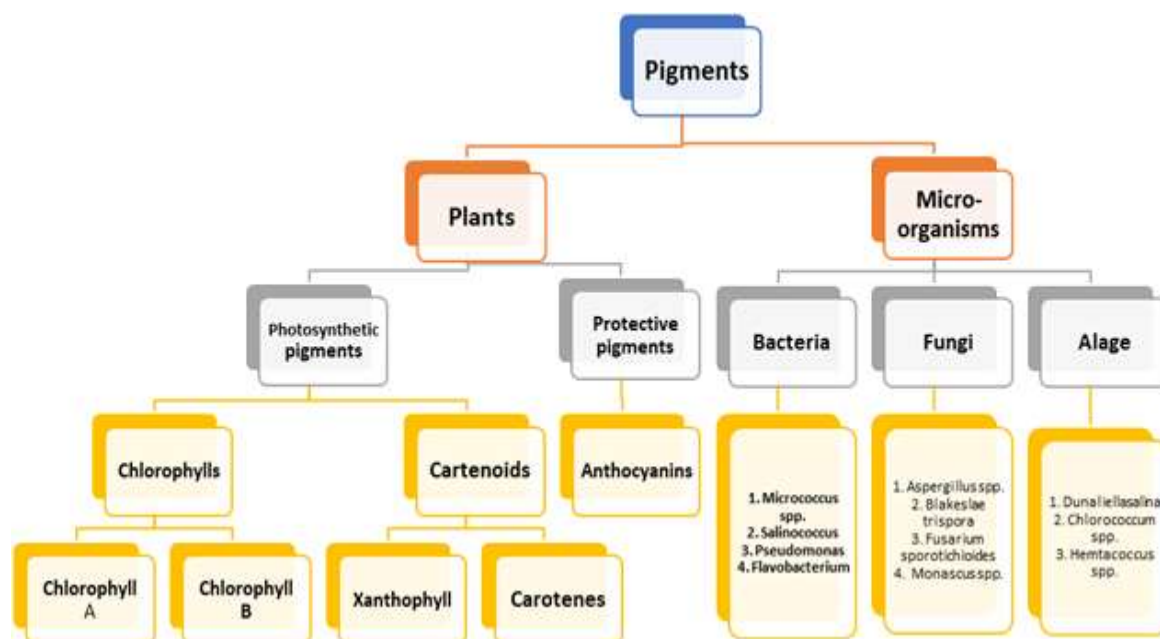


Figure 1: Different Types of Pigments.

Natural pigments have limited uses in food due to their low bioavailability, storage problems, and minor health effects. However, by stopping pigment deterioration, the encapsulating method fixed these problems. Pigments that are encapsulated have better stability and health-promoting properties [4]. Bacteria that are not phototrophic may utilize pigments that are essential to photosynthesis for other purposes. Numerous bacteria reside in dark environments that are shielded from sunlight, including the deep sea, underground, and inside the bodies of humans and animals. Most microbes can adapt to several pigment families without the need for sunshine [5]. It can also aid in resolving the public's rising anxiety about the harmful health impacts of artificial coloring added to food items. Furthermore, because toxic chemicals released into the environment during the production of synthetic colorants could be prevented, natural colorants would not only improve human health but also aid in the preservation of biodiversity. Baby food, breakfast cereals, pastas, sauces, processed cheese, fruit drinks, vitamin-enriched milk products, and certain energy drinks all include these natural colorants. Therefore, natural colors can satisfy the twin needs of probiotic health benefits and aesthetically pleasing colors in food items, in addition to being environmentally responsible [6]. Heterotrophic and autotrophic prokaryotes are the two main groups into which prokaryotes fall. Autotrophic prokaryotes have pigments that aid in photosynthesis; the most prevalent pigments in autotrophic prokaryotes are xanthene's, carotene, and chlorophyll. The production of some accessory pigments by heterotrophic prokaryotes aids in their ability to survive in harsh environments. For instance, the bacterium *Xanthomonas oryzae* naturally secretes the membrane-bound, yellow-coloured pigment xanthonoid. Furthermore, it has been demonstrated that xanthotoxin protects microorganisms from photodamage. These accessory pigments' production is essential for the taxonomic characterisation and identification of new bacteria as well as for determining the genetic relatedness between the new and existing species [7]. Bacteria, microalgae, and archaea (primarily haloarchaea) are examples of pigmented microorganisms, often referred to as chromogenic microorganisms, that have been isolated from a variety of environmental and geographical settings, including terrestrial, aerial, and marine settings [8]. Like plants and animals, prokaryotes are known to manufacture pigments. While some of these pigments shield photosynthetic bacteria from c

APPLICATION OF BACTERIAL PIGMENTS

Microbial pigments are known to have cytotoxic, antioxidant, antimicrobial, antimalarial, anticancer, antitumor, and antifouling properties. Their significance has been highlighted in a variety of applications, including food, cosmetics, medicines, and textiles [9,10].

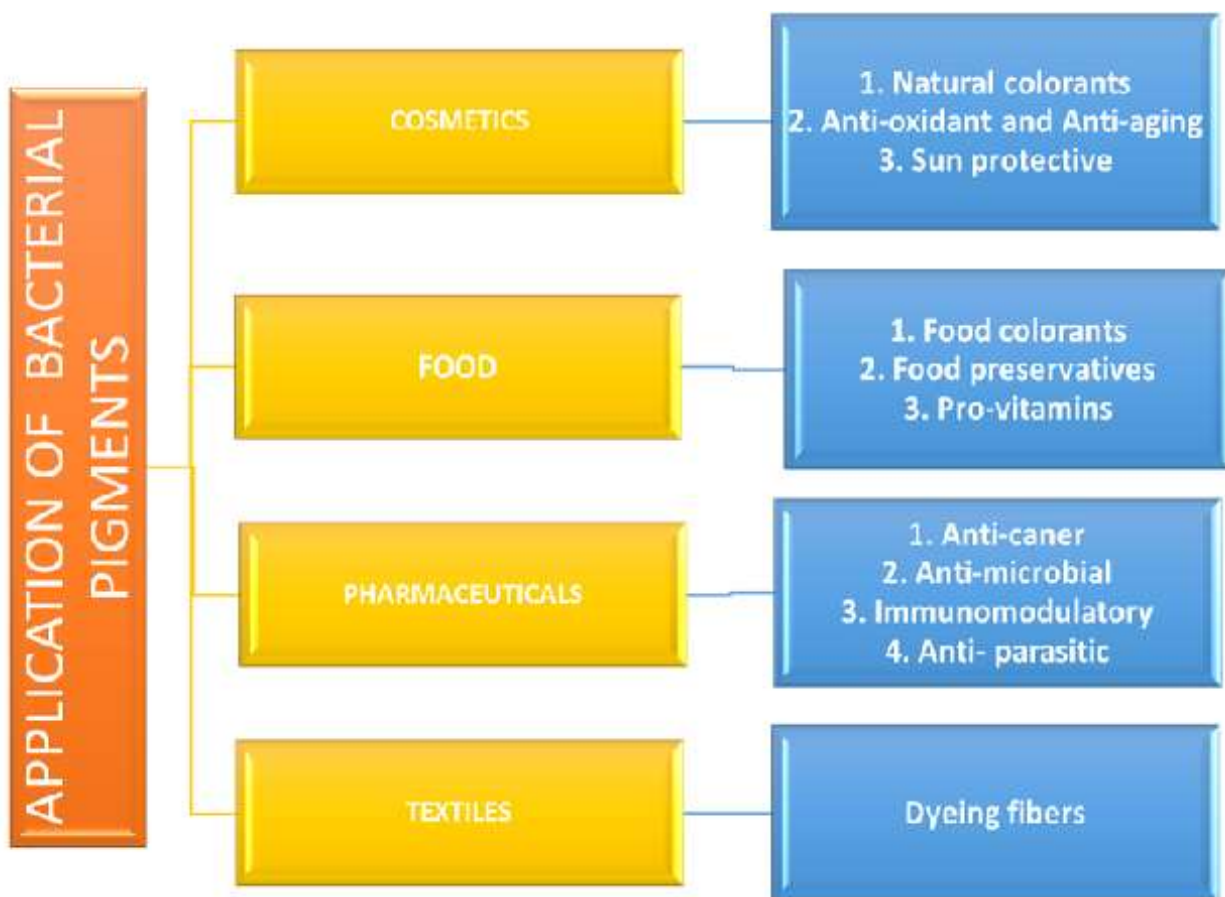


Figure 2: Application of Bacterial Pigments.

ROLE IN PHARMACEUTICALS INDUSTRY

The number of deaths from bacterial infections has significantly decreased since the development of antibiotics. Not only has the average human lifetime grown over the past few decades, but we have also improved our ability to handle medical emergencies. We are grateful for our ever-growing pharmaceutical sector, which funds the creation of new medications, oversees their manufacturing, and distributes them to the general public. But as the years go by, our understanding of contemporary medicine continues to be inadequate to meet the problems of the modern world. Multidrug-resistant (MDR) strains of pathogenic bacteria have emerged as a result of the careless distribution of strong antibiotics. This is among the difficulties that have left us powerless. The unresolved mysteries surrounding illnesses like cancer, which have an irreparable effect on patients and their families, are another. The pharmaceutical business was forced to explore a new avenue—"bacterial pigments"—in order to address the severe problems of antibiotic resistance and costly healthcare. Recent studies on bacterial pigments have reaffirmed their significance; they might be the next major development in contemporary medicine. A brief overview of recent advancements in the pharmaceutical industry's use of bacterial pigments for medicinal reasons is provided in the sections that follow [11]. According to earlier research, bacterial secondary metabolites and pigments in particular are extremely important for treating a variety of illnesses. They also have anticancer, antibacterial, and immunosuppressive characteristics. Phenols, quinols, flavonoids, polyketides, peptides, terpenoids, steroids, and alkaloids are a few examples of secondary metabolites with possible medicinal uses. These substances have exceptional, antimicrobial action, antiviral activity, antifungal activity of bacterial pigments antibacterial, antioxidant, inflammatory, immunosuppressive, and anticancer properties [12]. Cancer is the major problem all over the world. So, we are explained in details.

Anticancer Activity

According to WHO study, lifestyle-related risk factors that can be changed, such as smoking and other tobacco products, account for 35% of cancer-related deaths globally. Consumption of alcohol, in nations with low, medium, and high incomes; parasites; infections; exposure to UV light and tanning with UV-emitting devices; environmental tobacco smoking; dietary factors; hormone replacement therapy; and ionizing radiation [13,14,15]. Disrupted cell function is the cause of the malignant process. Genetic instability results from the accumulation of several genetic and epigenetic alterations inside the cell, which manifest as chromosomal or molecular abnormalities [12,16,17]. During the micro-evolutionary process of malignant transformation, cancer cells accumulate multiple genetic alterations that provide them with several capabilities [18]. Reducing cancer mortality via lowering cancer incidence is known as prevention. Avoiding carcinogenic exposures, changing lifestyle habits, and detecting malignant tumors early are ways to do this. According to epidemiologic studies, those who engage in greater physical activity are less likely than those who do not to get certain types of cancer. You do not necessarily acquire cancer just because you have one or more risk factors. It is possible to prevent some of the risk factors. Others, such as age and family history, are unavoidable. A number of elements can combine to transform a healthy cell into a cancerous one [19]. In actuality, chemical workers who are exposed to aromatic amines get bladder cancer. Histone deacetylases and histone methyl transferases, which may alter histone amino-terminal lysine and produce certain histone codes, are strongly linked to DNA methylation. This leads to the creation of inactive chromatin, which gives cancer cells their distinctive characteristics. It is commonly recognized that cancer cells exhibit dysregulation of thousands of genes. Numerous cancers have been firmly related to cigarette smoking. It has been demonstrated that quitting smoking lowers the risk of developing cancer. Obesity and alcohol use are two more possible modifiable cancer risk factors [20].

As a result, cancer is a severe issue that has an impact on everyone's health. Regretfully, it is a diverse disease at the tissue level, and this diversity poses significant obstacles to both the precise diagnosis and the effectiveness of treatment. The colon and rectum, prostate, lung and bronchus, and bladder have the largest percentages of cancer types in men. The breast, lung and bronchus, colon and rectum, uterine corpus, and thyroid are the areas in women where cancer is most common [21,22,23].

DEATH RATE OF CANCER IN INDIA

In 2022, India had a high cancer mortality-to-incidence ratio (64.47%), with roughly three out of every five cancer patients dying, ranking second only to China in terms of cancer fatalities worldwide. According to a study published in "The Lancet Regional Southeast Asia," India came in third place internationally in terms of the absolute number of cancer incidences, behind the United State and China, based on data from the Global Cancer Observatory (GLOBOCAN) 2022 [24]. The estimated number of cancer cases in India in 2023 is 1,496,972, up from 1,461,427 in 2022, according to the ministry, estimated that the number of cases of stomach cancer would rise to 54,023 in 2023 from 52,706 in 2022 [25]. The estimated number of cancer cases in India in 2023 is 1,496,972, up from 1,461,427 in 2022, according to the ministry. In response to a question in the Lok Sabha, SP Singh Baghel, Union Ministry of State for Health and Family Welfare, estimated that the number of cases of stomach cancer would rise to 54,023 in 2023 from 52,706 in 2022 [26]. In 1990, the death rate was 41.39 per 100,000 people; by 2021, it will be 60.44 per 100,000. This reflects a 46.02% growth over three decades. Between 1990 and 2021, the incidence and DALYs rates of cancer grew by 34.94% and 22.48%, respectively. A recent study showed a significant increase in the cancer burden in India from 1990 to 2021, underlining the necessity of preventive and early detection efforts [27].

CORELATION OF ANTI-CANCER AND BACTERIAL PIGMENTS

The constant division of cells, which leads to the accumulation of cells in a small region and the eventual formation of tumors, is a characteristic of malignant tissues. Somatic cells can have malignant tendencies due to a variety of circumstances, including carcinogenic chemicals, bad eating habits, oncogenic bacteria and viruses, and a number of other unknown causes [28]. Cancer is the second biggest cause of mortality globally, and its incidence has skyrocketed in recent years. The cause of it is people's unregulated exposure to carcinogenic substances produced by the industry [29].

It is possible to treat solid tumors using chemotherapy. However, because the morphology of cancer cells is identical to that of healthy cells, these medications are not specifically harmful to malignant cells. As a result, some of the nearby healthy cells are harmed in addition to the tumor cells. The quest for a novel anti-cancer medication is fueled by this disadvantage of current chemotherapy. Numerous bacterial pigments have shown strong anti-cancer properties. For example, the radioresistant bacterium *Deiphosopist Radiators* produces the red, non-photosynthetic pigment diatoxanthin, which is structurally a carotene. When normal cells operate, they produce free radicals, which can build up inside the cell and cause cancer [30]. Since several pigments extracted from marine Actinomycetes have also

demonstrated cytotoxic action against several human cancer cell lines, the marine microbiota is the subject of intense research. Actinomycetes, including *Streptomyces* species and *Saccharomonospora azurea* [31]. It is known that several *Streptomyces* species generate a variety of bioactive substances and pigments with anti-tumor properties. When looking for a new anticancer drug, *S. psammiticus* and *S. Aravosis* are the best options [32].

Natural pigments are suitable for cancer treatment because of their controlled cytotoxicity. The haloalkaliphilic archaeon *Naturalia* sp. M6 produces halo-archaeal carotenoids, which are another abundant source of anti-tumor bioactive chemicals. Through apoptosis-dependent and blockage matrix metalloproteinase (MMP)-9, which is in charge of malignant angiogenesis and metastasis, the *in vitro* investigations show potent anticancer action [33]. *Pseudomonas aeruginosa* actively produces a phenazine called pyocyanin, which was first shown to be lethal to human pancreatic cancer cell lines (Panc-1) [34]. Pyocyanin had a similar anti-cancer effect on human hepatoma cells (HepG2) and glioma cells of 66.34%. By generating high levels of ROS, such as hydrogen peroxide (H₂O₂) and superoxide (O₂⁻), which result in severe oxidative stress and cell damage, pyocyanin mainly inhibits the proliferation of cancer cell lines [35]. Around the world, cancer is a serious health concern. Since cancer treatment techniques like chemotherapy and radiation therapy have a number of adverse effects, new, efficient anticancer medicines must be developed [36]. Natural products are now being studied in an effort to create powerful anticancer drugs with strong antioxidant properties and low host cell toxicity [37]. Prodigiosin analogs and synthetic derivatives have also been shown to exhibit *in vitro* anticancer action. Prodigiosin's cytotoxic and anti-proliferative properties have been noted in human primary cancer cells from B-cell chronic lymphocytic as well as in cultured tumor cell lines [38].

Antibacterial Activity

The human community is constantly at risk from bacterial illnesses. Bacteria frequently develop resistance to antimicrobial medications as a result of their rapid mutation and spread. Public health is also hampered by antimicrobial medication resistance as it makes it harder and expensive to control these illnesses. In order to address antimicrobial medication resistance, researchers are increasingly turning to more innovative antimicrobials, such as bacterial pigments. For example, *Streptomyces* sp. JS520 produces a deep red pigment that has been demonstrated to offer sufficient defences against bacterial infections brought on by *Bacillus* and *Micrococcus* [39]. The antibacterial properties of halophilic bacterial pigments have been the subject of recent studies. Because they are natural compounds, these pigments don't harm people, which makes them more appealing for the manufacturing of antibiotics on a big scale. Additionally, pyocyanin has antibacterial properties against a variety of bacteria, both Gram-positive and Gram-negative. This characteristic results from pyocyanin's contact with the cell membrane's respiratory chain, which prevents the bacterial cells from actively carrying out their metabolic transport function [40]. Tetracycline is already an FDA-approved medication, and a bactericidal chemical prevents the bacterium from synthesizing proteins. There are several substances found in nature whose synthesis is dependent on quorum sensing; that is, the organism makes these substances to promote the selective growth of its kind and typically has an inhibitory impact on the competing species [41].

Antiparasitic Activity

Among the deadliest and rapidly proliferating vector-borne illnesses are parasitic infections. These include illnesses including helminthiasis, encephalitis, leishmaniasis, and malaria. These parasites interfere with the host's general growth by infesting the body and depriving it of vital nutrients. One-sixth of the world's population, or around one billion individuals, have had at least one parasitic illness [42]. These statistics are concerning in and of themselves, but they go beyond this. Economic depletion results from parasitic infections, which are not restricted to human hosts but also spread their undesired effects to plants and animals. Developing formulations that damage parasites without affecting the host is always difficult because of the intricate pathophysiology and evolutionarily enhanced virulence. Some strains of *Pseudomonas* species create bioactive pigments that have antiparasitic properties, according to research done on psychrotolerant bacteria from the Antarctic continent [43].

These kinds of studies demonstrate the true effectiveness of bacterial pigments and the unrealized potential that psychrophiles possess. Although pigments like violacein and deoxy violacein are widely used in the pharmaceutical sector as antimicrobials, their antiparasitic properties—particularly against strains of *Plasmodium falciparum* and *Trypanosoma cruzi*—have drawn more attention in recent years. Large-scale violacein production is being attempted in order to capitalize on its potential as an anti-plasmodium and anti-*Trypanosoma* medication [44].

Immunosuppressors

The patient's immune system frequently treats the organ tissue as non-self after receiving a solid organ transplant, which results in organ rejection. These individuals are administered immunosuppressive medications to reduce their

immunological response, resulting in immunodeficiency. Cycloprodigiosin hydrochloride, a non-toxic bioactive pigment that was discovered from the marine bacteria *Pseudoalteromonas dentifrices*, was shown to preferentially inhibit T-cell proliferation. It is also thought that other proapoptotic prodigiosin members affect the splenocytes in mice [45].

One of the earliest experiments ever carried out, they have paved the way for the potential use of bioactive pigments as immunosuppressive medications. The red pigment RP-063, which is produced by MS-02-063, a strain that is phylogenetically related to γ -proteobacterium *Hamell* sp., has been shown to have immunosuppressive activity. This activity differs from that of the other well-known compounds, as it inhibits the proliferation of lymphocytes and lowers the release of superoxide from these cells. B-cell and T-cell proliferation is known to be inhibited by 2, 2'-[3-methoxy-1'-amyl-5'-methyl-4-(1-pyrryl)] dipyrin-methene (MAMPDM), another prodigiosin. MAMPDM selectively inhibited T cells by inducing apoptosis in Con A-stimulated cells [46].

FACTOR AFFECTING OF BACTERIAL PIGMENTS

Several parameters influence pigments growth and output through microbial fermentation, including the types of fermentation, media components (carbon, nitrogen sources, minerals), pH, temperature, incubation period, moisture contents, and aeration. Microbial pigments are produced using both solid-state and submerged fermentation techniques. Solid-state fermentations provide the benefits of increased production and productivity, as well as the direct application of the fermented product as a colorant without isolation the product [47].

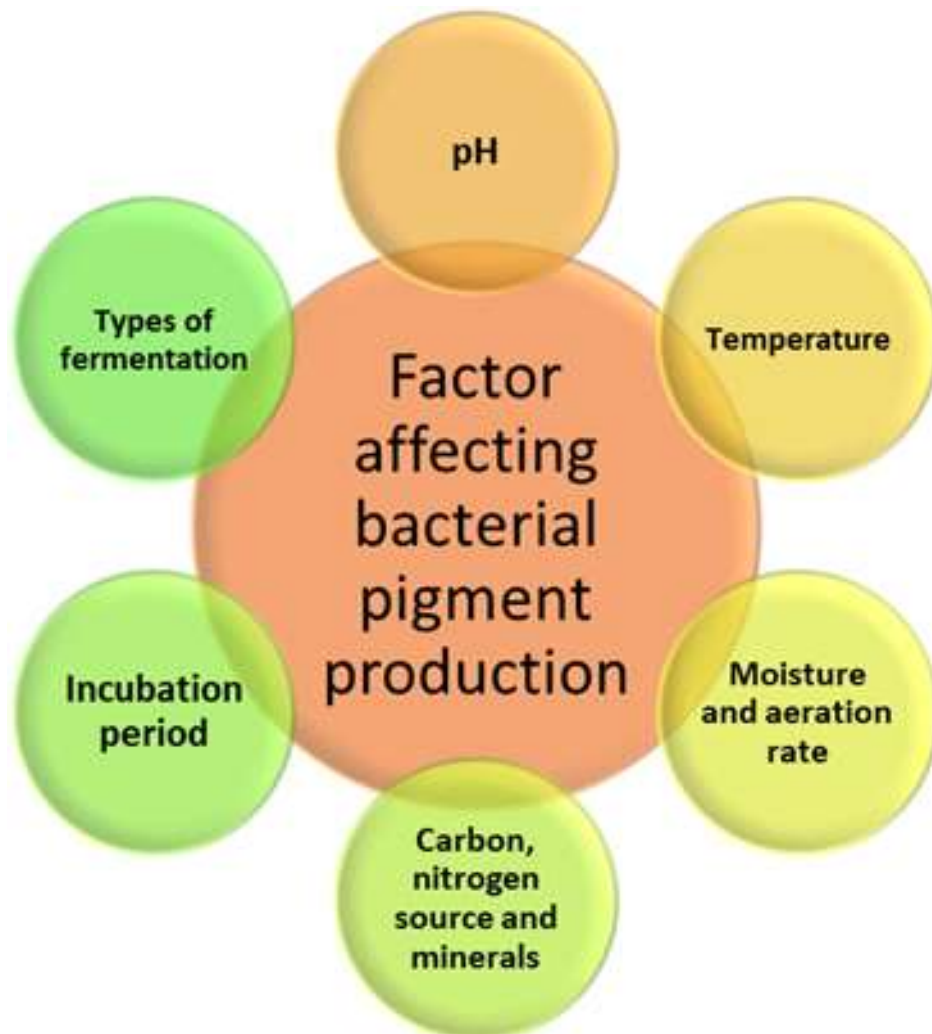


Figure 3. Different factors Affecting the Production of Microbial Pigments.

ADVANTAGES OF BACTERIAL PIGMENTS

Bacterial pigments are used traditionally in eastern nations and have been the focus of extensive research in recent decades due to their potential uses. The following are some advantages and benefits that bacterial pigments provide:

1. Growingly appealing to science due to its wide range of activities.
2. Wide strain selection and ease of replication.
3. Superior to other sources in terms of productivity and versatility.
4. Comparing fermentation to other chemical processes, it is naturally quicker and more efficient.
5. Genes are easily manipulated.
6. Easy and quick culture methods that enable bioreactor operation in real time.
7. Complexity of structure is appropriate for industrial requirements.
8. A simple liquid-liquid extraction method is used to recover bacterial pigments while lowering operating costs.
9. Inexpensive substrates for large-scale manufacturing [48].

Table 1: List of bacterial pigments with their biological activity.

MICRO-ORGANISMS	PIGMENTS	COLOURS	BIOACTIVITY	REFERENCE
Agrobacterium aurantia, Bacteria Para coccus	Astaxanthin	Pink-red	Anti-inflammatory, Antioxidant, Anticancer	[49]
Staphylococcus aureus, Flavobacterium spp.	Zeaxanthin	Yellow	Photo protectant, Antioxidant	[50]
Chromobacterium violacein	Violacein	Purple	Detoxify ROS, Antioxidant	[51]
Proteobacteria	Heptyl prodigiosin	Red	Anti plasmodial	[52]
Pseudomonas spp.	Phycocyanin	Blue, green	Cytotoxicity, Neutrophil apoptosis, proinflammatory	[53]
Brady rhizobium spp.	Canthaxanthin	Orange	Antioxidant, Anticancer	[54]
Serratia marcescens	Prodigiosin	Red	Anticancer, DNA cleavage	[55]
Pseudomonas guinea	Melanin	Black	Antioxidant activity	[56]

CONCLUSION

Bacterial pigments offer an exciting and sustainable source of bioactive compounds with wide-ranging pharmaceuticals potential. These pigments, including prodigiosin, violacein, and carotenoids, exhibit notable antibacterial, antiviral, anticancer properties, making them viable candidates for drug development strategies. Their natural origin and biocompatibility also align with current trends in green pharmaceuticals and personalized medicine. With the increasing demand for sustainable & non-toxic products, bacterial pigments provide a green solution that aligns with environmental safety standards. However, for large-scale commercialization, challenges such as low yield, strain optimization, & regulatory compliance need to be addressed microbiological advancements.

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