Therapeutic applications of bacterial pigments: a review of current status and future opportunities

Muhammad Numan^{1,2} · Samina Bashir¹ · Roqayya Mumtaz¹ · Sibgha Tayyab¹ · Najeeb Ur Rehman² · Abdul Latif Khan² · Zabta Khan Shinwari^{1,3} · Ahmed Al-Harrasi²

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Abstract

Non-toxicity, biodegradability and non-carcinogenicity of the natural pigments, dyes and colorants make them an attractive source for human use. Bacterial pigments are colored metabolites secreted by bacteria under stress. The industrial uses of bacterial pigments have increased many folds because of several advantages over the synthetic pigments. Among natural resources, bacterial pigments are mostly preferred because of simple culturing and pigment extraction techniques, scaling up and being time economical. Generally, the bacterial pigments are safe for human use and therefore have a wide range of applications in pharmaceutical, textile, cosmetics and food industries. Therapeutic nature of the bacterial pigments is revealed because of their antimicrobial, anticancer, cytotoxic and remarkable antioxidant properties. Owing to the importance of bacterial pigments it was considered important to produce a comprehensive review of literature on the therapeutic and industrial potential of bacterial pigments. Extensive literature has been reviewed on the biomedical application of bacterial pigments while further opportunities and future challenges have been discussed.

Keywords Bacteria · Natural pigments · Antibacterial · Anticancer · Antileishmania · Antioxidant

Introduction

Non-toxicity, biodegradability and non-carcinogenicity of the natural dyes and colorants derived from natural flora and fauna make them an attractive source for human use (Joshi et al. 2003). Synthetically synthesized pigments are mostly criticized because of various public and scientific concerns due to which the market value is also reducing (Koes et al. 1994). US environmental activists in 1960 demonstrated

against the synthetic food additives and colorants and his idea spread out globally. Because of its nutritional value, the activist campaigned for the use of natural pigments and colorants. Because of his campaign, the use of colorants and additives shifted towards natural sources, and currently, natural pigments are widely used nowadays (Krishnamurthy et al. 2002). Pharmacological and other viable health advantages of natural pigments over synthetic pigments have further boosted their use in market. Pigment, colorants and dyes isolated from the natural sources are widely used in everyday life such as the use of pigments in agriculture practices, paper production, textile industries and food production (Cserhádi 2006). Green technology favor less toxic and more natural material for the production line. Some synthetic dyes and colorants are prohibited in the market because of their carcinogenic precursor product and disposal effects of their industrial waste in the environment. On the other hand, natural pigments, colorants and dyes have high market value because of their various advantages such as safety and also have potential biological activities such as anticancer and antioxidant. These factors increase the thrust of exploring new sources of natural pigments and food colorants. Some industries such as textile, cosmetics and food

✉ Najeeb Ur Rehman
najeeb@unizwa.edu.om

✉ Zabta Khan Shinwari
shinwari2008@gmail.com

✉ Ahmed Al-Harrasi
aharrasi@unizwa.edu.om

¹ Department of Biotechnology, Quaid-i-Azam University, Islamabad 45320, Pakistan

² UoN Chair of Oman's Medicinal Plants and Marine Natural Products, University of Nizwa, Nizwa-616, Sultanate of Oman, Nizwa-616, Birkat Al Mauz, P.O Box 33, 616 Nizwa, Oman

³ Qarshi University, Lahore, Pakistan

industry are now producing bacterial pigments on commercial scale (Dufossé 2006). Natural colorants actually increase market value of a product. The increasing applications of natural pigments in different areas such as food, cosmetics, textile and pharmaceutical industries turned researchers to find potential compounds in these pigments that have important therapeutic applications. The toxic effect of many drugs compel pharmacist to search new sources of drugs that are safer in use and antibiotic of broad spectrum potential. The current increase in the drug resistance in pathogen might be due to the increased use of present antibiotics (Gupte et al. 2002). To overcome such type of drug resistance by pathogens, antibiotics demand to be developed from new sources. Currently, for the cancer that is the leading causative agent of death there is no reasonable drug available (Taylor et al. 2007). The demand for new drug expands with the increase spreading of new pathogens and very restricted availability for the control of drugs resistance of in-cancer patients. Products of microbes and actinobacteria in particular, isolated from novel ecosystem can be a potential alternative source for new drugs. Various studies reported the screening

of pigments isolated from various soil bacteria (Mellouli et al. 2003).

Considering the potential pharmacological potential of bacterial pigments, it was felt necessary to write a detailed review about various aspects of therapeutic abilities of these natural bacterial pigments. Extensive literature was studied for this purpose to cover nearly all health-related benefits of bacterial pigments. In this review, we cover many important aspects such as anticancer ability, antileishmanial ability, antibacterial ability and antioxidant potential of bacterial pigments. Despite health benefits, some applications of these pigments in food and textile industry have also been discussed. Schematic representation of pigment extraction is shown in Fig. 1 and the potential beneficial aspects are discussed below.

Why natural pigments?

The environmental safety, conservation and awareness have switched the trend towards the natural sources for coloring agents. Non-toxicity, biodegradability and

Fig. 1 Extraction of bacterial pigments

non-carcinogenicity of the natural dyes and colorants derived from natural flora and fauna make them an attractive source for human use (Joshi et al. 2003). Anthraquinones and flavonoids are natural products that are traditionally used as coloring agents which are commonly derived from animals and plants. Currently, as the trend is shifting towards the natural sources for the eco-friendly compounds, natural colorants are leading the market demand over the passage of time. These natural colorants and pigments are derived from many different sources such as insects, ores microbes and plants. Among these sources, microbes and bacteria in particular have the capacity to synthesize a wide of range secondary metabolites and pigments. Pigments extracted from bacteria have a diverse range of commercial applications (Table 1). It is an emerging field and is in the stage of infancy. Efforts are needed to develop a cheap media for bacterial growth to reduce its cost and make it feasible for commercial production (Joshi 2003; Venil and Lakshmana-perumalsamy 2009; Ahmad et al. 2012).

Compounds such as flavonoids, alkaloids and isoprenoids isolated from natural sources were used for fragrance, flavors and as colorants in ancient time. The trend of using natural products switched to synthetic products due to low availability and high price of the natural pigments, colorants and dyes in the previous decades. But the various safety and other toxic issues in synthetic pigments, the market once again is switching towards the natural pigments (Sowbhagya and Chitra 2010). One of the important advantages of the natural pigments is its pharmaceutical applications (Table 1). A lot of work is continued to explore a novel bacteria that can produce commercially important pigments (Li and Vederas 2009).

Table 1 Pigment producing microorganisms (Konuray and Erginkaya 2015)

Microorganism	Pigment color	Applications	References
<i>Neurospora</i> sp.	Orange–red	Anticancer	Huang (1964), Gerber (1975)
<i>Achromobacter</i>	Pink, orange, red	Anticancer; Antimalarial	Duerre and Buckley (1965), Kawauchi et al. (1997)
<i>H. alexandrinus</i>	Red	Antiplasmodial	Asker and Ohta (2002), Yamamoto et al. (1999)
<i>Bacillus</i> sp.	Pink, orange, Yellow	Antibacterial	Khaneja et al. (2010), Gerber (1975)
<i>Brevibacterium</i> sp.	Orange	Antioxidation	Guyomarc’h et al. (2000), Kim et al. (1999)
<i>C. michiganensis</i>	Creamish, Grayish,	Anticancer	Konuray and Erginkaya (2015), Lazaro et al. (2002)
<i>Pseudomonas</i> sp.	Brown, Yellow–green,	Antibiotic	Howarth and Dedman (1964), Kim et al. (2007)
<i>Arthrobacter</i>	Yellow	Cytotoxic	Galaup et al. (2015)
<i>C. infirmominiatum</i>	Red	Antibacterial	Herz et al. (2007)
<i>R. maris</i>	Deep red	Antibiotic	Ichiyama et al. (1989), Kim et al. (2007)
<i>Streptomyces</i> sp.	Blue, red, yellow	Antibiotic	Konuray and Erginkaya (2015), Palanichamy et al. (2011)
<i>Aspergillus</i> sp.	Red, Orange	Antibacterial	Joshi et al. (2003)
<i>A. glaucus</i>	Dark red	Anticancer	Konuray and Erginkaya (2015)
<i>B. trispora</i>	Cream	Tamjamines (BE-18591, Antibiotic)	Joshi et al. (2003)
<i>H. catenarium</i>	Red	Protection from UV irradiation	Joshi et al. (2003), Gerber (1975)
<i>H. gramineum</i>	Red	Protection from UV irradiation	Joshi et al. (2003), Kim et al. (2007)
<i>H. cynodontis</i>	Bronze color	Antibiotic	Joshi et al. (2003), Gerber and Gauthier (1979)
<i>H. avenae</i>	Bronze color	Antibiotic	Joshi et al. (2003)
<i>H. catenarin</i>	Dark maroon	Anti-inflammatory,	Joshi et al. (2003)
<i>M. purpureus</i>	Red, orange, yellow	Anticancer;	Mukherjee and Singh (2011)
<i>P. cyclopium</i>	Orange	Antiproliferative	Mapari et al. (2009)
<i>P. nalgioense</i>	Red	Antiproliferative	Chávez et al. (2011)
<i>Cryptococcus</i> sp.	Red	Algicidal	Joshi et al. (2003)
<i>P. rhodozyma</i>	Orange	Antiprotozoan	Miller et al. (1976), Johnson (2003), Yadav et al. (2014)
<i>Rhodotorula</i> sp.	Orange/red, Yellow	Anticancer	Yadav et al. (2014)
<i>Y. lipolytica</i>	Brown	Antiprotozoan	Carreira et al. (2001a, b)
<i>D. salina</i>	Red, Orange	Antiprotozoan	Arun and Singh (2013), Houbraken et al. (2012)
<i>S. roseus</i>	Reddish-pink	Anticancer; Algicidal	Davoli and Weber (2002)
<i>P. chrysogenum</i>	Yellow	Algicidal	Chávez et al. (2011); Houbraken et al. (2012)

Fig. 2 Applications of bacterial pigments in therapeutics

Pharmacological applications of bacterial pigments

Previous studies indicated that bacterial secondary metabolites and pigments in particular have immense importance in the treatment of various diseases and also have properties

such as anticancer, antibiotic and immunosuppressive compounds. Various secondary metabolites that have potential therapeutic activities are phenols, quinols, flavonoids, polyketones, peptides, terpenoids, steroids and alkaloids. These compounds have remarkable anticancer, immunosuppressive, inflammatory, antimicrobial and antioxidant activities

Fig. 3 Extraction and applications of bacterial pigments **Fig. 4** Applications of bacterial pigments

(Korkina 2007). Recently, a review has been published on the biosynthesis of these compounds from bacteria (Singh et al. 2017). With the passage of time the investigation of new, vital and bioactive compounds from bacterial sources increased as compared to other sources (Soliev et al. 2011). For example, anthocyanin, a compound that have diverse biological activities and positively affect health and have the property to reduce the risk of cancer (Kong et al. 2003; Katsube et al. 2003; Lazzè et al. 2004; Martin et al. 2003; Kim et al. 2012). Anthocyanin is also involved in reducing the chances of inflammatory insults and have role in modulating the immune response (Youdim et al. 2002; Wang and Mazza 2002) (Table 2). As another example, violacein has the properties such as antiviral (Sánchez et al. 2006), anticancer (Ferreira et al. 2004; Kodach et al. 2006), anti-protozoan (Matz et al. 2004), antioxidant activities (Konzen et al. 2006) and antibacterial activities (Lichstein and Van De Sand 1946; Nakamura et al. 2002) (Table 2). There are various other examples of bacterial pigments for the treatment of various diseases such as a compound prodigiosin, isolated from the *Serratia* culture broth have the cytotoxic as

Table 2 Biological applications of some important bacterial pigments

Compound name	Biological applications	Source	References
Anthocyanin	Cancer; inflammation; immune response	Bacteria	Kong et al. (2003), Katsube et al. (2003), Lazzè et al. (2004), Martin et al. (2003), Kim et al. (2012), Youdim et al. (2002), Wang and Mazza (2002)
Violacein	Antiviral; anticancer; antiprotozoan antibacterial activities	Bacteria	Sánchez et al. (2006), Ferreira et al. (2004), Kodach et al. (2006), Matz et al. (2004), Konzen et al. (2006), Lichstein and Van De Sand (1946), Nakamura et al. (2002)
Prodigiosin	Cytotoxic; antiproliferative potential; diabetes mellitus; B-cell chronic lymphocytic leukemia patients	Bacteria	Kim et al. (2003), Pandey et al. (2007), Campas et al. (2003), Kim et al. (2003)
Ant342 (F-YOP)	Chemotherapy of tuberculosis	Bacteria	Richard (1992)

Table 3 Cell lines tested against bacterial pigments for cytotoxicity

Cell type	Source of cells	Cell line	Activity of pigment against cell lines	Reference
Acute lymphoblastic leukemia	Human	MOLT-4	Found cytotoxic	Melo et al. (2000)
Fibroblast-like cell line from lung tissue	Chinese hamster	V79	Caused apoptosis	Melo et al. (2000)
Colon cancer	Human	KM12	Found cytotoxic	Melo et al. (2000)
Non-small-cell lung cancer	Human	NCI-H460	Found cytotoxic	Melo et al. (2000)
Kidney epithelial cells	Monkey	MA104	Found to inhibit cells growth	Andrighetti-Fröhner et al. (2003)
Hela-derived	Human	Hep2	Found to inhibit cells growth	Andrighetti-Fröhner et al. (2003)
Fetal kidney	Monkey	FRhK-4	Found to inhibit cells growth	Andrighetti-Fröhner et al. (2003)
Kidney	Monkey	Vero	Found to inhibit cells growth	Andrighetti-Fröhner et al. (2003)
Promyelocytic leukemia	Human	HL60	Caused apoptosis	Ferreira et al. (2004)
Chronic myelogenous leukemia	Human	U937	Less effective Compared to HL60	Ferreira et al. (2004)
Lymphoma	Human	K562	Less effective Compared to HL60	Ferreira et al. (2004)
Choroidal melanoma	Human	OCM-1	Moderately cytotoxic	Saraiva et al. (2004)
Uveal melanoma	Human	92.1	Moderately cytotoxic	Saraiva et al. (2004)
Colorectal adenocarcinoma	Human	DLD1	Found effective	Kodach et al. (2005)
Colorectal adenocarcinoma	Human	SW480	Found effective	Kodach et al. (2005)
Colorectal adenocarcinoma	Human	HCT116	Found effective	Kodach et al. (2005)
Cervical epithelial cells	Human	HeLa	Caused apoptosis	Lin et al. (2005)
Heterogeneous epithelial colorectal adenocarcinoma	Human	Caco-2	Found effective	Kodach et al. (2005), De Carvalho et al. (2006)
Colorectal adenocarcinoma	Human	HT29	Caused cytotoxicity	De Carvalho et al. (2006)
Erythroleukemia	Human	TF1	Caused cell death	Queiroz et al. (2012)

well as antiproliferative potential in various cell lines such as renal, colon, lung and ovarian cell lines (Fig. 2). Prodigiosin is also found in the B-cell chronic lymphocytic leukemia patients (Kim et al. 2003; Pandey et al. 2007; Campas et al. 2003). This compound is also reported for the treatment of diabetes mellitus (Kim et al. 2003). Another compound isolated from the yellow–orange pigment flexirobin, ant342 (F-YOP) from *Flavobacterium* sp. has been reported for the chemotherapy of tuberculosis (Richard 1992). If further research is performed on these bacterial pigments, these can open new ways of treating various deadly diseases.

Anticancer potential of bacterial pigments

Cancer is one of the most prominent causes of death in both male and female around the globe and around 6 million people are victim of this disease each year. Many drugs against cancer are developed and are in trials to date. But side effects and resistance to these drugs have also been discovered. Apoptosis is now one of the novel methods recognized to kill tumors without causing resistance or any other side effects (Lowe and Lin 2000). Apoptosis is currently focused for cancer treatment (McConkey et al. 1996); the present

anticancer drugs have been reported to trigger apoptosis of cancer cells that encourage the discovery of many other potentially novel compounds having same mechanisms from various sources such as marine organisms. Marine organisms are a diverse source of various natural products (Cragg and Newman 1999; Schwartzmann et al. 2000). About 3000 compounds in past few years have been reported from various marine sources while some of them entered into clinical trials (Schwartzmann et al. 2001; Carte 1996). Oceans contain millions of species (Nuijen et al. 2000) that could be the potential source of various novel therapeutic agents (Fenical 1997).

Many studies reported the anticancer ability of bacterial pigments, for example, Lin et al. (2005) studied the effect of pigments extracted from 12 different bacterial strains. They reported strong cytotoxic effect of these extracts on HeLa cells and showed that the extract have significantly inhibited the growth of HeLa cells in a time-dependent manner (Lin et al. 2005). Many other cell lines tested against bacterial pigments for cytotoxic potential are listed in Table 3, in which significant cytotoxic activity was observed against these cell lines (Choi et al. 2015). Other studies reported the potential use of anthocyanin, a compound that has diverse biological activities and positively affects health and has the property to reduce the risk of cancer (Kong et al. 2003; Katsube et al. 2003; Lazzè et al. 2004; Martin et al. 2003; Kim et al. 2012). Another example of bacterial pigments used for the treatment of various diseases is a compound prodigiosin, isolated from the *Serratia* culture broth. This compound has cytotoxic as well as antiproliferative potential in various cell lines such as renal, colon, lung and ovarian cell lines. Prodigiosin is also found in the B-cell chronic lymphocytic leukemia patients (Kim et al. 2003; Pandey et al. 2007; Campas et al. 2003; Ahmad et al. 2012). The cytotoxic and antiproliferative potentials of the analogs of prodigiosin and the derivatives of the synthetic indole of prodigiosin (Pandey et al. 2007) are well studied (Table 2). The potential cytotoxic effect of this compound has also been reported in cell lines cultured from tumors and also have significant activity against cancer cells derived from B-cell chronic lymphocytic of leukemia patients (Campas et al. 2003). Another compound (violacein) in bacterial pigments has the anticancer and antioxidant activity properties (Konzen et al. 2006; Ahmad et al. 2012). Despite these few compounds, there may be hundreds of other compounds in bacterial pigments that could have strong cytotoxic activity needs to be discovered (Table 3).

Antileishmanial efficiency of bacterial pigments

Leishmaniasis, a fatal and disfiguring disease caused by a protozoan leishmania. More than 12 million people are affected by this disease worldwide. The drugs developed 50 years ago for the treatment of the disease are not working efficiently and have toxic effects. In Brazil, the most common is *Leishmania amazonensis* and is linked with different disease forms, including hyperergic mucocutaneous, cutaneous, visceral leishmaniasis and anergic diffuse cutaneous (Leon et al. 1990, 1992).

Antileishmanial activity of bacterial pigments was only reported by Leon et al. (Leon et al. 2001). They reported that a compound named violacein showed significant antileishmanial activity. They recorded $EC_{50}/24\text{ h}$ value of $4.3 \pm 1.15\text{ }\mu\text{mol/L}$. They compared the value with pentamidine, a drug that is used for the treatment of leishmaniasis. They found that violacein is less active as compared to pentamidine. When pentamidine is used at a concentration of $16.8\text{ }\mu\text{mol/L}$, it inhibits 100% promastigotes while violacein is required at a concentration of $460.8\text{ }\mu\text{mol/L}$ to achieve same inhibition of promastigotes. They further included that although it is less active but has no side effects as compared to pentamidine that has toxic effects (Melo et al. 2000).

Antibacterial properties of pigments

Bacterial pigments are reported to have antibacterial activity against both Gram-positive and Gram-negative bacteria. August et al. (2000) reported that violet pigment isolated from *Chromobacterium violaceum* has broad spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria particularly *S. aureus* and *S. typhi* (August et al. 2000). Similar results were studied by Suresh et al. (Suresh et al. 2015). They found that the red pigment produced by *H. alkaliphilus* MSR1 has strong antibacterial activity against *S. aureus*, *S. typhi*, *K. pneumonia*, *E. coli* and *Salmonella paratyphi*. The summarized antibacterial results (Suresh et al. 2015) are given in Table 4.

Rashid et al. (2014) determined antibacterial activity of pigments isolated from fifteen different bacteria. In their study, they reported the antibacterial effect of pigments of different isolates against nine different Gram-positive and Gram-negative human pathogenic bacterial strains. The findings of their study are given in Table 4. Previous literature reported by Rashid et al. (2014) showed that the antibacterial activity of the pigments isolated from different bacteria was more effective against Gram-negative pathogenic strains than Gram-positive. (Rashid et al. 2014).

Table 4 Antibacterial activities of bacterial pigments

Activity (zone of inhibition in mm)		References									
<i>K. pneumoniae</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>V. cholerae</i>	<i>S. flexneri</i>	<i>S. typhi</i>	<i>B. megaterium</i>	<i>E. coli</i>	<i>B. subtilis</i>	<i>B. cereus</i>	<i>S. paratyphi</i>	<i>S. faecalis</i>
7	16	—	—	—	14	—	6	—	—	8	—
21	19	11	12	9	12	24	13	21	22	—	Suresh et al. (2015)
21	18	21	27	24	25	20	24	21	15	—	Rashid et al. (2014)
24	28	32	31	30	32	28	34	24	25	—	Rashid et al. (2014)
30	29	28	29	30	28	34	26	30	30	—	Rashid et al. (2014)
27	25	21	22	23	21	31	19	27	33	—	Rashid et al. (2014)
18	19	31	32	31	26	16	27	18	16	—	Rashid et al. (2014)
14	12	14	17	18	16	15	13	14	12	—	Rashid et al. (2014)
16	11	12	14	15	11	14	16	16	10	—	Rashid et al. (2014)
12	17	12	13	10	11	9	9	12	15	—	Rashid et al. (2014)
35	34	38	39	38	30	31	41	35	29	—	Rashid et al. (2014)
15	14	9	12	12	13	16	11	15	15	—	Rashid et al. (2014)
27	31	38	42	39	36	33	34	27	34	—	Rashid et al. (2014)
11	8	19	20	21	23	12	25	11	14	—	Rashid et al. (2014)
16	16	10	13	15	14	18	11	16	18	—	Rashid et al. (2014)
41	39	32	36	45	46	44	38	41	35	—	Rashid et al. (2014)
—	29.3	—	—	—	—	—	—	—	—	—	Radijasa et al. (2009)
—	6.5	—	—	—	—	—	—	—	—	—	Mohana et al. (2013)
—	7.9	—	—	—	—	—	—	—	—	—	Mohana et al. (2013)
—	8.7	—	—	—	—	—	—	—	—	—	Mohana et al. (2013)
—	9.5	—	—	—	—	—	—	—	—	—	Mohana et al. (2013)
—	10.8	—	—	—	—	—	—	—	—	—	Mohana et al. (2013)
—	12.5	—	—	—	—	—	—	—	—	—	Mohana et al. (2013)
—	18.5	—	—	—	—	—	—	—	—	—	Mohana et al. (2013)
—	6.7	—	—	—	—	—	—	—	—	—	Mohana et al. (2013)
—	7.6	—	—	—	—	—	—	—	—	—	Mohana et al. (2013)
—	8	—	—	—	—	—	—	—	—	—	Mohana et al. (2013)
—	9.5	—	—	—	—	—	—	—	—	—	Mohana et al. (2013)
—	10.5	—	—	—	—	—	—	—	—	—	Mohana et al. (2013)
—	18.5	—	—	—	—	—	—	—	—	—	Mohana et al. (2013)
—	—	—	—	—	—	—	—	—	—	—	Mohana et al. (2013)
2	2	—	—	—	—	—	—	10	5	—	Banerjee et al. (2011)

Monascus pigments that are usually yellow, orange and red in color are reported to have weak antimicrobial activity (Kim et al. 2006). Another study performed by Cheng and Tseng (Chen and Tseng 1989) showed that *Monascus purpureus* pigments exhibited antibacterial activity against *S. aureus* (Chen and Tseng 1989). Violacein, an active compound of bacterial pigments, is reported to have antimicrobial activity against Gram-positive bacteria and tend to inhibit their growth except *Clostridium welchii* (Duran et al. 2012). Umadevi and Krishnaveni (2013) also observed positive antibacterial activity of pigments against different human pathogenic bacterial strains such as *Klebsiella sp.*, *Staphylococcus sp.*, *Pseudomonas sp.* and *Escherichia sp.* They also found their sample negative against *Streptococcus sp.* (Umadevi and Krishnaveni 2013). Study performed by Radjasa et al. (2009) attributed the antibacterial potential of pigment isolated from a bacterial strain. They showed that the pigment is significantly active against a human pathogenic strain *Staphylococcus aureus*. Mohana et al. (2013) studied antibacterial activity of various bacterial pigments against two human pathogenic bacterial strains, *S. faecalis* and *Staphylococcus aureus*. Banerjee et al. (2011) suggested that the isolated pigment has antibacterial activity against *S. aureus*, *M. lutea*, *K. pneumonia*, *B. cereus* and *B. subtilis*. They also reported their isolated pigment is inactive against *S. cerevisiae*, *A. niger*, *P. aeruginosa*, *S. typhi* and *E. coli* (Banerjee et al. 2011). These studies showed that pigments extracted from bacteria have potential bactericidal activity against various human pathogenic strains. Activities as zone of inhibitions, measured in millimeter are given in Table 4.

Antioxidant capacity of bacterial pigments

Carotenoids, one of the pigments of natural origin plays a vital role and are present in human diet positively because of their properties, e.g., action as antioxidant, provitamin or possibly their role in tumor inhibition (Joshi et al. 2003; Koes et al. 1994; Kim et al. 2003). There has been an exponential increase of commercial interest in natural sources during the past few years because of the scientific evidences highlighting the benefits of natural dyes in animal and human health (Nakamura et al. 2002). The utilization of carotenoid-rich diet has been epidemiologically linked with lower disease risk (Kodach et al. 2006). Therefore, carotenoids are considered as one of the most valued classes of compounds for commercial applications, e.g., in chemical, pharmaceutical feed and food industries (Koes et al. 1994).

The biosynthesis of carotenoids is characteristic of the genus *Rhodotorula* (Koes et al. 1994; Kodach et al. 2006). Effectively identified as orange/red, yellow colonies. The core carotenoids synthesized in *Rhodotorula* species are torulene, torularhodin and carotene and small amount of

carotene (Koes et al. 1994; Joshi et al. 2003). Less explored bacterial carotenoids are torulene and torularhodin while more data are available for nutraceutical carotenoids, e.g., lycopene, carotene, etc. A small number of substances were depicted as “non-familiar” carotenoids, e.g., torularhodin, having provitamin A like activities.

Numerous microorganism's genera produce it in large amount, e.g., up to 0.1% of the dry weight of cell, possibly as a defense against free radicals and photo oxidation. Considerable antioxidant activity is shown by torularhodin (Ungureanu and Ferdes 2012) that stabilizes the membranes under stress conditions. The beneficial side of these carotenoids is their use as hormone and vitamin A and their antioxidant and anti-aging capability. They play a role in immune system enhancement and prevention of certain type of cancer (Matz et al. 2004). Torularhodin shows considerable antioxidant activities and is a unique carotenoid with carboxylic acid (Lichstein and Van De Sand 1946). For industrial applications, the most important carotenoid of genus *R. mucilaginosa* is torulene. The carotenoids having provitamin A like activity are differentiated by carboxylic group and are used as color additives for cosmetic and food. This makes torulene and torularhodin a hot topic for research in carotenoid biotechnology. It has been reported that the most important pigment torularhodin protects from oxidative stress (Matz et al. 2004).

As indicated by researchers, during oxygen loading, *R. glutinis* produces more torularhodin than carotene. Therefore, it can be assumed that in yeast cells, torularhodin show protection against active oxygen species (Matz et al. 2004; Lichstein and Van De Sand 1946). Potential effects of torulene and torularhodin on human health are unknown because of their absence in food material. However, the structural characterization of these carotenoids and consideration of their anticancer and other activities supports their use in cosmetics, food and feed. As a matter of fact, some yeast species having these carotenoids is consumed by animals, e.g., *Rhodotorula*, e.g., chicken feed (muscle to fat ratio is expanded, improves appearance and builds the nutritious value of the meat). Torulene can be used as additive similarly as other hydrocarbon carotenoids, e.g., lycopene or beta carotene. On the other side, torularhodin being an acidic pigment can be used similarly as the major carotenoids of annatto extract, norbixin and bixin and can replace them in meat products for example.

Torularhodin and torulene can function as carotenoid antioxidants such as lycopene and astaxanthin, and again, the solubility is increased in aqueous formulation because of the presence of terminal carboxyl group so torularhodin can be used in particular formulations. In all cases, the formulation technology is same for all carotenoid: extract solution in edible oils, pigment's oil-in-water emulsions, dispersible powders (Matz et al. 2004). Lycopene, the

strongest antioxidant present, is a symmetrical tetraterpene made up of eight units of isoprene. Potential producer of lycopene is fungi of the genera *Blakeslea* and *Phycomyces*. Imidazole, pyridine, methyl heptenone and cyclase inhibitor 2-(4-chlorophenylthio)-triethylamine are the chemical stimulators (CPTA enhances accumulation of lycopene in *P. blakesleeanus* and *Blakeslea trispora*).

The most important particularities of lycopene are suppression of tumor cell proliferation, e.g., MSF-7 tumor cells and excessive singlet oxygen-quenching activity. Lycopene is also used in beverages, surimi, dairy products, sweets and chocolates, nutritional food, soups, cereals for breakfast, chips, spreads, pastas, snacks, and sauces (Chandi and Gill 2011). Astaxanthin is an interesting carotenoid having high market price and increasing demand and commonly found in freshwater and marine animals (Parajó et al. 1998; Johnson et al. 1978). Its use as a supplement for poultry feeds and aquaculture is because of the fact that it is deposited in egg yolks and flesh. Astaxanthin can be produced by biotechnological or chemical means (Mellouli et al. 2003).

Pigments isolated from pieces other than bacteria are also reported to have significant antioxidant activity such as the *Phaffia rhodozyma* (red yeast) is thought to be one of the best candidates for astaxanthin biotechnological production (Mellouli et al. 2003; Parajó et al. 1998). Over the last few years, a number of research works in this area has been reported. Few deal with the astaxanthin production optimization, either analyzing the effect of the operational conditions (pH, temperature, aeration) or by considering the concentration and type of the carbon source (Mellouli et al. 2003). The astaxanthin large-scale isolation from this yeast is desirable because of its use as a pigment source in diet of fishes (Parajó et al. 1998). Because of biological properties, violacein shows antitumoral and antioxidant activity and alongside its anticancer activity, it acts against many infectious diseases, e.g., trypanosomiasis, malaria and leishmaniasis.

Violacein working capacity in different biological environments and its application in the area of medicine along with toxicological data show its potential benefits in the future. Similarly, violacein is also used in industries, e.g., in textiles and cosmetics, along agroindustry (Duran et al. 2012). Few species of the genus *Monascus* are used as natural food additive in East Asia as a natural food colorant for red soybean cheeses, red rice wines and fish and meat products (Kim et al. 2006). The efficacy of carotenoids as singlet oxygen or free radical scavengers, as anticancer agents, as immune response stimulants and as coloring agents for soft drinks, baked goods cooked sausage, and cosmetics additives is well known (El-Banna et al. 2012).

Other applications of bacterial pigments

The use of bacterial pigments becomes doubled in the present decade because it offers various advantages over synthetic pigments (Hendry and Houghton 1996; S. editors 2009; Demain 1980). Due to its fast growth, easy propagation and culturing, easily grown on cheap media sources, simple culture techniques make it very attractive. Bacterial pigments are considered safe for human health and their increased usage in various industries such as food, cosmetics, textile and pharmaceuticals industries has been noticed (Boo et al. 2011; Katsube et al. 2003; Lazzè et al. 2004). Various applications are briefly discussed below (Fig. 3).

Bacterial pigments in food industry

Food industry is aiming to develop food in various attractive colors. Industries are turning towards natural coloring agents because synthetic coloring agents and additives are found to have toxic health effects. Natural colorant is less abundant in market which increases the demand in food industry. This demand for natural pigments can be fulfilled by research in finding natural coloring agents (Aberoumand 2011). One way of obtaining natural food colorants is microbes which produce various colored pigments and have enormous advantages such as easy extraction, no seasonal variation, can be grown on cheap media and high yield in short time (Malik et al. 2012). Microorganisms are made to produce different colorants by inserting genes responsible for colored pigment production. Like natural food colorants these pigments are safe for human health and also preserve biodiversity, because release of harmful chemical into environment for the production of synthetic colorants can be stopped (Nagpal et al. 2011; Venil et al. 2013).

The high consumption of microbial pigments both as a nutritional supplement and colorants reflects its importance in the market and public well of using natural products. Limited number of colorants are approved for food industry in which some are recognized by their source of isolation such as vegetable juice and fruit juice while others have their specific chemical names, for example, canthaxanthin. Pigments which have their chemical names could be synthesized and isolated easily by any biotechnological sources. Major hurdle in the commercial production of these pigments is the technological limitations (Dufossé 2006).

Blue pigments along with other pigments of food grade have been isolated from soil bacteria that possess a natural color and potentially stable and has an excellent toxicological food profile. A team of researcher from University

of science and technology East China reported that blue color pigment has a potential source of edible pigments (Zhang et al. 2006). The current food market is looking for natural food colorants such as quinoline yellow, tartrazine and sunset yellow instead of artificial colorants. The annual growth rate of European food market between 2001 and 2008 is just 1%, while on the other hand, the market growth rate of food colorants has raised 10–15%. Being an environmental friendly and other probiotic health benefits, bacterial pigments are preferred to use as colorants in food products (Nagpal et al. 2011). Fish industry is already using these microbial colorants, for example, in farmed salmon the pink color is enhanced by microbial colorants. The commercial potential of some food colorants as an antioxidant has also been reported (Dufossé 2006). Currently, the FDA approved marketed pigments include carotene from *Blakeslea trispora* and Monascus pigments, riboflavin from *Ashbya gossypii*, Arpink Red from *Penicillium oxalicum* and astaxanthin from *Xanthophyllomyces dendrorhous* (Bohlke et al. 1999; Venil et al. 2013).

Application of pigments in textile industry

In textile industry, the production and consumption of pigments, dyes and dye precursors are approximately 1.3 million tons which cost almost US\$ 23 billion, and most of these are synthetically produced. But synthetic dyes have various limitations such as safety concerns and generation of hazardous wastes. The production of natural colorants gained interest in recent years in textile industry (Mapari et al. 2005). Presently, coloring agents are produced largely from non-renewable sources such as fossil oil. Beside economic efficiency and technical advancement, synthetic pigments face various challenges such as human health and safety concerns, environmental toxicity and dependence on non-renewable resources. Commercial production of these pigments through fermentation can serve as a source of chemical modification which can produce wide varieties of different colorants (Ahmad et al. 2012). Fermentation of microbial pigments can be a valuable source for the production of colorants. Microorganisms can synthesize wide varieties of pigments such as rubramines, quinones, flavonoids and carotenoids and have higher yield and less amount of residues as compared to plant and other animals (Hobson 1998). Despite of natural pigments and colorants, antimicrobial and bright color has been reported in anthraquinone type of compounds which could be a potential source of antimicrobial textile material (Frandsen et al. 2006) (Fig. 4).

Prodigiosin, a bright red pigment, was isolated from *vibrio* sp. (Ahmad et al. 2012). And it was suggested that it has many applications in various fields such as textile and

pharmaceuticals. In textile, prodigiosin can be used as dye for many silk, acrylics, nylon, wool, and fibers (Alihosseini et al. 2008). Pigments isolated from *Serratia marcescens* have the capability to color five different types of fabrics which include cotton, silk, polyester and polyester microfiber (Venil et al. 2013). The performance of dyeing depends on fibers and is different for every fiber. Colored fabrics have the capability to keep its color in sort of environmental conditions crocking/rubbing, washing and perspiration. Similar properties is also reported for another colorant *Janthinobacterium lividum*, which is used for dyeing vinylon, nylon, wool, cotton and silk (Shirata et al. 2000). To dye a material, it is boiled with pigment-producing bacterial cell or dipped in the pigment extract. The color intensity can be varied and it depends on the duration of dipping time and dye bath temperature. Dyeing efficiency of violacein (violet pigment) and prodigiosin (red pigment) has been tested in different fabrics and their results suggested that the red pigment prodigiosin has the ability to dye acrylic, and violacein was observed to dye jacquard rayon, and pure rayon and silk. Prodigiosin and violacein have application in batik (gown-like dress used in Asia) making (Ahmad et al. 2012).

Among these batiks, the most popular one includes flowers, leaves and the geometrical design. The design is first drawn by pencil on the fabric and then melted wax is applied over it the technique is usually known as “canting”. When the waxing process is completed then dyes or bacterial pigments are applied on the fabric with the help of brush. The tone of the color is adjusted by the addition of ethyl acetate or acetone. Ethyl acetate is generally used for purple and red color pigment, and acetone is used for yellow pigment. The material or fabrics is then immersed in the boiling water which contain fixing materials such as copper sulfate, iron sulfate and alum which not only remove wax but also fix the pigments on the fabrics. The fabric is then sun dried (Ahmad et al. 2012).

Challenges and opportunities

Other than the common advantages of the bacterial pigments such as easy extraction and eco-friendly synthesis, there is a massive potential of their use in various industries such as in pharmaceutical, food, textile and cosmetic. Bacteria are usually easy to culture and scaled up easily for large-level productions. The production of pigments can be enhanced by genetic or metabolic engineering. They are economical and free of the use of any hazardous chemicals. The metabolic engineering or synthetic biology can not only increase the production of bacterial pigment, but also could make bacteria (or microbes) as a common platform for the heterogenetic production of pigment from fungi, plant and animal, which will extensively expand the scale of bacterial pigments. To

date, a very small percentage of the bacterial flora has been explored for the extraction and isolation of pigments. Hence, it can be inferred that further exploration of the novel bacterial strains can lead to the potential novel pigments which can have diverse uses.

It is estimated that only 1% of the microbial world has been explored while the rest can be explored for bacterial-based pigments. On the contrary, synthetic pigments are produced by the use of toxic chemicals that are harmful for the humans and environment. To overcome, we strongly recommend isolation of bacterial strains from novel environments and study them for bacterial pigments.

Among the major challenges to overcome for the commercialization and widespread applications of bacterial-based pigments, is the awareness of the fact that the bacterial-derived pigments are relatively safe to their synthetic counterparts. Despite of many applications, bacterial pigments are facing some challenges in their way of commercialization. The most serious challenge is the contamination of bacterial cultures. However, if proper practices are followed, sterile environment for the bacterial cultures can be maintained. Further research on the biomedical potential in terms of clinical trials on animals and human beings should be carried out to uncover the real potential of therapeutic bacterial derived pigments.

Concluding remarks

Bacterial pigments are actually colored secondary metabolites secreted during stress conditions. Bacterial pigments have diverse range of applications in various industries such as pharmaceutical, food and textile industries. Due to its potential activity against many human pathogenic bacterial strains, it can be a potential drug to cure patients infected with these pathogenic bacterial strains. Similar effects were observed for anticancer and antileishmanial activities. These bacterial pigments are active against some cell lines that mean if further research is performed on these pigments, these can help in the treatment of cancer. Bacterial pigments also showed strong antioxidant activity helpful in scavenging of free radicals. Despite of therapeutic applications, bacterial pigments also have applications in food and textile industries. In food and textile industries, these pigments are used as colorants. If further research is performed, these bacterial pigments can be of potential commercial interest.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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