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REVIEW

Microbial pigments as natural color sources: current trends and future perspectives

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Abstract Synthetic colors have been widely used in various industries including food, textile, cosmetic and pharmaceuticals. However toxicity problems caused by synthetic pigments have triggered intense research in natural colors and dyes. Among the natural Sources, pigment producing microorganisms hold a promising potential to meet present day challenges. Furthermore natural colors not only improve the marketability of the product but also add extra features like anti oxidant, anti cancer properties etc. In this review, we present various sources of microbial pigments and to explore their biological and clinical properties like antimicrobial, antioxidant, anticancer and anti inflammatory. The study also emphasizes upon key parameters to improve the bioactivity and production of microbial pigments for their commercial use in pharmacological and medical fields.

Keywords Natural colors · Microbial pigments · Food · Fermentation · Bioactivity · Chemical structure

Introduction

Colors are the most pleasing and first parameter to be noticed about any article by the receptor. Artificial or synthetic colors mostly used by the food processing and cosmetic industries are reliable and economical as compared to the natural colorants which are expensive, less stable, and possess lower intensity (Joshi et al. 2003). Organizations like the World Health Organization (WHO), the U.S. Food and Drug Administration (FDA), and the European Food Standards Authority (EFSA) have recommended the safe dosage of artificial colors in food, drug and cosmetic items (Clydesdale 1993; Wissgot and Bortlik 1996; Wodicka 1996). However, many synthetic colorants have been banned or being banned due to their hyperallergenicity, carcinogenicity and other toxicological problems. These adverse effects of synthetic colors have made the scientific community skewed towards natural colors (Reyes et al. 1996). Many research efforts have been made to replace synthetic pigments with natural pigments because nature is a rich source of colored pigment producing organisms including plants, animals and microorganisms. Recent Research has prominently projected the value of natural colors over that of artificial/synthetic colors. In 2011, global sales of natural colors amounted to an estimated $600 millions, up by almost 29 % from 2007, depicting annual growth in excess of 7 %.

Microorganisms are known as a potential source for biopigment production due to their advantages over plants in terms of availability; stability; cost efficiency; labor; yield and easy downstream processing (Joshi et al. 2003). Varieties of bio pigments have been produced such as carotenoids, melanins, flavins, quinines, monascins, violancein using microorganisms (Duffose 2006). Cultivation of microorganisms can be attained through solid state and submerged fermentation on natural raw material / industrial organic waste. Many of the microbial pigments not only act as coloring agents in various food processing and cosmetics industry but also possess anticancer, antioxidant, anti-inflammatory, anti microbial activities (Venil and Lakshmanaperumalsamy 2009). Furthermore there is huge demand for coloring agents in industries like textile, plastic, paint, paper and printing.

Only limited research studies are available on exploration of microorganisms for color/pigment production especially in Indian scenario which really points towards exploring microbial pigments in more detail. The present review will lead us to explore the potential of microorganisms to produce pigments and further discusses about various strategies for their production and applications thereof in various fields.

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Microbial sources of natural color

Microorganisms are the most versatile tools in biotechnology to produce variety of molecules including enzymes, antibiotics, organic acids and pigments. Recent studies have shown that microorganisms are a promising source for natural colors. The presence of pigments has been reported among the entire microbial world including Bacteria, Fungi, Yeast, algae & protozoa (Table 1). These microorganisms can be isolated/cultured/purified from various environmental sources such as water bodies, soil, plants, insects and animals (Fig. 1).

Fermentation strategy

Advancements in fermentation techniques have lead to the easy production and isolation of color pigments. Microbial pigments can be produced either by solid substrate fermentation or by submerged fermentation. In solid substrate fermentation (SSF), the cultivation of microbial biomass occurs on the surface of a solid substrate (Araújo et al. 2010; Grossart et al. 2009). This SSF technique has many potential advantages including savings in wastewater and yield of the metabolites. On the other hand, in submerged fermentation, microorganisms are cultivated in liquid medium aerobically with proper agitation to get homogenous growth of cells and media components (Cho et al. 2002). Furthermore researchers investigated the influence of various process parameters such as carbon source, temperature, pH, aeration rate on pigment production as well (Vasanthabharathi et al. 2011). However, due to the high cost of using synthetic medium, there is a need to develop new low cost process and extraction procedure for the production of pigments. Efforts are on to utilize the waste organic material for large scale production of microbial pigments. Some studies have focused on production of carotenoids from waste material such as whey, apple pomade and crushed pasta (Lampila et al. 1985). Such kind of waste utilization procedures not only lower down the production cost but also act as potent waste management tool as well.

Bio-pharmacological activities

Microorganisms are known to produce a variety of biologically and pharmacologically active compounds. An increasing number of studies have been carried out to find antioxidant, anticancer, antimicrobial activities using microbial pigments. It can be an alternative for synthetic compounds in food and pharmaceutical technology so as to develop new drugs in order to treat various pathological disorders. Medicinal significance of some of the important microbial pigments is discussed below along with their chemical structures (Fig. 2).

Antioxidant

The chronic diseases such as cancer, diabetes, cardiovascular and autoimmune disorders are known to associate with free radicals. Microbial pigments like Carotenoid, naphthaquinone and Violacein have been shown to have a potent antioxidant activity due to their biological functions (Duran et al. 2012; Lampila et al. 1985; Patel et al. 2007). Bacterial pigment xanthomonadin showed antioxidant activity by inhibiting photodynamic lipid peroxidation in liposome and offered protection against photodamage (Rajagopal et al. 1997). Studies revealed that yellow pigment called staphyloxanthin, from *Staphylococcus aureus* prevents carbon tetrachloride induced oxidative stress in swiss albino mice (Kurjogi et al. 2010). Patel et al. (2007) were successful in producing an antioxidant pigment naphthaquinone from *Comamonas testosteroniand* and they proposed its protective role against superoxide free radicals. Violacein, an another versatile microbial pigment has shown protection against oxidative damage in gastric ulceration by stimulating mucosal defence mechanism (Antonisamy and Ignacimuthu 2010; De Azevedo et al. 2000; Duran et al. 2003)

Antimicrobial

The development of drug resistance in human pathogenic microorganisms prompted researchers to look for better antimicrobial agents. In current scenario, the treatment of infectious diseases has become difficult due to the emergence of multidrug resistance pathogens (Keith et al. 2000). Such evolutionary changes in pathogenic microorganisms necessitate for the development of a newer generation of antimicrobial agent. Therefore the question of investigations into the natural antimicrobial agents is a valid one to tackle such problems (Tuli et al. 2013). Nakamura et al. (2003) reported that violacein not only caused growth inhibition but also the death of bacteria. Furthermore violacein is known to possess anti fungal (Shirata et al. 1997), antiviral (Andrighetti-Frohner et al. 2003) and antiprotozoal activity (Costa et al. 2005; Lopes et al. 2009; Nakamura et al. 2003). Endophytic fungal pigment was found to be superior to the commercial antibiotic Streptomycin against human pathogenic bacteria, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Salmonella typhi* and *Vibrio cholera* (Visalakchi and Muthumary 2010) Prodigiosin, a red color pigment from serratia marcescens was also shown as an antibacterial agent against gram+ve and gram -ve bacteria (Mekhael and Yousif 2009). However with the emergence of antimicrobial resistant bacterial strains, there is a need to search for new and novel antibiotics and the pigments are required to be investigated further based upon their promising bioactivities. Most of the studies mentioned above point towards their bacteriostatic role showing antibiotic like activity. The need is to

Table 1 List of pigment producing microorganisms and their proposed bioactivities

Sr no.	Pigment	Color	Microorganism	Activities	Status	Reference
1	Astaxanthin	Pink-red	*Haematococcus pluvialis Agrobacterium aurantiacum**	Antioxidant, photoprotectant, Anti-cancer, Anti-inflammatory	RP	Reyes et al. 1996
2	Canthaxanthin	Orange	*Bradyrhizobium* Spp.*	Antioxidant, Anti-cancer	RP	Lorquin et al. 1997; Mathews-Roth 1982; Chew et al. 1998; Duffose 2006
3	Cycloprodigiosin	Red	*Pseudoalteromonas denitrificans*	Anti-plasmodial, Anti-cancer	DS	Kim et al. 1999; Yamamoto et al. 1999
4	Granadaene	Orange–red	*Streptococcus agalactiae*	Antioxidant, detoxify ROS	DS	George and Nizet 2009; Rosa-Fraile 2006
5	Heptyl prodigiosin	Red	*α-Proteobacteria*	Anti-plasmodial	DS	Lazaro et al.2002
6	Indigoidine	Blue	*Corynebacterium insidiosum*	Anti-microbial, *Phaeobacter* sp	DS	Starr 1958; Cude et al. 2012
7	Prodigiosin	Red	*Serratia marcescens, Pseudoalteromonas rubra*	Anti-cancer, DNA Cleavage, Immunosuppressant	IP	Feher et al. 2008; Deorukhkar et al. 2007; Melvin et al. 2000; Tsuji et al. 1990
8	Pyocyanin	Blue, green	*Pseudomonas* Spp.*	Cytotoxicity, Neutrophil apoptosis, Ciliary dysmotility, Pro-inflammatory	IP	Baron and Rowe 1981
9	Rubrolone		*Streptomyces echinoruber***		DS	Iacobucci and Sweeney 1981; Schüep et al. 1978
10	Scytonemin		*Cyanobacteria*	Anti-inflammatory, Anti-proliferative	–	Stevenson et al. 2002
11	Staphyloxanthin	Golden	*Staphylococcus aureus*	Antioxidant, detoxify ROS	–	Liu et al. 2005a, 2005b; Clauditz et al. 2006
12	Tryptanthrin		*Cytophaga/Flexibacteria* AM13,1Strain	–	–	Wagner-D¨obler et al. 1996
13	Undecylprodigiosin	Red	*Streptomyces* spp	Anti-bacterial, anti-oxidative, UV-protective, Anti-cancer	–	Gerber 1975; Stankovic et al. 2012; Liu et al. 2005a, 2005b
14	Violacein	Purple	*Janthinobacterium lividum, Pseudoalteromonas tunicate, Pseudoalteromonas spp. Chromobacterium violaceum*	Antioxidant, detoxify ROS	–	Duran et al. 2012; Matz et al. 2004; Konzen et al. 2006
15	Xanthomonadin	Yellow	*Xanthomonas oryzae*	protection against photodamage	–	Rajagopal et al. 1997
16	Zeaxanthin	Yellow	*Staphylococcus aureus, Flavobacterium spp.**, Paracoccus Zeaxanthinifaciens, Sphingobacterium Multivorum*	–	DS	Hammond and White 1970
				Fungi		
17	Ankaflavin	Yellow	*Monascus* spp.*	Anti-tumor, Anti-inflammatory	IP	Hsu et al. 2011
18	Anthraquinone	Red	*Penicillium oxalicum**	Anti-fungal, virucidal	IP	Andersen et al. 1991; Agarwal et al. 2000; Venil and Lakshmanaperumalsamy 2009
19	Canthaxanthin	Orange, Pink	*Monascus roseus*	Antioxidant, Anti-cancer	–	Mathews-Roth 1982; Chew et al. 1998; Cooney et al. 1966; Dufossé 2009
20	Lycopene	Red	*Fusarium Sporotrichioides*, Blakeslea trispora**	Antioxidant, Anti-cancer	RP/DS	Di Mascio et al. 1989; Giovannucci et al. 2002
21	Monascorubramin	Red	*Monascus* spp.*	Anti-micrbial, Anti-cancer	IP	Blanc et al. 1994
22	Naphtoquinone	Deep blood red	*Cordyceps unilateralis**	Anticancer, Anti-bacterial, Trypanocidal	RP	Prathumpai et al. 2006; Nematollahi et al. 2012; Ventura et al. 2009
23	Riboflavin	Yellow	*Ashbya gossypi**	Anti-cancer, anti-oxidant, protection against cardiovascular diseases, in vision	IP	Unagul et al. 2005; Hong et al. 2008; Powers 2003
24	Rubropunctatin	Orange	*Monascus* spp.*	Anti-cancer	IP	Blanc et al. 1994; Zheng et al. 2010

Table 1 (continued)

Sr no.	Pigment	Color	Microorganism	Activities	Status	Reference
25	β-carotene	Yellow-orange	*Blakeslea trispora**, *Fusarium sporotrichioides, Mucor, circinelloides, Neurospora crassa, Phycomyces, Blakesleeanus*	Anti-cancer, Antioxidant, suppression of cholesterol synthesis	IP	Costa et al. 2005; Dufossé 2009; Lopes et al. 2009; Cerdá-Olmedo 2001; Terao 1989
				Algae		
26	Astaxanthin	Red	*Haematococcus pluvialis*	Antioxidant, photoprotectant, Anti-cancer, Anti-inflammatory	-	Terao 1989; Guerin et al. 2003
27	β-carotene	Orange	*Dunaliella salina*	Anti-cancer, Antioxidant, suppression of cholesterol synthesis	–	Kobayashi et al. 1993; Jacobson and Wasileski 1994; Fuhrman et al. 1997
				Yeast		
28	Astaxanthin	Red, Pink-red	*Phaffia rhodozyma**, *Xanthophyllomyces, Dendrorhous**	Antioxidant, photoprotectant, Anti-cancer, Anti-inflammatory	DS	Ramirez et al. 2000; Florencio et al. 1998; Flores-Cotera and Sanchez 2001
29	Melanin	Black	*Saccharomyces, Neoformans*	–	–	Vinarov et al. 2003
30	Torularhodin	Orange-red	*Rhodotorula* spp.	Antioxidant, Anti-microbial	–	Sakaki et al. 2000; Ungureanu and Ferdes 2012
				Archea		
31	Canthaxanthin	Orange	*HaloferaxAlexandrines*	Antioxidant, Anti-cancer	–	Lorquin et al. 1997; Mathews-Roth 1982; Chew et al. 1998; Duffose 2006
				Protozoan		
32	Hemozoin	Brown– black	Plasmodium spp.	–	–	George and Nizet 2009; Kumar 2007

*industrial status adopted from Dufossé(2006)

DS Development stage; *IP* Industrial production; *RP* Research project

Fig. 1 Representation of various colors producing microorganisms on a Petri plate

improve ways to produce, purify and characterize such antimicrobial agents (pigments).

Anticancer

The role of microbial pigments to induce apoptosis and cell cycle inhibition has been reported by many studies (Montaner et al. 2000; Pandey et al. 2007). Apoptosis is mainly characterized by a series of distinct changes in cell morphology such as blebbing, loss of cell attachment, cytoplasmic contraction, DNA fragmentation and many other biochemical changes including activation of caspases through extrinsic and/ or intrinsic mitochondrial pathways. Prodigiosin, from *Serratia marcescens* showed a potent apoptotic effect against human cervix carcinoma cells in a dose dependent manner with a mean IC50 of 700 nM (Kavitha et al. 2010). Anti proliferative effect of prodigiosin has also been investigated in the standard 60 cell line panels of human tumor cells derived from lung, colon, renal, ovarian, brain cancers, melanoma and leukemia (Venil and Lakshmanaperumalsamy 2009). Furthermore prodigiosin

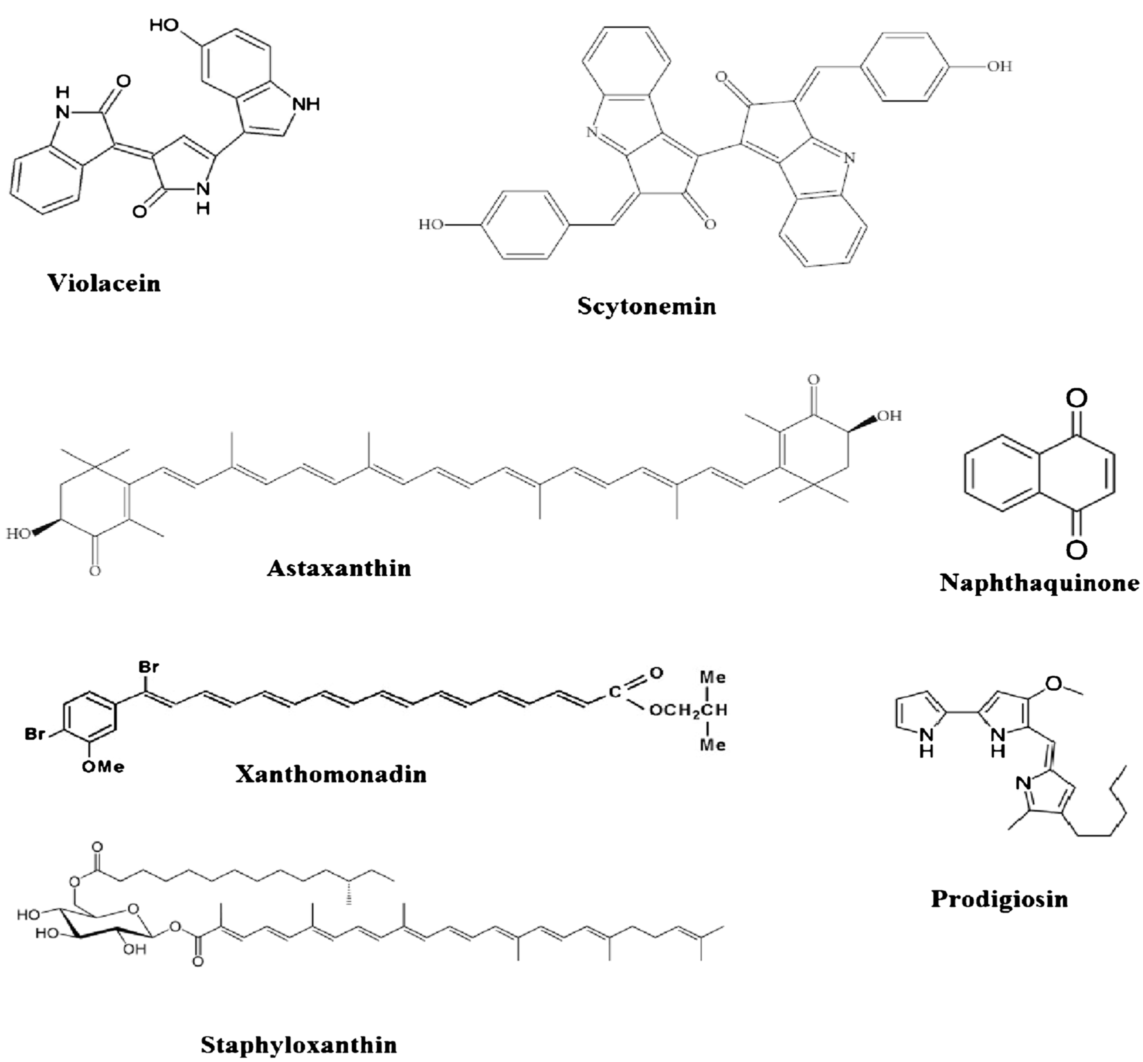

Fig. 2 Chemical structures of some pharmacologically active microbial pigments

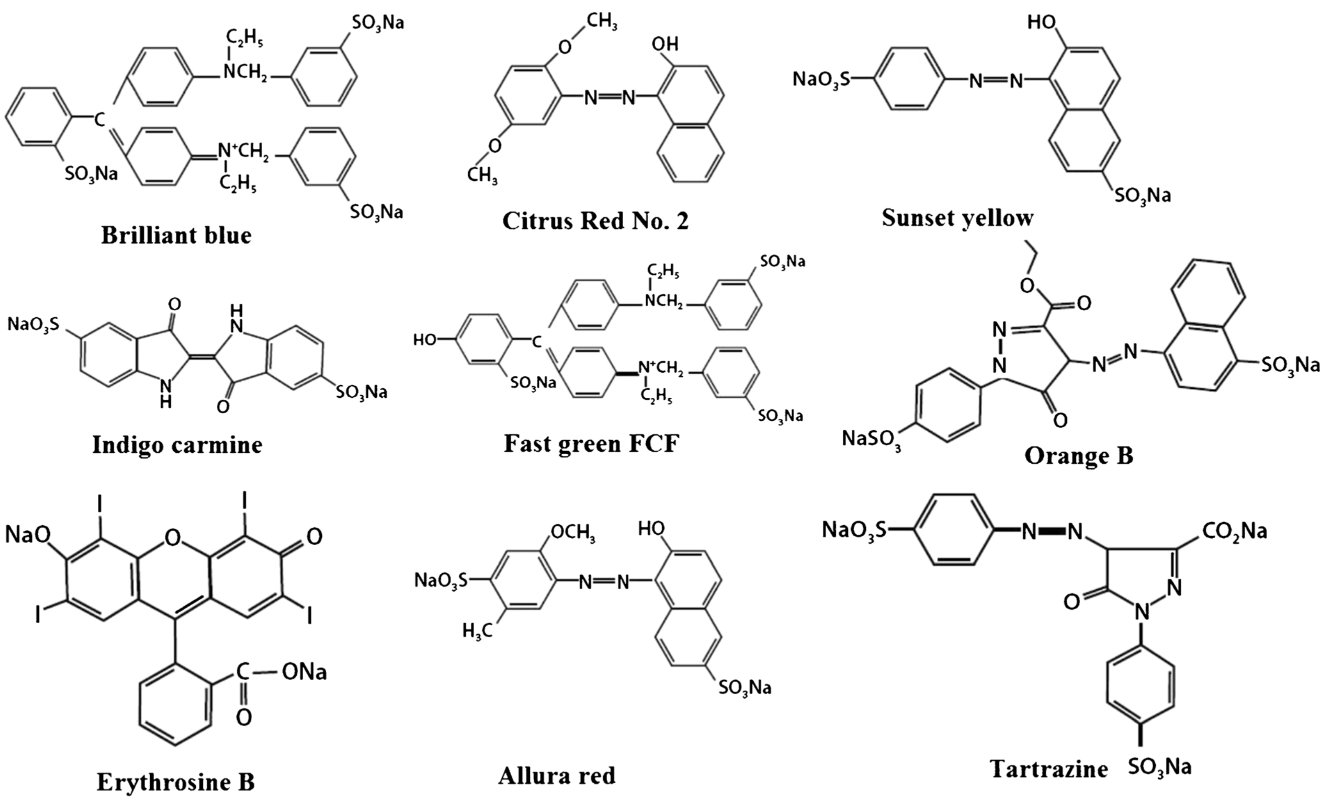

Fig. 3 Chemical structures of various synthetic coloring agents used by industries

analogues and its synthetic indole derivatives have shown in vitro anticancer activity (Han et al. 2001). Ferreira et al. (2004) investigated the cytotoxic effect of violacein on HL60 leukemia cells through tumor necrosis factor (TNF) signaling cascade, which leads to translocation of nuclear factor B (NF B), and activation of p38 mitogen-activated protein kinase (p38 MAPK) and caspase-8 (Sakaki et al. 2000). In addition involvement in apoptotic pathway, microbial pigments, are also known to arrest cell cycle at certain check points. Scytonemin, a yellow green pigment isolated from aquatic *cyanobacteria* showed anti-proliferative effect by inhibiting the activity of cell cycle regulatory protein kinase (Stevenson et al. 2002).

Immuno regulation

Earlier evidences suggest that microbial pigment has potent immuno modulatory effects. Immuno suppressive activity of prodigiosine, metacycloprodigiosin and prodigiosine analogues has been reported through inhibition of polyclonal proliferation of T cells (Han et al. 2001; Kavitha et al. 2010). Recent studies have shown that violacein affects the T cell and IgE mediated inflammatory and anaphylactic response in sheep RBC-induced hypersensitivity and ovalbumin–induced active paw anaphylaxis (Antonisamy and Ignacimuthu 2010). Another important class of pigments comprises of carotenoids produced by bacteria, fungus and algae which are known to

Table 2 Economics for pigment production

Color	Synthetic Pigment		Natural Pigment			
			Insect/Plant		Bacterial/Fungal	
	Name*	Price/100 g*	Name	Price/100 g#	Name	Price/100 g#
Violet	Erioglaucine	140	NA	NA	Violacein	5 X 10^7
Red	Toluidine	800	Cochinel (Insect)	50–80	Prodigiosin	5 × 10^7
	Allura Red AC	80–90	Annato extract (Plant)	80		
Orange /Yellow	Orange G	150	Saffaron (Plant)	1400	Carotenoids	1000
	Tetrazine	2100–2200				

*Sigma, # Venil et al. (2013)

enhance immune response. Lo et al. (2013) reported the mechanistic approach to identify the role of carotenoid lutin to induce matrix metalloproteinase-9 expression and phagocytosis through intracellular ROS generation and ERK1/2, p38 MAPK, and RARβ activation in murine macrophages.

Anti inflammatory

It has long been understood that the inflammatory activities are related to cancer progression. Cancer cells are known to express variety of cytokines, chemokines and their receptors which play an important role to mediate inflammatory responses (Arias et al. 2007; Farrow et al. 2004; Nelson et al. 2004; Wang et al. 2009). Many anti-cancer compounds can be used to treat inflammatory diseases as well (Rayburn et al. 2009). Previous studies reported that expression of cytokines, such as IL-6, IL-8, G-CSF, IFN-γ, and MIP-1β were upregulated in carcinoma (Rayburn et al. 2009). Therefore it is essential to inhibit such inflammatory mediators so as to develop a potent strategy to tackle and prevent cancer. Stevenson et al. (2002) evaluated the anti inflammatory as well as anti proliferative effect of scytonemin pigment extracted from *cynobacteria*. Recent studies investigated the molecular mechanisms of scytonemin, responsible for anti inflammatory effect in lipopolysaccharide (LPS)-stimulated macrophages. Kang et al. (2011) found significantly inhibition of nitric oxide (NO), in addition to downregulation of inducible nitric oxide (iNOS); TNF-α and IL-1β mRNA by scytonemin. Further more study demonstrated the attenuation of LPS-induced NF- B/Rel activation in macrophage cells (Kang et al. 2011).

Industrial role of microbial pigments

Many Companies like food, cosmetics and pharmaceuticals are widely using synthetic pigments because they are cheaper, more stable, and brighter than natural colors. Chemical structures of some synthetic coloring agents such as Brilliant Blue, Indigo Carmine, Citrus Red No. 2, Fast Green FCF, Orange B, Erythrosine B, Allura Red and Tartrazine have been shown in Fig. 3. Studies are suggestive of the fact that inadequate intake of such artificial colors in food supply may lead to harmful effects including carcinogenicity, genotoxicity and neurotoxicity (Hayashi and Matsui 2000; Ishidate and Sofuni 1984; Matula and Downie 1984; McGregor and Brown 1988; Price and Suk 1978; Patterson and Butler 1982; Sasaki and Kawaguchi 2002).· More positive adaptability and acceptance of customers' towards natural colors is encouraging industries to use them into their products. The natural colorings, like *Monascus* pigments, astaxanthin from *Xanthophyllomyces dendrorhous*, Arpink Red from *Penicillium oxalicum*, riboflavin from *Ashbya gossypii*, β-carotene (a Precursor to vitamin A) from *Blakeslea trispora* are already being used in many food items (Duffose 2006). However, efforts are being made to reduce the production cost of such fermentation based microbial pigments. In order to assess the production cost, economic comparison has been drawn between natural and synthetic pigments (Table 2).

Conclusions and future perspectives

Public perception towards natural colors has been increased due to health safety and eco-friendly nature. Microbial pigments being an important source for natural colors possess wide range of medicinal properties. More rigorous efforts are required to have a cheap organic substrate for the growth of color producing microorganisms. Also one need to look into the influence of various process parameters on the rate of production of microbial pigments. Studies should be more directed towards delineating the mechanism of action behind pharmacological activity of microbial pigments which would be very helpful in designing a novel strategy for the management of dreadful diseases like cancer. Future investigations need to be more focused on the chemical structure of microbial pigments and their structure-function relationship.

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