The world demands new solutions and products to be used as dyes for industrial applications. Microbial pigments represent an eco-friendly alternative as they can be produced in large amounts through biotechnological processes and do not present environmental risks, as they are easily decomposable. Moreover, some of these metabolites are recognized for their biological activities, which qualify them for potential uses as food colorants and nutraceuticals, protecting against degenerative diseases related with oxidative stress. Because of their genetic simplicity as compared with plants, microorganisms may be a better source to understand biosynthetic mechanisms and to be engineered for producing high pigment yields. Despite the origin of the pigmented microorganism, it seems very important to develop protocols using organic industrial residues and agricultural byproducts as substrates for pigment production and find novel green strategies for rapid pigment extraction. This review looks for the most recent studies that describe microbial pigments from microalgae, fungi, and bacteria. In particular, the underexploited tools of omics science such as proteomics and metabolomics are addressed. The use of techniques involving mass spectrometry, allows to identify different protein and metabolite profiles that may be associated with a variety of biotechnologically-relevant pathways of pigment synthesis.

Keywords: bioactive metabolites, microbial pigments, extraction, proteomics, metabolomics

INTRODUCTION

Pigments have become an essential part of our daily lives and have extensive applications in many areas, such as agriculture, textiles, cosmetics, pharmaceuticals, foods, among others (Yusuf et al., 2017; Venil et al., 2020a). Synthetic dyes have been produced on a large scale to respond the high demand for improving the color appearance of diverse products. They still have an advantage in terms of large-scale production at economical price with consistent color quality and numerous color variation outweigh the benefits of natural dyes. However, several studies show that synthetic dyes can cause adverse effects in terms of consumer and occupational health and have a negative impact on the environment (Fuck et al., 2018; Zerin et al., 2020). Synthetic dyes are non-renewable, non-biodegradable, sometimes carcinogenic, and cause toxic waste pollution, presenting a huge challenge in disposing the byproduct waste in a cost effective way (Azman et al., 2018; Ramesh et al., 2019).

Many natural pigments besides fulfilling their function of giving color are known as interesting bioactive compounds with potential health benefits. These compounds have a wide range of applications in medicine, food, pharmacology, agrochemicals, cosmetics, among others (Venil et al., 2020b). Numerous microbial bioactive pigments have been discovered and many of them show antioxidant, anti-inflammatory, and/or antimicrobial properties (Ramesh et al., 2019).
The high demand for natural products is impelling an exponentially growing market, and the annual increase rate of the colorant market is estimated at ~7% and is expected to reach $7.79 billion by the year 2020 (Dikshit and Tallapragada, 2018). Thus, the organics market and pigment industries represent vast commercial sectors that would be shortly dominated by microbial pigments (Novoveská et al., 2019). In comparison to plant and animal sources, microbial pigment production by fermentation technology is more dynamic and economic, resulting in biodegradable compounds that may have wide industrial applications as colorants (Silva et al., 2019; Venil et al., 2020a). Although microbial pigments are not widespread in colorant formulations, they represent an important alternative that has the long-term ability to compete with synthetic dyes (Zerin et al., 2020). The successful application of microbial pigments relies on high production yields, reasonable production costs, regulatory approval, pigment characterization, and stability to environmental factors such as temperature and light (Morales-Oyervides et al., 2017).

In this mini-review, recent studies describing pigments extracted from microalgae, fungi and bacteria are discussed, including potential industrial applications. This article focuses on the importance of finding natural microbial bioactive pigments and the need of understanding the metabolic pathways involved in their synthesis. The requirement for green methodologies for rapid pigment extraction and purification is also addressed.

MICROBIAL BIOACTIVE PIGMENTS

Pigments are extensively produced among microorganisms, including microalgae, fungi and bacteria. Although there is still no precise classification of all pigments that can be naturally synthesized by microorganisms, in vitro and in vivo studies indicate that some of these molecules can be helpful in the prevention or treatment of degenerative diseases (Shen et al., 2018; Sajjad et al., 2020). Some examples of microbial pigments showing bioactivities are presented in Supplementary Table 1.

Bioactive Pigments From Microalgae

Microalgae genera as Nostoc, Dunaliella, Scedesmus, Nannochloropsis, Haematococcus, Murielopsis, Chlorella, Phaeodactylum, Spirulina, Arthrosira, Porphyridium, Agardhiella, Polysiphonia produce different groups of pigments, such as carotenoids, chlorophylls and phycobiliproteins (PBPs), known as non-toxic water-soluble proteins mostly found in Rhodophyta (red algae), Cyanobacteria, and Cryptophyta (Yusuf et al., 2017; Noreha-Caro and Benton, 2018; Arashiro et al., 2020). Due to their strong absorbance and fluorescence properties as well as antioxidant and free radical scavenging activities, PBPs have been widely employed in food, cosmetics, pharmaceutical, and biomedical industries (Sonani et al., 2016). Some antioxidant pigments from microalgae are shown in Supplementary Figure 1. Microalgae pigments have additional biological functions, such as anti-inflammatory, antiangiogenic, neuro- and hepatic-protective, antiviral, anti-obesity, anti-diabetic, anticancer, and anti-osteoporotic. They also may help to regulate cardiovascular diseases, cognitive function, protect from UV rays, enhance immune functions, present antiaging property, and prevent some blood-related disorders (Ambati et al., 2018; Saini et al., 2018).

Bioactive Pigments From Yeast and Filamentous Fungi

Fungi belonging to the Monascaceae, Trichocomaceae, Nectriaceae, Hypocreaceae, Pleosporaceae, Cordycipitaceae, Xylariaceae, Chaetomiaceae, Sordariaceae, Chlorociboriae families have been described as potent pigment producers (Ramesh et al., 2019). Certain genera of yeast like Rhodotorula, Sporidiobolus, Sporobolomyces, Xanthophyllomyces, and Pichia have also been recognized as pigment producers. Some of them have been reported to be prolific producers of torulene and torularhodin, β-carotene, poly-hydroxy carotenoids among others (Cipolatti et al., 2019; Kot et al., 2019).

Fungal pigments are mostly carotenoids, melanins and polyketides, namely flavins, phenazines, quinones, monascins, violacein and indigo, presenting a wide spectrum of colors (Supplementary Figure 2). Valuable bioactive properties like anticancer, antioxidant, antimicrobial, anti-inflammatory and immune-suppressor have been associated with fungal pigments (Mapari et al., 2009; Lopes et al., 2013). Thus, they present applications in the food and healthcare industries, as dyeing agents in the textile industry, and as cosmetic additives due to the capacity of absorb harmful UV rays (Chen et al., 2019; Lagashetti et al., 2019; Sajjad et al., 2020).

Bioactive Pigments From Bacteria and Actinobacteria

Most common bacterial pigments are carotenoids, aryl polyenes that in some cases are esterified with a dialkylresorcinol system, melanins, phenazines, quinones, tambjamines, prodigiosines, violacein (Supplementary Figure 3). These pigments are reported for their antioxidant and UV protection properties, and many bacterial pigments demonstrated potential biomedical applications such as antimicrobial, antimalarial, and anticancer properties (Sajjad et al., 2020).

The most common pigments from actinobacteria are melanins with colors ranging from black through brown to olive, carotenoids with colors ranging from red, yellow, and pink through to violet and thirdly, actinorhodin-related blue pigments (Rao et al., 2017). Pigments from the carotenoids group are also described, showing antioxidant activities and being harmless for safe use as a natural colorant in cosmetic, food, pharmaceutical and textile industries (Parmar and Singh, 2018).
TABLE 1 | Agro-industrial by-products used to produce orange and red pigments from Monascus strains.

| Strain        | Substrate                      | Process*                     | References               |
|--------------|--------------------------------|------------------------------|--------------------------|
| M. ruber LEB A4-5 | Corn steep liquor               | SmF, 30°C, 300 rpm           | Hamano and Kilikian, 2006 |
| M. purpureus NRRL 1992 | Grape waste                   | SmF, 25°C, 100 rpm           | Silveira et al., 2008    |
| M. ruber MTCC2326   | Rice brokens                   | SST                          | Rajagopal et al., 2009   |
| M. purpureus CMU001 | Meal from corn, peanut, soybean, coconut residue | SST, 30°C, 14 days           | Nimnoi and Lumyong, 2009 |
| M. purpureus NRRL 1992 | Sugarcane bagasse             | SmF, 27°C, 125 rpm           | Silveira et al., 2013    |
| M. purpureus ATCC 16436 | Cob corn + glycerol       | SST, 30°C, 150 rpm           | Embaby et al., 2018      |
| M. purpureus ATCC 16365 | Orange peel                  | SSF                          | Kantifedaki et al., 2018 |
| M. purpureus LG-6 | Rice straw hydrolysate         | SmF 30°C, 150 rpm            | Liu et al., 2019         |
| M. purpureus CMU001 | Brewer’s spent grain           | SmF, pH 6.5, 350 rpm         | Silbir and Goksuungur, 2019 |
| M. purpureus FTC5357 | Oil palm frond              | SST, 30°C                    | Daud et al., 2020        |

*SmF, submerged fermentation; SST, solid-state fermentation.

MICROBIAL PIGMENT PRODUCTION USING AGRO-INDUSTRIAL BYPRODUCTS

A relevant aspect for the sustainable production of microbial pigments is the definition of an appropriate growth media, which should be cost-effective and result in high pigment yields. In this regard, the importance of recycling agro-industrial byproducts as growth substrates for microbial pigment production has been reported (Korimilli et al., 2020; Venil et al., 2020a). Bioconversion of agri-food waste to value-added products is very important toward zero waste and circular economy concepts. To reduce the environmental burden, food researchers are seeking strategies to utilize agro-industrial residues for microbial pigments production and further biotechnological exploitation in functional foods or value-added products (Usmani et al., 2020). Diverse agro-industrial wastes have been investigated for production of the well-known Monascus pigments (Table 1), and some processes using such inexpensive substrates presented high pigment yields (Embaby et al., 2018). In addition, industrial wastewaters are successfully used for production of phycocyanins and carotenoid pigments by microalgae (Singh et al., 2019; Arashiro et al., 2020).

Intracellular carotenoids (β-carotene, γ-carotene, torulene, and torularhodin) from Rhodotorula species have been produced by using different agro-industrial byproducts as sugarcane bagasse, wheat bran, rice bran, silage, whey, raw glycerol, corn steep liquor, sugarcane molasses, waste chicken feathers, fruit waste extract, and many others (Sharma and Ghoshal, 2019; Korimilli et al., 2020). These pigments could have applications in food and feed as well as in health, pharmaceutical products and cosmetics, generating a market value expected to reach over $2.0 billion by 2022 (Elfeky et al., 2019; Tang et al., 2019).

The economic viability of industrial-scale facilities that produce powdered astaxanthin and astaxanthin oil mixture from wheat bran and olive pomace was evaluated in a simulated solid-state fermentation study. An economic analysis was conducted for different fermentation conditions to identify the plant capacity that optimizes the process economics for a cost-effective bioprocess. The techno-economic analysis demonstrated that producing astaxanthin from agro-industrial waste is a feasible and promising technology (Dursun et al., 2020).

GREEN PROTOCOLS ON MICROBIAL PIGMENTS

Extraction Protocols

Microorganisms offer a tremendous diversity of pigmented molecules, but the methodologies and protocols applied for their extraction and purification are tedious, involving multiple steps, the use of diverse organic solvents, and still giving incongruent results. The variety of extraction protocols employed for microbial pigment extraction can be seen in Supplementary Table 1. The choice of extraction protocol is crucial, as the extraction solvents and conditions can drastically influence the final composition, quality, and efficiency of the process (Soares et al., 2016).

In order to minimize the use of organic solvents and preserve as much as possible the qualitative and quantitative compositions of the pigmented molecules, ecologically friendly methodologies have been investigated. Although these techniques have been employed for extraction of many bioactive substances, their effective application for extraction microbial pigments should be further explored (Kalra et al., 2020; Martínez et al., 2020). Some characteristics, advantages and disadvantages of these green methodologies are detailed in Table 2.

Ultrasound-assisted extraction (UAE) has been recognized as an efficient and environmentally safe extraction method. Enzymatic UAE was used for obtaining the natural food colorant C-phycocyanin from dry biomass of Arthrospira platensis and this method resulted in the highest yield (92.73 mg/g dry biomass) and extraction efficiency (78%) among the methods studied (Tavanandi and Raghavarao, 2019). Microwave assisted extraction (MEA) has been considered an excellent technique for the isolation of microalgae pigments due to its reproducibility, rapidity, uniform heating, and high extraction yields (Pasquet et al., 2011). As the most safe, non-toxic, non-flammable, non-corrosive solvent, water can be used as a green solvent in MAE and UAE for efficient extraction of several metabolites from...
TABLE 2 | Green methodologies for microbial pigment extraction.

| Method                              | Driving force       | Principle                                                                 | Advantages                                                                 | Disadvantages                                                                 |
|-------------------------------------|---------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Ultrasound assisted extraction (UAE) | Acoustic cavitation | High-intensity ultrasound pressure waves accelerate the tissue rupture and releasing intracellular substances into a small amount of solvent | Fast, improved extraction yields, apparatus simple and easy to handle, safe, reduced solvent amount | Filtration step required, possible deterioration of compounds at high frequencies |
| Microwave assisted extraction (MAE) | Microwave power     | Microwave radiation frequencies ranging from 300 MHz to 300 GHz as source of energy | Fast, reproducible, uniform heating, high extraction yields, easy to handle, reduced solvent amount | Filtration step required, expensive, risk of explosion depending on solvent |
| Pressurized liquid extraction (PLE) | Heat plus solvent under pressure | Automated advanced technique to conventional solvent extraction methods such as reflux, SoxHlet extraction, percolation or maceration | Reduced extraction time, reproducible, no filtering required | Possible degradation of thermo-labile compounds |
| Supercritical fluid extraction (SFE) | Pressure plus supercritical fluid | Use of liquefied CO₂ as the supercritical fluid for the extraction of bioactive molecules from solid matrices | Fast, high selectivity, extraction of thermo-labile substances | High cost of equipment, poor extraction of polar substances, many parameters to optimize |
| Pulsed electric field assisted extraction (PFE) | Electric field | Electroporation or electro-permeabilization, exposing the sample to short impulses of high intensity electric field | Use of green solvents, easy to scale up, extraction of thermo-labile substances, direct extraction from biomass | High cost of equipment, affected by air bubbles, efficiency highly dependable on medium conductivity |
| Ionic liquids assisted extraction (ILE) | Solvent contact | Tailor-made solvents for extensive extraction of natural compounds | Direct extraction from biomass, enhanced extraction yields | Cost for larger industrial use, limited availability, relative higher viscosity |

*Compiled from Medina-Torres et al. (2017), Kaira et al. (2020).*

Microbial matrices. An alternative to traditional extraction by organic solvents is to accomplish the extraction by CO₂ based supercritical fluid extraction (SFE) method (Da Silva et al., 2016; Khaw et al., 2017). SFE has been recognized as a green sustainable technique for the selective isolation of molecules, including thermo-labile compounds. The employment of SFE for carotenoids extraction from diverse substrates from laboratory to the commercial scale have been reported (Kitada et al., 2009; Goto et al., 2015).

In addition, pressurized liquid extraction (PLE; also known as accelerated solvent extraction—ASE) (Lebeau et al., 2017), pulsed electric field (PEF)-assisted extraction (Martinez et al., 2020), and ionic liquids (IL)-assisted extraction (Mussagy et al., 2019) have been described as efficient and feasible green methods to improve the extraction yield of pigments from microbial biomass. All these techniques have pros and cons (Table 2) and despite the advances in extraction methodologies, improved green methods are still necessary.

### Purification Protocols

Column chromatography and preparative thin layer chromatography are usual techniques for pigment purification. Polymeric resins and non-ionic adsorption resins have been used for the separation and purification of microbial pigments. The selected resin will adsorb the target pigment from the culture broth, making the process easier, with lower operational cost and solvent consumption. This method yielded a concentrated and partially purified pigment from *S. marcescens* with total recovery of 83%, which was much higher as compared to other conventional methods (Wang et al., 2004). A study using macroporous polymeric adsorption resins demonstrated the promising potential of HP-20 resins for the recovery and purification of prodigiosin from *Serratia marcescens* fermentation broth (Juang and Yeh, 2014).

Despite these methods can be adequate to reach the required purity for commercial applications, several technological advances are still necessary to improve the separation and purification of pigments from culture broth to reduce the energy and process costs (Wang et al., 2004; Venil et al., 2014).

### HIGH-THROUGHPUT METHODOLOGIES IN MICROBIAL PIGMENT PRODUCTION

The emerging of “omics” tools for large-scale microbial examination at the molecular level have proven to be effective for bio-prospection and characterization of microorganisms and their metabolites (Luzzatto-Knaan et al., 2015). Although these methodologies have been widely applied to microbiological research, they are still underestimated for the study of pigment synthesis by microorganisms. Thus, high throughput technologies can be useful to provide advanced knowledge on biosynthetic pathways and discovery of new microbial pigments. A possible workflow considering the use of “omics” sciences coupled with the well-studied and advanced genetic methodologies is presented in Supplementary Figure 4.
Genomics and Metagenomics

Genomics approach may help the searching for gene clusters involved in pigment biosynthesis. The genomic analysis shows the microbial capacity to produce specific secondary metabolites even if they remain silent or cryptic under laboratorial culture conditions. Indeed, approximately 90% of the biosynthetic genes clusters for secondary metabolites has been observed to be included into these categories (Baltz, 2017). Different recent works include the detection of pigment gene clusters (Liao et al., 2019; Xu et al., 2019; Mandakovic et al., 2020). The genome information given by the industrial strain *M. purpureus* YY-1, compared with closely related filamentous fungi, showed adaptation to starch-based foods. Moreover, correlated transcriptomics analysis revealed the highly expressed genes for pigments production on carbon starvation, providing useful insights for industrial applications (Yang et al., 2015). Pan-genomics analysis was used for identification of the tryptophan genes cluster as indispensable on the production of blue pigments by *Pseudomonas fluorescens* (Andreani et al., 2015). Moreover, genomics information becomes indispensable for improving microbial pigment production through genetic manipulation (Venil et al., 2020b), and supports the identification and/or confirmation of produced pigments by novel microorganisms (Varasteh et al., 2020).

Metagenomics analysis of assembled genomes from different microbial phyla, even from uncultured samples, permits to acquire information from unknown microorganisms. In this regard, next-generation sequencing platforms have given a strong contribution for the metagenomics study of microbial networks in a community (Jindal, 2020). This latter omics methodology permitted to overcome the problem of uncultivable microorganisms and to identify novel pigments from extremophile microorganisms, for example from hot springs (Thiel et al., 2019) or marine sources (Rambo et al., 2020). Metagenomics may overcome some limitations of normal laboratory methodologies to study microorganisms from these extreme environments (Sticone and Brandelli, 2020). Thus, metagenomics can be very useful to prospect novel microbial pigments.

Proteomics and Metabolomics

Proteomics is a powerful tool for identification of proteins on a large scale, providing a general overview of the total proteins expressed by an organism under determined conditions (Aslam et al., 2017). The comparative proteomics approach has been used to study proteins related to pigment production. Although works are mostly associated with plant pigments, more recently the microbial pigments production has been investigated by proteomics approach. These studies include the synthesis of pigments by *Monascus purpureus* under high ammonium chloride concentration (Zhou et al., 2020), the polyextremophilic bacterium *Deinococcus radiodurans* in response to oxidative stress (Gao et al., 2020), the pigmentation factors in *Pseudomonas fluorescens* ITEM 17298 (Quintieri et al., 2019), and the air-isolated *Aspergillus* sp. from International Space Station (Blachowicz et al., 2019).

Metabolomics include all the analytical profiling techniques that permit the identification of a large number of metabolites present in biological samples. Combining high-throughput analytical chemistry and multivariate data analysis, metabolomics offers a window on metabolic mechanisms (Manchester and Anand, 2017). In recent studies, untargeted metabolomics approach was selected as a good methodology to search and study the metabolic routes on pigments synthesis (Parrot et al., 2019; Fan et al., 2020). The combination of quantitative proteomics and metabolomics define correlations between abundance of natural products, such as pigments, and changes in the microbial protein pool, allowing the detection of biosynthetic enzyme clusters of the producing strains (Song et al., 2014; Du and Van Wezel, 2018).

Pigment Synthesis Through Genetic Engineering

Previous studies have shown that “omics” strategies can help in understanding the roadblocks in the production of pigments and to counter that, genetic engineering technologies can be used to increase pigment production for large scale applications (He et al., 2017; Lin et al., 2017). The overexpression of gene clusters associated with pigment biosynthesis can be achieved through strategies activating transcriptionally silent gene clusters and/or recombinant DNA technologies to increase the biosynthesis of secondary metabolites (Kjærbolling et al., 2019). The integration of “omics” results with genetic engineering approaches sometimes can support the analysis of the biosynthesis of microbial secondary metabolites and help on the development of a consolidate integrated strategy for the discovery of bioactive compounds (Palazzotto and Weber, 2018), including pigments.

A recent review detailed the recent advancements on engineered microbial systems contextualizing the possibility of using agri-food waste biomass as growth substrates (Usmani et al., 2020). From our point of view, this is a very interesting aspect to be exploited by pigmented microorganisms, eventually with bioactivities, by using organic wastes supporting a circular economy. Recent works have reinforced the use of metabolic engineered microorganisms for pigments production (Mohammad et al., 2020) and the application of these methodologies to produce microalgae biopigments (Saini et al., 2020). Different research groups around the world are directing the research to the use of metabolic and genetic engineering for pigment production, including the use in foods subjected to regulatory approval (Sen et al., 2019; Kalra et al., 2020; Venil et al., 2020b).

CONCLUSIONS AND PERSPECTIVES

Microbial pigments have huge potential applications in multiple areas, including health, since some of them display relevant biological activities. The advances in microbial biotechnology have been useful for improvement of cultivation protocols, allowing maximum pigment yields by growing dyed microorganisms on waste materials. The omics science can
helps on understanding of biosynthetic routes, thus providing important information that can be used to stimulate the production of these pigments for possible use in biotechnological scale. Future research should be conducted for improvement in methodologies for pigment extraction and purification, seeking for environmentally safe approaches reducing solvent use and energy inputs, easy methodologies that allows feasible scale-up. Regulatory challenges are associated with the use of microbial pigments in foods, nutraceuticals and cosmetics as the current legislation is often based on local and tradition. Although native pigment-producing microbes represent the greater regulatory and consumer acceptance, the main challenge to commercialize either native or non-native microbial pigments is the regulatory hurdles and associated consumers’ preference. In addition, an adequate toxicity evaluation of promising bioactive pigments is necessary to warrant the delivery of such natural products with health benefits. Furthermore, a clear multidisciplinary aspect is associated with microbial bioactive pigments, connecting biotechnology, food and biomedical sciences to provide molecules with both colorant and nutraceutical functions, and potential health benefits.

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MP-J and PS participate in bibliography research and writing of the manuscript. AB performed the conceptualization and writing. All authors revised the final version of the manuscript.

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**SUPPLEMENTARY MATERIAL**

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