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Review

Lycopene: Progress in microbial production

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ABSTRACT

Background: Carotenoids are an important group of natural and liposoluble pigments found in plants and microorganisms, displaying yellow, orange or red color. They act as membrane-protective antioxidants which efficiently scavenge $^1O_2$. Lycopene is a red carotenoid with potential in alleviating chronic disease such as some types cancers and coronary heart disease, its production is from vegetable sources (e.g. tomatoes) and chemical synthesis; nonetheless, due to the increasing interest of this molecule, alternative methodologies to produce higher amounts have been developed.
Scope and approach: This review discusses the biotechnological and economic impact of the microbial production and recovery of lycopene as an alternative bioprocess to obtain this carotenoid.
Key findings and conclusions: Microbial production of lycopene can be promoted with the addition of inhibitors that prevent chain cyclization during the biosynthesis of β-carotene or genetic engineering; also, the optimization of culture medium and growth conditions of the microorganism can be performed. Actually, potential applications of lycopene imply that its biotechnological production has become increasingly necessary, and reports have described its production using metabolic engineering.

1. Introduction

Carotenoids are an important group of natural and liposoluble pigments found in plants and microorganisms, displaying yellow, orange or red color. Some carotenoids act as precursors of Vitamin A as well as membrane-protective antioxidants which efficiently scavenge $^1O_2$ and trap peroxyl radicals (ROO*) (Avalos & Carmen Limón, 2015; Cardenas-Toro et al., 2015; Mokhtar et al., 2016; Stajčić et al., 2015). Also, anticancer, antiproliferative and pro-differentiation activities has been attributed. Carotenoids are commercially used as nutritional supplements, food and cosmetic colorants and animal feed with a global market of $1.5 billion by 2014, with an expected increase to $1.8 billion by 2019 (BCC-Research., 2015; J. Kim et al., 2012; M. J. López-Nieto et al., 2004a,b; Marova et al., 2012; Petrik, Obruca, Benesova & Marova, 2014; Reyes, Kao & Katy, 2014). Carotenoids are divided into two groups: carotenes (carbon and hydrogen molecules) such as β-carotene and lycopene, and xanthophylls (carbon, hydrogen and oxygen molecules) such as lutein, zeaxanthin and violaxanthin. For example the lutein and zeaxanthin are the main carotenoids found in wheat, they have antioxidant activity and together with meso-zeaxanthin make up macular pigments responsible for reducing the amount of light irradiation reaching the photoreceptoral layer of the retina (Berrow, Bartlett & Eperjesi, 2011; J. Kim et al., 2012; Mellado-Ortega, 2012). Astaxanthin is the carotenoid that provides salmon and crustaceans their characteristic coloration (Montanti, Nghiem & Johnston, 2011). Furthermore, β-carotene is one of the most studied carotenoids because of antioxidant activity and pro-Vitamin A character, widely applied in the field of food and cosmetics (H. Chen & Zhong, 2015; Wenjiao Ge et al., 2015). Lycopene (Fig. 1) is a red carotenoid with potential in alleviating chronic disease, such as cancer and coronary heart disease, is a more potent ROS scavenger, also, has been demostred to induce cell-to-cell communication and modulate hormones and immune system (George, Kaur, Khurdiya, & Kapoor, 2004; Stajčić et al., 2015). It obtained from vegetable sources (e.g. tomatoes) and chemical synthesis, however, due to the increasing interest of this molecule, alternative methodologies to produce higher amounts have been developed (H. a. Z. Chen, Q., 2015; W. Ge et al., 2015; M. J. López-Nieto et al., 2004a,b; Y. Sun, Yuan, & Vriesekoop, 2007). In view of above introduction, this review discusses the microbial production of lycopene as an alternative to obtain this carotenoid as well as the biotechnological and economic impact.

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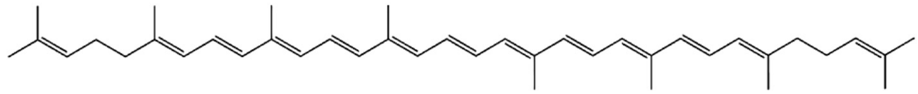

Fig. 1. Molecular structure of all-*trans* lycopene.

2. Physicochemical properties and stability of lycopene

Lycopene is a carotenoid intermediate of the β-carotene biosynthetic pathway found in tomato, watermelon, guava and papaya conferring colors red, yellow and orange in these fruits and has an important role in photosynthesis (S. Choudhari, Ananthanarayan, & Singhal, 2009; Frengova & Beshkova, 2009). Lycopene is an unsaturated lipophilic isoprenoid pigment, of 40 carbon atoms, with a molecular weight of 536.8 g/mol, containing 11 conjugated and 2 non-conjugated double bonds in an *all*-trans form (Agarwal, Sharma, Kaul, Abdin & Singh, 2014; Honda et al., 2015; Y. Kim et al., 2011; Omoni & Aluko, 2005).

Oxidation and isomerization from *all*-trans to *cis*-isomer are the main forms of degradation of lycopene (Colle, Lemmens, Van Buggenhout, Van Loey & Hendrickx, 2013; J. Chen, Shi, J., Xue, S., and Ma, Y., 2009). Lycopene stability is affected by different factors such as heat, light, certain chemical reaction, pro-oxidant conditions and other environmental conditions. Mayeaux et al. (Mayeaux, Xu, King & Prinyawiwatkul, 2006) evaluated the thermal stability of pure lycopene standard and reported that 50% of lycopene was degraded at 100 °C after 60 min, 125 °C after 20 min and 150 °C after less than 10 min. Moreover, Chen et al. (J. Chen, Shi, J., Xue, S., and Ma, Y., 2009). Investigated the degradation kinetics and isomerization of lycopene in water- and oil-based tomato model systems and reported that 80 and 100 °C heating favored the stability of lycopene in oil-based products. At 120 and 140 °C the isomerization increased and total lycopene and *cis*-isomers are degraded in broth products. On the other hand, Shi et al. (J. Shi, Dai, Kakuda, Mittal, & Xue, 2008) evaluated the effects of heating and exposure to light of lycopene: Exposure to light caused no significant change to total and all-*trans* lycopene, however, *cis*-isomer lycopene reduction was significant, and the changes were 30% lower than untreated samples. Pereira et al. (dos Santos et al., 2016) evaluated the stability of nanoencapsulated lycopene during photosensitization with illumination provided by a 150 W filament lamp (in the absence of oxygen, in an air-saturated condition with methylene blue and without MB) this authors reported that the rate of lycopene loss increased with the increase in temperature in presence of MB and air. Lycopene is an open chain unsaturated carotenoid, therefore it is more reactive towards oxygen. Despite of its instability, lycopene is widely used as a supplement in functional foods, feeds, nutraceuticals and pharmaceuticals, and as an additive in cosmetics (Y. Chen et al., 2013), then the total loss of lycopene may vary depending on temperature of heating and the method of heating of matrix, well as the presence of oxygen or light. However, encapsulation, nano-encapsulation and other techniques to promote the stability can be developed.

3. Biological properties

Lycopene is the primary carotenoid found in human serum. It has roused considerable interest due to its beneficial effect on human health, e.g. cancer and tumor prevention, cardiovascular protection, antiproliferative and antioxidant activities (Heber & Lu, 2002; Hsiao et al., 2004; X.-J. L. Wang, Xue-Gang; Wang, Peng; Hu, Guang; Zhang, Tong-Cun., 2014a,b) (Marova et al., 2012; Wenli, 2001). Moreover, the decreased risk of cancer has been linked to consumption of products rich in lycopene (Feofilova, Tereshina, Memorskaya, Dul'kin, & Goncharov, 2006; Heber & Lu, 2002; Omoni & Aluko, 2005; Pohar, Gong, Bahnson, Miller & Clinton, 2003). Beneficial effects of lycopene supplementation of diet in prostate cancer treatment has been observed in addition, reduction of total cholesterol concentration in the human body by lycopene consumption have been reported in clinical studies (Prasad & Mishra, 2014).

All carotenoids appear to be absorbed by duodenal mucosal cells by passive diffusion; nevertheless, lycopene absorption depends on various factors such as concentration, matrix, genetics, and conjugation with other molecules (Srivastava & Srivastava, 2015). Several epidemiological studies have evaluated the role of lycopene as a potential *in vivo* antioxidant. Matos et al. (Matos, Capelozzi, Gomes, Mascio Di & Medeiros, 2001) investigated the effect of lycopene pretreatment on lipid peroxidation in rats subjected to intraperitoneal ferric nitrilotriacetate and five days of lycopene treatment prevented oxidative damage. Mellert et al. (Mellert et al., 2002) evaluated the toxicity of synthetic crystalline lycopene in Wistar rats (oral administration for 13-week, doses of 0, 500, 1500 ad 3000 mg/kg body weight/day) and the results showed the absence of any significant toxicologi findings. Also, Jonker et al. (Jonker, Kuper, Fraile, Estrella & Rodríguez Otero, 2003) tested the toxicity of lycopene from *B. trispora*, as a suspension in sunflower oil in Wistar rats for 90 days, and the results did not provide any evidence of toxicity of lycopene at dietary levels up to 1.0%.

Due to biological properties of lycopene, alternative biotechnological methodologies to produce higher and more stable lycopene have been developed, e.g. the use of microorganisms including some fungi, yeasts, algae and engineered bacteria (M. J. López-Nieto et al., 2004a,b; Sivathanu & Palaniswamy, 2012; X.-J. L. Wang, Xue-Gang; Wang, Peng; Hu, Guang; Zhang, Tong-Cun., 2014a,b).

4. Microbial production of lycopene

Carotenoids are produced by two biosynthetic pathways; 2-*C*-methyl-D-erythritol-4-phosphate (MEP) pathway and mevalonate pathway (MVA). Eukaryotes generally use the MVA pathway (Das et al., 2007): first conversion of acetyl-CoA to 3-hydroxy-3-methyl glutaryl-CoA (HMG-CoA) is performed. Subsequently HMG-CoA is converted to mevalonic acid (MVA). MVA further converted into isopentenyl pyrophosphate (IPP) that is isomerized to dimethylallyl diphosphate (DMAPP). DMAPP then condenses with a molecule of IPP to form geranyl pyrophosphate which condenses with a molecule of IPP to farnesyl pyrophosphate and finally geranylgeranyl pyrophosphate (GGPP). Condensation of two molecules GGPP leading to phytoene, then phytoene molecule is desaturated for lycopene formation. Cyclization leads to the formation of cyclic carotenoids (Fig. 2) (Frengova & Beshkova, 2009; Miziorko, 2011; Srivastava & Srivastava, 2015). *Blakeslea trispora* is filamentous fungi producer β-carotene, which is converted by lycopene cyclization. The accumulation of lycopene can be promoted with the addition of inhibitors (Table 1) that prevent chain cyclization during the biosynthesis of β-carotene, also, the optimization of culture medium and growth conditions of the microorganism can be performed.

López-Nieto et al. (M. J. López-Nieto et al., 2004a,b). Evaluated imidazole and pyridine at concentration of 0.2–0.8 g/L for lycopene