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Bioscience Research

Print ISSN: 1811-9506 Online ISSN: 2218-3973

Journal by Innovative Scientific Information & Services Network

REVIEW ARTICLE BIOSCIENCE RESEARCH, 2023 20(2): 638-646. **OPEN ACCESS**

Advances in 1,3-Propanediol production: A comprehensive review of current strategies, Technologies, and Future Perspectives

Su Chern Lim[1,2,3], Yen Min Koh[1,2,3], Solleh Ramli[1,2], Maizatulakmal Yahayu[1,2], Ismail Ware[1,2], Daniel Joe Dailin[1,2], Siti Zulaiha Hanapi[1,2], Eng San Lim[3]and Hesham Ali El-Enshasy[1,2,4*]

[11]Institute of Bioproduct Development (IBD), Universiti Teknologi Malaysia (UTM), 81310, Skudai, Johor, **Malaysia**
[2]Faculty of Chemical and Energy Engineering, Universiti Teknologi Malaysia (UTM), 81310, Skudai, Johor, **Malaysia**
[3]HG Biochemical Sdn. Bhd., Johor Bahru, Johor, **Malaysia**
[4]Bioprocess Development Department, City for Scientific Research and Technology Applications (SRTA), New Burg Al Arab, Alexandria, **Egypt**

***Correspondence:** henshasy@ibd.utm.my **Received: 22-04-2023, Revised: 18-06-2023, Accepted: 21-06-2023 e-Published: 26-06-2023**

In recent times, there are rising concerns about environmental and economic trends, which have prompted an expanding attention pertaining to ecotechnology. One intriguing approach is the utilization of industrially obtained by-products to produce value-added chemical products through bioprocesses, specifically fermentation process via microbial actions. Among the biological substances produced commercially, 1,3-propanediol (1,3-PDO) has been gaining attention. Although bioprocesses are exceptionally feasible from an environmental and economic perspective, they present a few drawbacks, which are inhibition of product and substrate, accumulation of by-products and low yields. In particular, on account of the production process of 1,3-PDO, intermediates formation such as 3-hydroxypropionaldehyde (3-HPA) and undesired secondary products will lead to cell growth inhibition and eventually cause a decrease in 1,3-PDO yield. In this article, factors influencing 1,3-PDO production was discussed. This review article also explains the background, properties as well as applications of 1,3-PDO, the mechanisms of 1,3-PDO production, including chemical and microbial methods, and the microorganisms for 1,3-PDO production.

Keywords: 1,3-propanediol (1,3-PDO), chemical methods, microbial methods, microorganisms

INTRODUCTION

In recent times there are rising concerns about environmental and economic trends, which have prompted an expanding interest in green science technology (Nordin et al. 2020). An intriguing approach is the utilization of industrial byproducts to obtain high value-added chemicals through bioprocess, specifically microbial fermentation (Dailin et al. 2019; Mohamad et al. 2019). The use of renewable energy is an essential aspect of resolving today's energy and ecological concerns, and the transformation of renewable matter into compounds with added value is frequently discussed with this objective in mind (Rao and Rathod, 2019). This is because bioprocesses are more advantageous as compared to chemical processes. Biotechnological processes depict eco-sustainability as they can utilize sustainable crude material as a substrate for the growth of microorganisms and production of biological substances without accumulating toxic wastes or by-products and harsh working conditions (Islam et al. 2022; El Enshasy et al. 2022). In addition to that, green science technology can also lessen the dependency of the chemical industry on fossil fuels. However, different microbial biofactories have been used in green chemistry to produce high value chemicals using fermentation technology. Of these biofactories, lactic acid bacteria (LAB) have been considered as one of the most potential biofactories based on its Generally Regarded As Safe (GRAS) status according to FDA, long history in food industries, high growth rate, capability to grow in semi-defined and completely defined medium (Dailin et al. 2016; Hatti-Kaul et al. 2018).

Among the biological substances produced commercially, 1,3-propanediol (1,3-PDO) is gaining popularity. This organic compound, with a chemical formula of $CH_2(CH_2OH)_2$, is well known for its status as a 'specialty chemical' because of its high market price of approximately 30 US dollars per kg contrasted with 2 US dollars per kg for other biological substances produced from petrochemical feedstocks, as well as its low production or availability (da Silva Ruy et al. 2020). The 1,3-PDO market is developing tremendously on a

worldwide scale and in fact, it has accomplished more than 100 million pounds every year. The market trend is mainly due to the increasing production of commercial products from 1,3-PDO. The worldwide demand for 1,3-PDO reached 60.2 kilotons in 2012, and it is anticipated that this number will increase by over twofold over the following 7 years, eventually reaching 150 kilotons (Lee et al. 2015).

In the past, 1,3-PDO was produced chemically. However, there are other routes to 1,3-PDO production which involve microbial action through the fermentation process utilizing glycerol as a substrate. The production of value-added 1,3-PDO from glycerol, which is a waste product that results from producing biodiesel at excess capacity, has shown significant potential and has garnered a lot of interest (Sun et al. 2016; Gerardy et al. 2018). As mentioned previously, the production of biodiesel results in a significant amount of glycerol being produced as a waste product. On this account, attributable to the growth of the biodiesel industry, this biological transformation is now acquiring substantial interest from the global market.

Undeniably, as the major by-product obtained from the biodiesel production process, there should be proper management of glycerol before disposal (Kandasamy et al. 2019). Notwithstanding, proper management of glycerol would lead to extra costs that can be neglected by employing crude glycerol in place of purified glycerol to make a variety of glycerol-based compounds. In the production process of biodiesel, 1 ton of this by-product (raw glycerol) is yielded for every 10 tons of biodiesel that is produced. European Union has established an imperative target of 14% for biofuel in the European transport sector by the year 2030 (Panoutsou et al. 2021). As a result, there is a significant increase in the crude glycerol production quantity causing a decline in its price value.

Since the production cost can be enormously affected by the accessibility and cost of the substrate, many researchers have made a lot of endeavors to establish an optimized production process favorable for crude glycerol (Manuale et al. 2017; Freitas et al. 2018; Sun et al. 2018; Kumar et al. 2019; Kaur et al. 2020). All these efforts would allow for achieving the objectives of waste valorization and manufacturing of high value-added compounds through sustainable bioprocess. Indeed, many studies have shown that in recent years, employing wastes or by-products obtained from industry as renewable substrates in bioprocesses has been the focus of green bioprocesses development (Bušić et al. 2018; Dahiya et al. 2018; Li et al. 2018; Silkina et al. 2019; Usmani et al. 2021; Leong et al. 2021).

Albeit the favorable process conditions such as undemanding working conditions, reduction of unwanted by-products and absence of costly and dangerous metal catalysts, there are still some drawbacks to the biotechnological process identified with exceptionally low yields and usage of impure raw materials which can be harmful to the microorganisms (Dolejš et al. 2019). Thus, up to now, numerous types of research have been done on the point of enhancing production yields, which include metabolic and genetic modification, as well as process development such as cell immobilization, batch, fed-batch and continuous fermentation, and utilization of co-substrates.

Background of 1,3-propanediol production process

In the last decade, there is increasing attention to shifting the focus of the chemical industry from fossil-based raw materials to a more sustainable raw materials for a more environmental-friendly chemical production process (Rao and Rathod, 2019). For the chemical industry to achieve competency and versatility, various raw chemical substances have been distinguished by the bioprocess industry for their capability of acting as building blocks for the production of extensive varieties of bio-based or chemical products (Rao and Rathod, 2019). The valuable platform chemicals identified by bio-based industry are 1,3-propanediol (1,3-PDO), 3-hydroxypropionic acid (3-HP) and 3-hydroxypropionaldehyde (3-HPA) (Sun et al. 2018). While the number of existing industrial production for 3-HP and 3-HPA are scarce (Kumar et al. 2013a), there are the widely recognized commercial production of 1,3-PDO by chemical approaches, known as the Degussa and Shell processes, with 3-HPA formed as an intermediate in both processes.

According to the history of the 1,3-PDO production, the oldest known cultivation process with glycerol as substrate in a mixed culture containing presumably *Clostridium pasteurianum*, was made known by a researcher named August Freund. Thereafter, in 1990s, research on 1,3-PDO commenced when a company named Shell reported a new commercial production process of a polymer produced by polycondensation of 1,3-PDO and terephthalic acid (Lee et al. 2015). According to several studies, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Clostridium* and *Lactobacillus* are among the bacteria genera recognized for their potential to yield 1,3-PDO (Ju et al. 2020; Zhang et al. 2021; Zhu et al. 2021). Until now, many researchers have targeted on optimization of the fermentation process of 1,3-PDO by using pure culture or genetically modified microbes.

1,3-propanediol properties

1,3-PDO is an organic compound that can be represented by a chemical formula of $CH_2(CH_2OH)_2$. This non-combustible diol has the characteristics of low toxicological profile and highly soluble in most of the common solvents such as alcohols, ethers and water. Together with the aforementioned characteristics, 1,3-PDO has a unique chemical structure of 2 hydroxyl groups (OH) on carbon 1 and carbon 3 of the compound, which renders it excellent for polycondensation processes, and adds to its tremendous potential in industrial applications.

1,3-propanediol applications

Dimethyl terephthalate (DMT), polytrimethylene terephthalate (PTT) polyesters, and terephthalic acid (TPA) polycondensation are the most recognized polymers among the plastics produced from 1,3-PDO (Kluge et al. 2018). Polymers are essential for our daily life: from plastic cups to airplanes, most of the items that existed in our everyday life are made of composite polymers. Various properties are required for various applications.

Polytrimethylene terephthalate (PTT) is a novel type of polyester, which is especially engaging for applications in carpeting, clothing and garments, engineering thermoplastic, films and monofilaments industries (Kim et al. 2018). In the synthesis of PTT, 1,3-PDO is polymerized with terephthalates as it acts as a monomer (Kim et al. 2018). As for thermoplastic polyurethanes (TPU), the role of 1,3-PDO as a chain extender or building block can enhance abrasion resistance and thermal stability, as well as give it a linear structure which makes it stronger mechanically (Rashmi et al. 2013). Nowadays, the utilization of these polymers in the commercial production of materials such as textile fibers, plastics and films booming significantly (Kim et al. 2018).

Aside from being utilized as decomposable plastic raw material, 1,3-PDO is also found to be applicable in the chemical industry. In this case, 1,3-PDO can be used in the solvent system as it can enhance flexibility while at the same time maintaining stability properties. Besides, when 1,3-PDO is used in adhesives, resins and laminates, it can diminish the inborn viscosity. Other than that, the application of 1,3-PDO in cosmetic products boosts durable effects and obstruction endurance of the products. As an industrial biocide for the avoidance of biofouling in cooling systems, 1,3-PDO is also used in the production of high-strength glasses and in engine coolant formulations. These formulations have minimal corrosion effects and lower toxicity than ethylene glycol, thus they are preferable to using ethylene glycol. Due to its low toxicity and stability, it may be used in personal care and household products as well. Lastly, 1,3-PDO plays a crucial role in various types of medicines such as vitamin H and immunosuppressive medications (Leja et al. 2011; Kaur et al. 2012).

Methods of 1,3-propanediol production

1,3-PDO is an essential chemical in industry and is a constituent of industrial polymers which are the major commodity of reputable companies namely Dupont's Sorona®, Shell Chemical's CorterraTM and CDP Natureworks®. To date, there are two distinct strategies for 1,3-PDO production, which are chemical and microbial mechanisms, that have been employed in the industry.

Chemical methods for 1,3-propanediol production

Referring to Figure 1 below, there are two notable chemical strategies for 1,3-PDO production, which are the hydroformylation of ethylene oxide to 3-HPA, then hydrogenation, and the hydration of acrolein (Lee et al. 2015).

The first strategy for 1,3-PDO manufacturing uses ethylene oxide as its base material and is often referred to as the 'Shell' method. Hydroformylation of ethylene oxide yields 3-HPA, which is subsequently hydrogenated to yield 1,3-PDO in a two-step process. The second technique, the "Degussa-DuPont" method, employs acrolein to be the raw material (Lee et al. 2015). In this process, acrolein is hydrated to form 3-HPA, and it is subsequently hydrogenated in order to yield 1,3-PDO.

Though the aforementioned strategies seem fascinating and advantageous, the chemical synthesis of 1,3-PDO uses fossil feedstock and presents several drawbacks, for instance, high operating temperature, high working pressure, and the presence of catalysts. As a result, the production cost of 1,3-PDO through chemical synthesis turns out to be exceptionally high.

Chemical methods for 1,3-propanediol production - ethylene oxide

With ethylene oxide as the feedstock, the hydroformylation process to yield 1,3-PDO undergoes a two-step process (Mondal et al. 2017). Researchers from Shell Chemical Company have greatly investigated this chemical synthesis pathway of 1,3-PDO. The first step shows the reaction of ethylene oxide towards carbon monoxide in the presence of an organometallic catalyst to obtain a hydroxy aldehyde. When it comes to the second step, a process called hydrogenation will reduce the hydroxy aldehyde to a diol. The best organometallic catalyst is a homogeneous cobalt catalyst, which influences ethylene oxide's ring opening before adding carbon monoxide to form the three-carbon hydroxy aldehyde. It is also feasible to use heterogeneous organometallic catalysts. According to Mondal et al. (2017), the aldehyde reduction step may use a copper chromite catalyst as the source of hydrogen in conjunction with synthesis gas, which are hydrogen and carbon monoxide.

Researchers from Shell Chemical Company have filed a patent illustrating the process of a homogeneous bimetallic catalyst made from a 1:1 proportion of a cobalt compound and a ruthenium compound alongside a 1,2-diphospholanoethane ligand. When there is synthesis gas and the conditions of increased temperatures and pressures, the catalyst will react with ethylene oxide in methyl tert-butyl ether to produce an approximate 90% yield of 1,3-PDO in a single reaction (Allen et. al., 2002).

Albeit this technique uses a catalyst, the application of petroleum-based starting material and methyl tert-butyl ether as a solvent is contrary to the concept of green chemistry. Lately, a study demonstrated successful hydroformylation of ethylene oxide performed in expanded solvents (Powell et al. 2007). However, there is a constructive disadvantage in this method as the 1,3-PDO produced from hydroformylation pathway contains

approximately 10 times the degree of impurities as compared to the 1,3-PDO produced from the microbial fermentation method (da Silva Ruy et al. 2020).

Chemical methods for 1,3-propanediol production - acrolein

Acrolein is another main feedstock for the chemical synthesis of 1,3-PDO. This strategy has been extensively studied by scientists from Degussa and DuPont. As shown in Figure 1, this two-step process consists of the formation of 3-HPA by hydration to acrolein, then followed by the process of catalytic hydrogenation to produce 1,3-PDO. Acid catalysts commonly act as an intermediary in the first step. When ion exchange resins are employed, the selectivity of the addition falls at about 70 to 80%.

A molecular sieve made from silicoaluminophosphate was used in research (Tsunoda & Nomura, 2002) that revealed a 96% selectivity when the procedure was carried out in an aqueous solution at 608°C. Although acrolein is currently produced through the oxidation of propylene, numerous studies have revealed that glycerol may be converted to acrolein rapidly by employing sufficient amounts of sulphuric acid as catalyst in a heated and pressurized water (Watanabe et al. 2007; Ott et al. 2006). In another study, at 90% conversion of glycerol, the selectivity of acrolein produced is at 80% (Watanabe et al. 2007). 3-HPA reduction has been investigated with various catalysts and supports. One of the drawbacks is that the nickel catalysts were inhibited due to the impurities in the feedstock. A ruthenium catalyst on a microporous or mesoporous support was disabled (Besson et al. 2003). Utilizing a macroporous support for the ruthenium catalyst can attain 98% yields of 1,3-PDO from 3-HPA reduction.

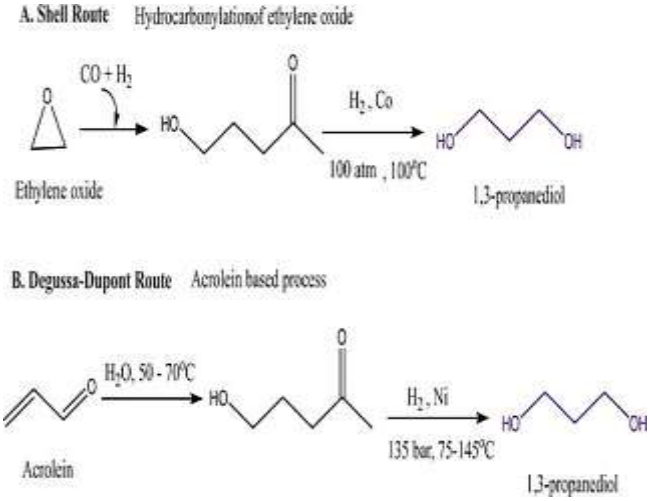

Figure 1: Chemical synthesis strategies for 1,3-PDO production (Lee et al. 2015)

Microbial method for 1,3-propanediol production

Other than chemical approach, microbial transformation of substrates to 1,3-PDO is an appealing alternative approach. As compared to the chemical approaches aforementioned, the microbial fermentation process is considered one of the most favorable 1,3-PDO production pathways.

This approach is undemanding and little to no poisonous by-products are produced during the process. The biological transformation of glycerol into 1,3-PDO is commonly accomplished by microbial fermentation methods using aerobic or anaerobic microorganisms (Nakagawa et al. 2012; Amada et al. 2011; Daniel et al. 2010). *Clostridium*, *Enterobacter* and *Lactobacillus* are among the microbes commonly employed in the fermentation process (Yazdani & Gonzalez, 2007). In a bacterial cell, the biological transformation of glycerol into 1,3-PDO is performed at an operating temperature of 37°C and at atmospheric pressure. Firstly, with the B12-dependent enzyme, glycerol is dehydrated to 3-HPA, followed by 3-HPA reduction with enzyme NADH-oxidoreductase to produce 1,3-PDO as shown in Figure 2 below.

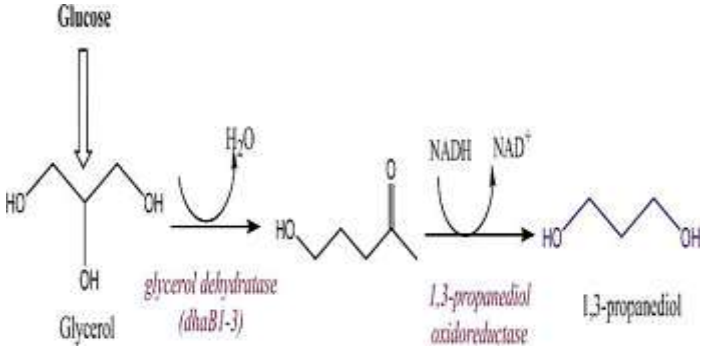

Figure 2: Microbial fermentation for the production of 1,3-PDO (Shanthi, 2019)

Microorganisms for 1,3-propanediol production

Due to the rising demand for biofuels and biopolymers, many researchers have been focusing on increasing efficiency and reducing the costs of production. Bioprocess is very advantageous environmentally and economically for the production of biochemicals as it permits the utilization of sustainable raw materials for 1,3-PDO synthesis.

Microbial production through fermentation process reveals appealing pathway in producing bio-based chemicals from renewable resources, as reported in several studies employing both wild-type and genetically modified microorganisms.

From a commercial perspective, outstanding rates of conversion and yields of products have been achieved through the use of various microorganisms capable of converting glycerol to 1,3-PDO, among which are *Klebsiella pneumoniae*, *Clostridium butyricum*, and *Lactobacillus* species, or their enzymes in heterologous hosts (Zhao et al. 2009; O'Brien et al. 2004).

Klebsiella (Huang et al. 2012; Oh et al. 2011; Cheng et al. 2007), *Citrobacter* (Maervoet et al. 2014),

Clostridium (Kaeding et al. 2015; Wilkens et al. 2012), and *Lactobacillus* (Ricci et al. 2015; Jolly et al. 2014; Pflügl et al. 2014) can naturally transform glycerol into 1,3-PDO by using glycerol as a substrate and 3-HPA as an intermediate. As reported in several studies, a mutant strain produced from of *Klebsiella pneumoniae* is able to yield 102.7 g/L of 1,3-PDO (Oh et al. 2011) and *Clostridium butyricum* yielded a maximum of 94 g/L of 1,3-PDO (Wilkens et al. 2012). DuPont and Genencor International are companies that employed genetically engineered *Escherichia coli* to produce a highest yield of 135 g/L of 1,3-PDO by using glucose as the substrate (Maervoet et al. 2011).

Factors affecting the production of 1,3-propanediol

Various factors affecting the 1,3-PDO production have been reported for *Klebsiella*, *Citrobacter* and *Lactobacilli* (Torino et al. 2001; Hao et al. 2008b; Celinska, 2010). The first factor to be discussed here is aeration. The metabolism of glycerol for the aforementioned microbes may be affected in different ways by aeration. *Lactobacillus panis* PM1 predominantly generates 1,3-PDO in anaerobic or microaerobic settings (Khan et al. 2013), but *K. pneumoniae* prefers aerobic settings over anaerobic settings (Hao et al. 2008a). As reported by Kang et al. (2013), the yield of 1,3-PDO and other metabolites were examined at varying pH, temperature and starting glycerol concentrations to understand the mechanisms of 1,3-PDO production by *Lactobacillus panis* PM1.

Lactobacillus panis PM1 uses external glycerol to be the electron acceptor, leading to 1,3-PDO generation (Kang et al. 2013). Even though glycerol has no impact on the development of *Lactobacillus panis* PM1, high concentration of glycerol (300 mmol/L) inhibited 1,3-PDO synthesis. The ultimate yield of 1,3-PDO in the 300 mmol/L glycerol medium decreased from 87.52 to 64.72 mmol/L whereas ethanol production elevated from 41.71 to 48.08 mmol/L when glycerol was raised from 150 to 300 mmol/L. This study indicated that glycerol fermentation competed with ethanol production and therefore provided an alternative pathway for *Lactobacillus panis* PM1 to undergo regeneration of NAD+, consistent with other studies (Khan et al. 2013).

The presence of an external supply of glycerol caused the NAD+ regeneration process to switch from the ethanol synthesis to glycerol reduction to 1,3-PDO. As a result, the amount of ethanol produced dropped by 22% when there was 150 mmol/L of glycerol present. To put it another way, the reduction in ethanol synthesis resulted in extra NADH that was subsequently employed to make 1,3-PDO. According to Grahame et al. (2013), glycerol with exceedingly high concentrations inhibited glycerol conversion to 1,3-PDO, and the ratio of glucose to glycerol was found to be a significant element for favorable 1,3-PDO production.

Table 1: The effect of initial glycerol concentrations on the yield of end products (Kang et al. 2013)

Glycerol (mmol/L)	Metabolite production (mmol/L)			
	1,3-PDO	Ethanol	Lactate	Succinate
0	–	53.57 ± 0.94	56.21 ± 3.01	10.97 ± 0.02
150	87.52 ± 0.52	41.71 ± 0.37	58.39 ± 0.23	10.91 ± 0.02
300	64.72 ± 0.46	48.08 ± 0.67	59.91 ± 0.24	11.58 ± 0.36

Temperature and pH were other key parameters that influenced the amount of 1,3-PDO that was produced. According to research by Kang et al. (2013), the generation of 1,3-PDO in a 37°C culture was strongly impacted by the pH (4.5 or 6.5), with a drop of 12% from 87.52 to 77.45 mmol/L under the lower pH condition of 4.5. The growth of *L. panis* PM1 was nearly two times as fast at 37°C as it was at 30°C in both pH conditions; however, the culture at the lower temperature (30°C) produced higher amount of 1,3-PDO at both pH conditions, which are 12% increment at pH 6.5 and 23% increment at pH 4.5, than the culture at 37°C did. The optimal conditions for producing 1,3-PDO include growing at a temperature of 30°C and a pH of 4.5.

Table 2: The effect of initial pH and culture temperature on the yield of end products (Kang et al. 2013)

Conditions	Metabolite production (mmol/L)			
	1,3-PDO	Ethanol	Lactate	Succinate
pH 6.5/37°C	87.52 ± 0.52	41.71 ± 0.37	58.39 ± 0.23	11.38 ± 0.02
pH 6.5/30°C	99.54 ± 0.53	40.10 ± 1.58	52.11 ± 0.06	11.49 ± 0.08
pH 4.5/37°C	77.45 ± 0.68	23.52 ± 0.46	55.41 ± 0.27	10.31 ± 0.04
pH 4.5/30°C	100.78 ± 0.48	34.80 ± 0.60	55.93 ± 0.31	10.15 ± 0.05

Approaches for improving biotechnological production of 1,3-propanediol

Several techniques have been investigated to optimize biotechnological processes for the production of 1,3-PDO (Gonzalez-Pajuelo et al. 2006; Hartlep et al. 2002), specifically to those utilizing raw glycerol derived from biodiesel as primary feedstock since it is readily available and inexpensive ingredient (Chatzifragkou et al. 2010). An approach to enhance production could be the use of nonpolar solvents like hexane or petroleum ether to pre-treat raw glycerol (Anand & Saxena, 2012); however, this would markup the production costs in industrial scale.

As reported by Hartlep et al. (2002), the combination of *P. farinose* with *K. pneumoniae* was compared and evaluated with another combination of recombinant *E. coli* with *K. pneumoniae*. In contrast to recombinant *E. coli*, *P. farinose* was reported to generate high levels of acetate in the culture medium, which ultimately hampered 1,3-PDO synthesis.

Low yields of desired products and high amount of unwanted secondary products such as lactic acid, ethanol, butanol, succinic acid, acetic acid, and many more, along with identical chemical structures to the desired products, thereby complicates the downstream phase, are problems shared by most of the aforementioned production

pathways (Zhu et al. 2009; Ashok et al. 2011; Kumar et al. 2013a, b), despite having high production rates. The overall output of 3-HP and 1,3-PDO was 0.77 mol yield per mol glycerol after a successful genetic modification of *K. pneumonia* with the goal of minimizing lactic acid generation (Kumar et al. 2013b).

CONCLUSION

In the last decade, one of the great achievements of green science technology was the production of 1,3-PDO with high versatility and added value through biological processes with the use of sustainable industrial waste as a substrate. The declining availability of fossil feedstock, the accelerating environmental crisis and the rising demand for an environmentally sustainable industry depict deep gaps in the conventional method of chemical production. Marketing economical and cost-effective bio-based 1,3-PDO has become the focus and challenge for the development of an eco-sustainable and leading industry. Therefore, this review has discussed several factors affecting 1,3-PDO production and the approaches to improve 1,3-PDO production through the application of various types of microorganisms to achieve a high yield of 1,3-PDO. Utilizing microorganisms to convert glycerol into the very valuable 1,3-PDO enables for the simultaneous accomplishment of two objectives: resource utilization and waste disposal, which lowers manufacturing costs. These factors, along with research aimed at optimizing the downstream process to produce bio-based products of high purity and the implementation of policies to support the bio-industry, are what will bring an end to reliance on fossil fuels and advance the development of eco-friendly bioprocesses.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

ACKNOWLEDGEMENT

The authors would like also to thank HG Biochemical Sdn. Bhd., Malaysia and Ministry of Science, Technology, and Innovation (MOSTI), Malaysia for financial support through project No. RD1019E1340 and grant No. R.J130000.7609.4C328.

AUTHOR CONTRIBUTIONS

SCL was involved in data collection and writing the manuscript. HAE designed and supervised the project. YMK, SBR, MBY, IBW, DJD, SZBH, ESL and HAE reviewed the manuscript. All authors read and approved the final version.

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