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Review

Beyond PHA: Stimulating intracellular accumulation of added-value compounds in mixed microbial cultures

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HIGHLIGHTS

- Dissolved oxygen has a greater impact on the type and amount of produced compound.
- PHA production is favored at dissolve oxygen concentrations lower than 3 mg/L.
- Dissolved oxygen concentrations above 3 mg/L favor the synthesize of PG and TAG.
- OLR and cycle length were identified to have an impact on the accumulation of PHA.

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ABSTRACT

This review compiled and analyzed the operational conditions (dissolved oxygen, feast and famine ratio, sequential batch reactor cycle length, organic loading rate (OLR), pH, C/N, and temperature) established during the feast and famine culture strategy for the mixed microbial cultures (MMC) selection to understand how these variables could affect the synthesis of polyhydroxyalkanoates, polyglucose, triacylglycerides, levulinic acid and adipic acid from non-fermented substrates. According to the reported information, the dissolved oxygen has a greater impact on the type and amount of produced compound. In a lesser extent, the OLR and the cycle length were identified to have an impact on the accumulation of polyhydroxyalkanoates, whose accumulation was favored at lower OLR and longer cycle lengths. Thereby, the information of this work will allow the design of future strategies for the simultaneous accumulation of compounds of interest other than the polyhydroxyalkanoates or understand the operational conditions that would optimize the polyhydroxyalkanoates production.

1. Introduction

Biological processes to produce high added-value compounds have been gaining interest since these processes are part of the efforts to move from an economy based on fossil fuels to an economy of renewable sources (Jeong et al., 2018). In this sense, microbial cells are capable of storing compounds that serve as raw materials for a variety important application such as PG (Polyglucose) and TAG (Triacylglycerides) (Argiz et al., 2021; Gujjala et al., 2019; Hernández and Alvarez, 2010). On another hand, the microbial cells can store high added-value compounds such as levulinic acid (LA), adipic acid (AA) and polyhydroxyalkanoates (PHA) (Pinto-Ibieta et al., 2020; Rodriguez-Perez et al., 2018; Chen et al., 2014; Hernández and Alvarez, 2010).

The biological production of high added-value compounds can be carried out using pure culture or mixed microbial cultures (MMC). The use of MMC can reduce the production costs associated with both the sterilization process and the carbon source required by a pure culture (Rodriguez-Perez et al., 2018). The involvement of different microorganisms in a MMC can be beneficial due to the performance of cooperation between the involved strains, tending to be more robust to changes in operating conditions than pure cultures and enhancing the consumption of complex substrates (Mohamad Fauzi et al., 2019; Fra-

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Vázquez et al., 2018; Queirós et al., 2014). Therefore, the use of MMC can be interesting for using residual biomass and by-product as feedstocks, minimizing both the operational cost and ecological footprint of these processes (Mohamad Fauzi et al., 2019; Yin et al., 2019).

Nowadays, research about MMC is mainly focused on PHA production. Commonly, PHA production by using MMC implies an acid fermentation for the amendment of the residual biomass into easily assailable volatile fatty acids (VFA), widely recognized as a preferred substrate for PHA production (Korkakaki et al., 2016; Valentino et al., 2015).

The use of MMC feed with non-fermented organic waste that can be directly used as carbon source is an alternative to the implementation of acidogenic fermentation stages that has been reported in a lesser extent. Non-fermented organic waste allows the simplification of the PHA production process, which could reduce the time and cost of operation. However, the studies reported about non-fermented organic waste do not present clear trends towards PHA production, reporting accumulations in a wide range from 5% w/w up to 77% w/w (Fang et al., 2019; Pokój et al., 2019; Mohamad Fauzi et al., 2019; Castro et al., 2018; Moita Fidalgo et al., 2014).

In addition to PHA production, it seems that non-fermented waste as feed for MMC could simultaneously favor the accumulation of PG, TAG, LA and/or AA (Pinto-Ibieta et al., 2020; Pinto-Ibieta, 2020; Fra-Vázquez et al., 2018; Moralejo-Gárate et al., 2013a). The accumulation of these interest compounds different from PHA by MMC has not been explored in deep. According to the literature, most of the reported studies only focused on the identification and quantification of PHA, whereas the accumulation in parallel of other compounds is not usually addressed (Heepkaew and Suwannasilp, 2020; Uma and Gandhimathi, 2019; Mohamad Fauzi et al., 2019; Pokój et al., 2019; Fang et al., 2019; Cui et al., 2016; Huang et al., 2016; Chen et al., 2014). Since the accumulation of other compounds could have a high economic interest, it is necessary to evaluate the reported information to determine the factors that could be related with the production and accumulation of each different compound by MMC fed with non-fermented waste.

Therefore, this review aims to analyze the studies that have reported MMC capable to accumulate PG, TAG, PHA, LA and/or AA, using non-fermented waste raw materials as carbon sources subjected to F/F culture strategy. The review critically evaluates the available information to found a relation between the operational conditions that could favor the accumulation of a certain target compound.

2. Types of microbial storing compounds using MMC feed with non-fermented substrate.

PG is a glucose polymer with α-1,4 and α −1,6 linkages, which is accumulated by several bacteria, i.e. strains of Mycobacterium, Corynebacterium, and Rhodococcus (Hernández and Alvarez, 2010). The production of PG by bacteria is advantageous compared with carbohydrates from other higher plants or green algae due to a lack of a cellulose cell wall in the bacteria. The presence of a cellulose cell wall typically requires additional pretreatments and expensive conversion processes for releasing the PG contained inside the cells (Arias et al., 2020). The PG accumulation has been reported using MMC feed with different substrate as carbon source, such as glycerol (Fra-Vázquez et al., 2018; Freches and Lemos, 2017; Moralejo-Gárate et al., 2013a, 2013b, 2011;), succinic acid (Tajparast and Frigon, 2013) and bio-oil (Moita et al., 2014; Moita and Lemos, 2012).

TAG are accumulated as intracellular lipid granules, and they can be extracted and used as biodiesel feedstock (Argiz et al., 2021; Fra-Vázquez et al., 2018). Intracellular storage of TAG by pure cultures has been widely reported, for example, by oleaginous yeasts or bacteria (Argiz et al., 2021; Gujjala et al., 2019; Tamis et al., 2015). Meanwhile TAG production using MMC has been lower reported using as feedstock residual fish-canning oil (Argiz et al., 2021), crude glycerol (Fra-Vázquez et al., 2018), hydrocarbons wastewater (Castro, A. R. et al., 2018), bio-oil (Tamis et al., 2015).

LA is a platform molecule that allows the production of a wide range of compounds applied in the chemical, food, and agrochemical industry, being considered within 12 molecules with the highest added-value in the world (Lappalainen and Dong, 2019).

AA is used for the production of nylon 6,6, a polymer with very high demand by textile and automotive industries (Riveiro et al., 2020). It also can be used as an intermediate to produce different compounds like cyclopentanone and 1.6-hexanediol, which are implicated in fragrances industries and resins production, respectively (Corona et al., 2018; Raj et al., 2018)

Nowadays, LA and AA have been produced using processes based on acid hydrolysis at high pressures and temperatures, using waste and/or by-product of lignocellulosic biomass as raw material (Jeong et al., 2018). These LA and AA production processes are related to high economic and environmental costs due to the equipment needed to work at high temperatures and high pressures, generating contaminating residues including high volumes of acid, solvents and, spent catalysts (Corona et al., 2018; Bart and Cavallaro, 2015). To address these problems, the LA and AA biological production using pure cultures by fermentation of pentoses and hexoses have been reported (Nikel and de Lorenzo, 2018; Raj et al., 2018). Recently, has been reported the LA and AA production using MMC feed with hemicellulose hydrolysate rich in pentoses obtained as a by-product of bio-composites production with sugarcane bagasse fibers (Pinto-Ibieta et al., 2020).

PHA are biodegradable polyesters that can be produced in bioprocesses from renewable resources in contrast to fossil-based biorecalcitrant polymers, PHA production has been widely reported for pure culture of bacteria using different carbon source, including VFA, glucose and xylose (Cassuriaga et al., 2018; Valentino et al., 2015; Yu and Stahl, 2008). On the other hand, the MMC for PHA production has been reported using different non-fermented substrate, such as pure and crude glycerol (Heepkaew and Suwannasilp, 2020; Pokój et al., 2019; Mohamad Fauzi et al., 2019; Fra-Vázquez et al., 2018; Freches and Lemos, 2017; Moita et al., 2014; Moralejo-Gárate et al., 2013a, 2013b, 2011; Dobroth et al., 2011), reduced sugar (Yin et al., 2019; Huang et al., 2016), Bio-oil (Moita Fidalgo et al., 2014; Moita et al., 2014), starch (Cui et al., 2016), rice winery (Fang et al., 2019), oily bilge rich in hydrocarbons (Uma and Gandhimathi, 2019), residual fish-canning oil (Argiz et al., 2021).

3. Simultaneous synthesis of different compounds using MMC fed with the non-fermented substrate

Simultaneous accumulation of the previous listened compounds has been reported. For example, PG and PHA simultaneous accumulation has been widely observed when glycerol is used as non-fermented feedstock (Freches and Lemos, 2017; Moita Fidalgo et al., 2014; Moita et al., 2014; Moralejo-Gárate et al., 2013a, 2013b, 2011). Likewise, it has been reported that is possible TAG and PHA simultaneous accumulate using residual fish-canning oil as feedstock (Argiz et al., 2021) and hydrocarbons wastewater (Castro et al., 2018). PG, TAG and PHA were simultaneously accumulated when the glycerol was used as feedstock (Fra-Vázquez et al., 2018). Recently, simultaneous production of LA, AA and PHA has been reported from synthetic hemicellulose hydrolysate enriched in xylose (Pinto-Ibieta et al., 2020).

Fig. 1 shows a summary of the reported metabolic pathways to obtain different compounds from non-fermented substrates. Fig. 1.A. shows the metabolic pathway to obtain TAG and PHA from waste fish oil. While metabolic pathway for the synthesis of PG and PHA from glycerol are showed in Fig. 1.B. On the other hand, the reported metabolic pathway for the synthesis of LA and AA from xylose is described in Fig. 1.C.

Argiz et al. (2021) informed that the dominant metabolic pathway between TAG synthesis from waste fish oil or PHA synthesis from the same substrate depended on the variables imposed during MMC

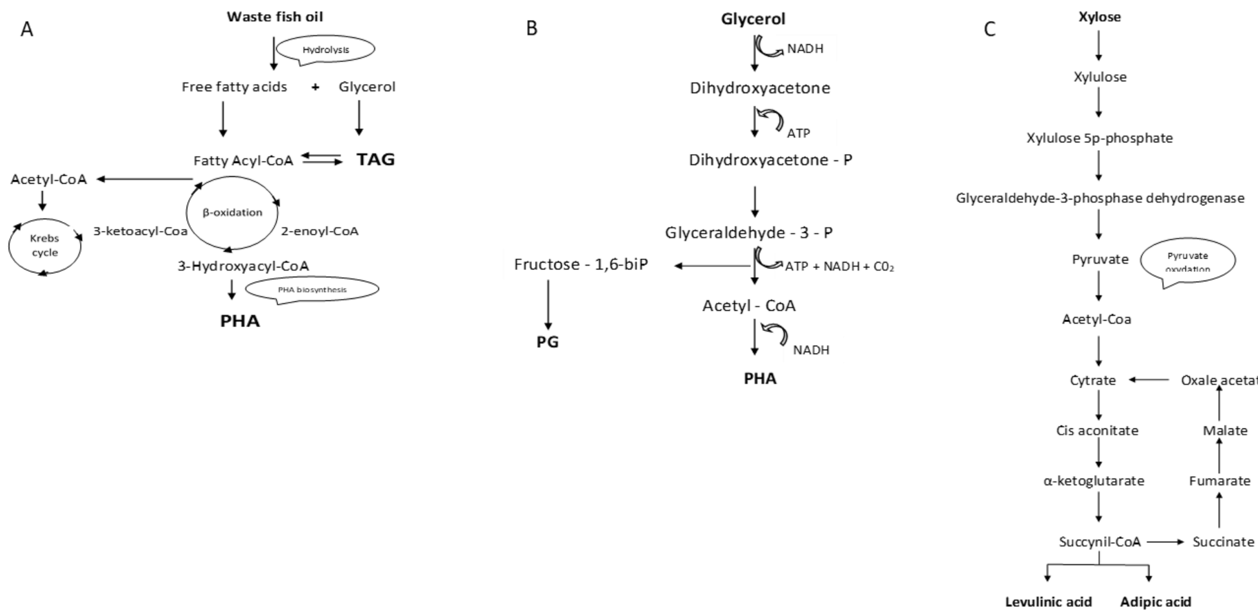

Fig. 1. Metabolic pathway proposed for PG, TAG, LA, AA and PHA from different substrate. (A) PHA and TAG from waste fish oil (Argiz et al., 2021); (B) PHA and PG from glycerol (Moralejo-Gárate et al., 2013a); (C) LA and AA from xylose (Lee et al., 2019). PHA: Polyhydroxyalkanoates; TAG: Triacylglyceride; PG: Polyglucose; LA: Levulinic acid; AA: Adipic acid.

selection stablished in the feast and famine culture strategy. Therefore, the compound type produced (PG, TAG, PHA, LA and/or AA) by a mixed microbial culture could be depends on the metabolic pathway that is favored according to the environmental and operational conditions of the culture system in which these microorganisms are found.

4. Operational conditions in the feast and famine (F/F) culture strategy

F/F culture strategy is usually carried out in a sequential batch reactor (SBR), which works alternating excess and lack of external substrates (Oliveira et al., 2017). This alternation of substrate availability is a favorable condition for microorganisms with the capacity to store organic compounds, such as acetate, propionate, and lactic acids, as PG, TAG, PHA, LA and AA. These microorganisms store organic compounds during the initial feast phase, which is a competitive advantage over other microorganisms, as they can use these stored compounds as an internal carbon source in the coming famine phase (Guo et al., 2016; Lee et al., 2015).

F/F culture strategy for PHA production using MMC has reached even the industrial scale (Dietrich et al., 2017). Nevertheless, F/F culture strategy has also been reported in PG, TAG; LA and AA production using MMC (Table 1). This section aims to relate the operational conditions that favor the synthesis or accumulation of a certain target compound. The operational conditions, based on the information reported in literature, are: Dissolved oxygen (DO), F/F ratio, SBR cycle length, organic loading rate (OLR), pH, C/N, and temperature (Table 1).

4.1. Dissolved oxygen (DO)

Fig. 2 shows the percentage of PG, TAG, PHA and LA accumulated as a function of DO concentrations during the operation of SBR reactors in the feast phase reported by several authors (Castro et al., 2018; Fra-Vázquez et al., 2018; Freches and Lemos, 2017; Moita et al., 2014; Moralejo-Gárate et al., 2013a, 2011). As it can be seen, PG production trended to occur when the DO concentration during the feast phase was above 3.5 mg/L (Fig. 2, Table 1) (Castro et al., 2018; Fra-Vázquez et al., 2018; Freches and Lemos, 2017; Moita et al., 2014; Moralejo-Gárate et al., 2013b, 2011). For example, MMC fed with glycerol at a DO concentration of 4.5 mg/L reached a PG production of 30 %w/w (Table 1) (Moralejo-Gárate., 2013a). The same authors reported that PG accumulation increased around 20% when the DO concentration during the feast phase increased from 4.1 to 5.1 mg/L in experiments using pure glycerol as carbon source with and OLR of 1.42 gCOD/(L-·d) and 24 h of cycle length (Table 1) (Moralejo-Gárate et al., 2013a, 2011). The relation between DO concentration and PG accumulation has been related with maintaining a sufficient oxygen supply into the reactor to allow microorganisms to get enough energy for the production of protein, glycogen, and other cellular components concurrently by taking up substrate (Venkata Mohan and Venkateswar Reddy, 2013).

In Fig. 2 it can be observed that TAG accumulation trend to occur at DO concentrations higher than 3 mg/L (Argiz et al., 2021; Castro et al., 2018; Fra-Vázquez et al., 2018). MMC fed with glycerol and 3.6 mg/L of DO reached an accumulation up to 26% w/w of TAG (Table 1) (Fra-Vázquez et al., 2018). Similarly, MMC fed with wastewater rich in hydrocarbons, maintaining a concentration of DO of 5.5 mg/L in all cycles, accumulated up to 23% w/w of TAG (Castro et al., 2018). Tamis et al., (2015) obtained a 25% w/w of TAG using soybean oil as feedstock at an OLR of 1.3 g COD/(L·d) and an airflow input was 1.5 L/min (Table 1). However, the DO concentration during the cycle was not reported, making difficult the comparison of the results with the other reviewed authors.

Respect to LA production, Fig. 3 shows that LA accumulation increased from 13 to 32 %w/w when DO concentration decreased from 2.6 to 1 mg/L (Pinto-Ibieta et al., 2020). This indicates that LA accumulation could be favored at DO lower that 3 mg/L.

Concerning PHA accumulation (Fig. 3), PHA production was <20% w/w when DO concentration was higher than 2.5 mg/L. Contrary, DO lower than 2.5 mg/L allowed to microorganisms reaching >20% w/w of PHA accumulation (Table 1) (Heepkaew and Suwannasilp, 2020; Mohamad Fauzi et al., 2019; Castro et al., 2018; Fra-Vázquez et al., 2018; Freches and Lemos, 2017; Cui et al., 2016; Moralejo-Gárate et al., 2013b; Dobroth et al., 2011). For example, a MMC fed with glycerol as carbon source, and DO maintained at concentrations of 4 and 5.5 mg/L resulted in PHA accumulations of 5 and 6% w/w, respectively (Heepkaew and Suwannasilp, 2020; Moita et al., 2014). Contrary, when the DO concentrations were 0.5 and 2 mg/L using glycerol as substrate, PHA production reached values of 77 and 55% w/w, respectively (Mohamad

Table 1
Operational conditions compilation for F/F culture strategy using MMC fed with non-fermented waste as carbon source.

Authors	Carbon source	Inoculum	PHA %w/w	TAG %w/w	PG %w/w	LA/AA %w/w	Cycles (h)	Air L/min	pH/°C/rpm	OLR g_{COD}/(L·d)	C/N	DO mg/L	F/F
(Moralejo-Gárate et al., 2011)	100% glycerol	Municipal WWTP	20	No data	10	No data	24	1	7/ 30/ No data	1.42	100/ 2.3	4.1	0.08
(Moralejo-Gárate, et al., 2013a)	100% glycerol	municipal WWT	16	No data	30	No data	24	1	7/ 30/ 400	1.42	100/ 2.3	5.1	0.08
(Moralejo-Gárate et al., 2013b)	100% glycerol	Municipal WWTP	7	No data	15	No data	6	1	7/ 30/ 400	5.7	100/ 2.3	5.1	0.37
(Heepkaew and Suwannasilp, 2020)	100% glycerol	Municipal WWTP	10	No data	No data	No data	CSTR	No data	7/28/ No data	1.5	100/1	4.3	No data
(Dobroth et al., 2011)	Crude glycerol	Municipal WWTP	54	No data	No data	No data	4 days	No data	No data	No data	No data	2	No data
(Moita et al., 2014)	71.7% Glycerol 25.6% Methanol 2.6% FFA/FAME	MMC acclimatized using bio-oil	5	No data	15	No data	12	1	7.8/ 23/ 400	1.8	100/8	6	0.04
(Fra-Vázquez et al., 2018)	Glycerol 66% Methanol 20% Lipids 11%	Municipal WWTP	6.7	25.5	7.9	No data	24	6	7/ 30/ No data	1.2	100/6	3.7	0.042
(Mohamad Fauzi et al., 2019)	Glycerol 89% moisture 7% salt 1.7%	Municipal WWT	77 78 27	No data	No data	No data	24	1	7/30/ No data	0.9 2.5 3.2	100/ 0.2	0.5	0.2
(Freches and Lemos, 2017)	70% Glycerol 30% Methanol	MMC selected with glycerol	15 9 <1	No data	15 9 11	No data	24 12 6	1	8/21/ 400	1.5	100/6	5	0.11 No data
(Pokój et al., 2019)	glycerol 82%	Municipal WWT	6 10 8	No data	No data	No data	12	No data	7/ 22/ 100	1.2 2.7 3.6	100/ 12	>3.5	No data
(Tajparast and Frigon, 2013)	Succinic Acid	Municipal WWTP	15	No data	8	No data	8	1.5	7/300	1.2	100/ 55	No data	No data
(Huang et al., 2016)	Xylose	Municipal WWTP	24	No data	No data	No data	12	No data	7.5/No data	2.9	100/4	No data	No data
(Yin et al., 2019)	Reduced sugar	Municipal WWTP	10	No data	No data	No data	12	No data	7/28/ 330	No data	No data	No data	No data
(Pinto-Ibieta et al., 2020)	hemicellulose hydrolysate rich in xylose	Municipal WWTP	3	No data	No data	37/0	12	4	7/25/ 60	90mMC/ d	45/2/1	<1	1
(Pinto-Ibieta, 2020)	hemicellulose hydrolysate rich in xylose	Municipal WWTP	3	No data	No data	7/5	12	4	7/25/ 60	60mMC/ d	30/ 0.9/ 0.1	3	0.17
(Tamis et al., 2015)	Soybean-oil	Municipal WWTP	No data	25	No data	No data	12	1.5	7/30/ 1000	1.3	100/ 14	No data	No data
(Moita and Lemos, 2012)	Bio-oil	Municipal WWTP	10 gCOD PHA/ gCOD biomass	No data	<5 gCOD PHA/ gCOD biomass	No data	12	No data	8/24/ 250	2	100/5	1.8	0.1
(Argiz et al., 2021)	Residual fish-canning oil	Municipal WWTP	26	18	No data	No data	12	No data	No data /30/ No data	No data	No data	3	No data
(Cui et al., 2016)	Glucose Starch	Water from estuarium	25	No data	No data	No data	12	No data	No data/ 30	2.5 2.8	100/ 4.1	1.8 1.5	0.25 0.41
(Fang et al., 2019)	Rice winery	Municipal WWTP	5 5 11	No data	No data	No data	6	1.7	7/28	1.2 2.4 3.6	2.3gN/ L	No data	No data
(Uma and Gandhimathi, 2019)	Oily bilge rich in hydrocarbons	MMC from contaminated oil	55 62 80	No data	No data	No data	24	No data	7/ room T°/No	2.8 2 1	100/ 1.6 100/ 2.3 100/ 4.5	No data	No data
(Moita Fidalgo et al., 2014)	Pure bio oil; Destilated bio-oil	MMC acclimatized using bio-oil	10 17	No data No data	>5 0	No data No data	Selection community: F/F bio-oil as a substrate (three consecutive pulses of 30 Cmmol/L, each), no addition of N (nitrogen in bio-oil was not complete consumed). 18 Nmmol of total nitrogen per litre was added to the system, preventing a complete growth inhibition. 12 h						
(Castro et al., 2018)	Hydrocarbons wastewater	WWTP (containing lubricant and oil-waste)	<5	23	No data	No data	Multi stage enrichment biomass process (nitrogen rich) with successive F/F cycles (no nitrogen) in batch mode 250 ml, 5gCOD L-1, pH 7, 5–6 mg OD/L (75% of saturation) In all experiment, 22°C, 150 rpm.						

COD: chemical oxygen demand; PHA: Polyhydroxyalkanoates; TAG: Triacylglyceride; PG: Polyglucose; LA: Levulinic acid; OLR: organic loading rate; C/N carbon nitrogen ratio; DO: dissolved oxygen; WWTP: Wastewater treatment plant; MMC: Mixed microbial culture; F/F: Feast and famine.

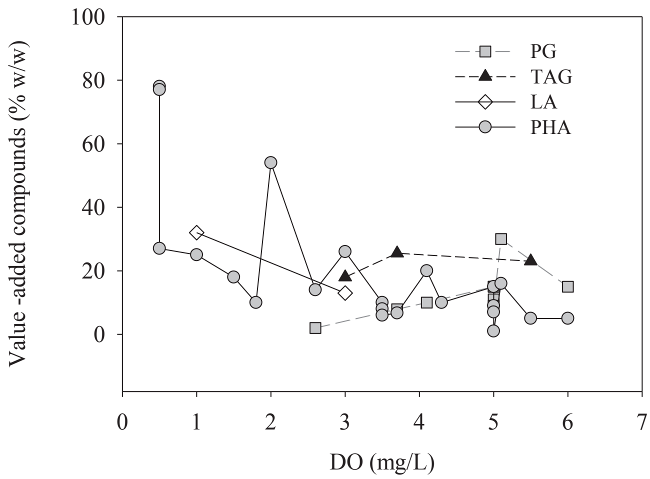

Fig. 2. PG, TAG, PHA and LA production as a function of dissolved oxygen (DO) where PG, Polyglucose; TAG, Triacylglycerides; PHA, Polyhydroxyalkanoates; LA, Levulinic acid.

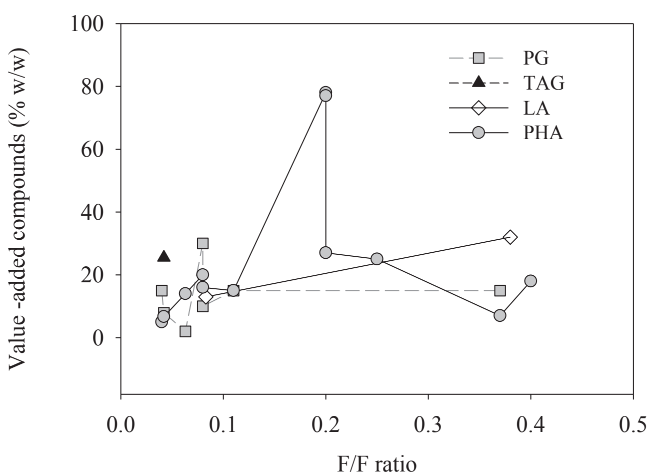

Fig. 3. PG, TAG, PHA and LA production as a function of feast and famine ratio where PG, Polyglucose; TAG, Triacylglycerides; PHA, Polyhydroxyalkanoates; LA, Levulinic acid; F/F ratio, feast and famine ratio.

Fauzi et al., 2019; Dobroth et al., 2011). Probably, the decrease in the production of PHA at DO concentrations higher than 2.5 mg/L obtained by the above authors would drive to microorganisms to use alternative metabolism pathways, favoring the accumulation of other compounds. In this sense, Venkata Mohan and Venkateswar Reddy (2013) reported that PHA biosynthesis and accumulation from VFA occur if an excess of carbon source is provided under oxygen limiting conditions.

From the reviewed literature can be concluded that controlling DO concentration is crucial to favor a targeted accumulation of a certain compound. Consequently, and due to its importance in the process outcome, it would be interesting to standardize the measurement and report of DO concentration. Some studies reported only the supplied air flow, whereas DO concentration in the system was missed, limiting the comparability of the results (Uma and Gandhimathi, 2019; de Oliveira et al., 2019; Fang et al., 2019; Tamis et al., 2015; Tajparast and Frigon, 2013). Meanwhile, other studies make no mention of either the airflow supplied or the DO conditions into the system (Heepkaew and Suwannasilp, 2020; Huang et al., 2016; Liao et al., 2018; Yin et al., 2019).

4.2. Feast/Famine ratio

According to Fig. 3, PG production was not related to the F/F ratio (Fra-Vázquez et al., 2018; Freches and Lemos, 2017; Moita et al., 2014; Moralejo-Gárate et al., 2013a, 2013b, 2011). Similar PG accumulations were obtained at different F/F reported ratios (Fig. 3). For example, 15% w/w of PG was obtained with an F/F ratios of 0.04, 0.11, 0.37 d_{feast}/d_{famine} (Freches and Lemos, 2017; Moita Fidalgo et al., 2014; Moralejo-Gárate et al., 2013b). For TAG accumulation was not possible to establish any trend related to F/F ratio since only one of the reviewed studies reported the F/F ratio (Fra-Vázquez et al., 2018). LA accumulation using synthetic hemicellulose hydrolysate as carbon source, reached 32% w/w with an F/F ratio of 0.38 d_{feast}/d_{famine}, whereas the LA production decreased to 13% w/w when the F/F ratio decreased to 0.08 d_{feast}/d_{famine} (Table 1, Fig. 3). It is worth to note that this trend could also be explained by differences in the DO concentration at each assay (Pinto-Ibieta et al., 2020).

The highest accumulations of PHA shown in Fig. 3 were obtained at F/F ratios close to 0.20 d_{feast}/d_{famine}, which can be considered as the optimal reported value for PHA production when using VFA as carbon source (Lorini et al., 2020; Zheng et al., 2021). However, some of the reported PHA values at these F/F ratios might be also due to the low DO concentrations applied as discussed in section 4.1, i.e. lower than 2 mg/L (Cui et al., 2016; Mohamad Fauzi et al., 2019). In fact, PHA production was independent of F/F ratio at DO concentrations higher than 3 mg/L (Table 1, Fig. 3) (Fra-Vázquez et al., 2018; Freches and Lemos, 2017; Moita et al., 2014; Moralejo-Gárate et al., 2013a; Moralejo-Gárate, et al., 2013b). For example, at F/F ratios of 0.37 and 0.04 d_{feast}/d_{famine}, PHA accumulated at values of 7 and 5% w/w, respectively (Moita et al., 2014; Moralejo-Gárate et al., 2013b).

It has been described that biomass growth can be strongly influenced by F/F ratio, noting that a decrease in the F/F ratio could restrain the physiological adaptation of the microbial culture, causing growth limitations (Cabrera et al., 2019; Zheng et al., 2021; Albuquerque et al., 2010). As the accumulation of a targeted compound is related to the total biomass present (de Oliveira et al., 2019), the optimization of the F/F ratio could favor the accumulation of such target compound.

4.3. Cycle length

According to Fig. 4, a relation between the cycle length and the

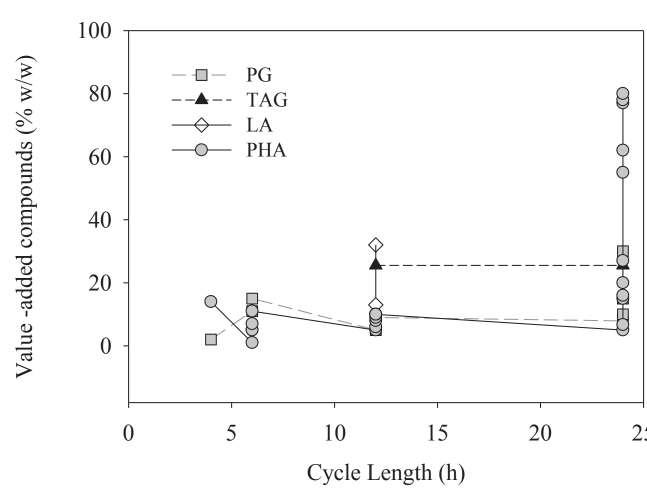

Fig. 4. PG, TAG, PHA and LA production as a function of cycle length where PG, Polyglucose; TAG, Triacylglycerides; PHA, Polyhydroxyalkanoates; LA, Levulinic acid.

accumulation of PG and TAG was not clearly shown. TAG production was independent of the cycle length since no significant changes were observed in the TAG accumulation in cycles of 12 or 24 h of length, reaching yields of 25% w/w of TAG in both cycles (Fig. 4) (Fra-Vázquez et al., 2018; Tamis et al., 2015). Similarly, PG production was neither clearly dependent of the cycle length (Fra-Vázquez et al., 2018; Freches and Lemos, 2017; Moita Fidalgo et al., 2014; Moita et al., 2014; Moralejo-Gárate et al., 2013a, 2013b, 2011). It is worth to notice that Moralejo-Gárate et al., (2013b) indicated that shortening the cycle length from 24 to 6 h resulted in a significant increase of PG production over PHA. For LA production was not possible to establish any tendency, since the reported conditions for LA accumulation were set at the same cycle length, i.e. 12 h (Pinto-Ibieta et al., 2020).

Fig. 4 shows that PHA accumulation might be favored when the cycle length is stablished at 24 h (Mohamad Fauzi et al., 2019; Uma and Gandhimathi, 2019). PHA production reached up to 80% w/w at 24 h cycle length using oily bilge rich in hydrocarbons (Uma and Gandhimathi, 2019). Similarly, Mohamad Fauzi et al. (2019) reported 77% w/w of PHA accumulation using crude glycerol as feedstock at 24 h cycle length. To the contrary, cycle length of 12 h showed a competition between PHA and PG accumulating bacteria, and cycle length of 6 h favored the PG accumulating bacteria (Freches and Lemos, 2017).

4.4. pH

According to Fig. 5, it cannot be observed any relation between pH and PG, TAG, LA and PHA production. For example, accumulated PG was around 10% w/w at pH 7 and at pH 8 (Freches and Lemos, 2017; Moralejo-Gárate et al., 2011). The studies evaluating TAG and LA production were all carried out at pH 7 and, therefore, no conclusions can be obtained (Fig. 5). At this pH 7, a wide range of TAG productivity, i.e. from 5 to 30% w/w, have been observed (Fang et al., 2019; Fra-Vázquez et al., 2018; Moita et al., 2014; Moralejo-Gárate et al., 2013a, 2013b, 2011). Fig. 5 shows that PHA production also presents strong variations for experiments done at the same pH. For example, at pH 7, a productivity higher than 70% was achieved, using glycerol at an OLR of 2.5 g COD/(L·d) and a DO concentration of 0.5 mg/L during the feast phase, whereas, at the same pH 7, productivities as low as 5% w/w have been also reported using the same carbon source at a similar OLR (with 1.8 g COD/(L·d) (Mohamad Fauzi et al., 2019; Moita et al., 2014). The latest low productivity is most likely a consequence of the high DO concentration, i.e. 6 mg/L, which, as previously described, it has a strong influence in the accumulation of PHA. Using VFA as carbon source several researchers indicated that the optimal pH value to maximize the PHA yield is the neutral pH (Amulya et al., 2016; Lee et al., 2015; Venkata Mohan and Venkateswar Reddy, 2013). Extracellular pH above 7 induces a negative electrical difference across the cell membrane, leading to a higher energy requirement for VFA uptake, and thus, reducing PHA accumulation capacity (Filipe et al., 2001).

4.5. Organic loading rate (OLR)

Relation between PG production and operational OLR was not found, as different PG yields were observed at the same OLR (Fig. 6). For example, 10 and 30% w/w of PG were obtained when pure glycerol was fed with an OLR of 1.42 g COD/(L·d) (Moralejo-Gárate et al., 2013a, 2011). While 15% w/w of PG was accumulated by feeding pure glycerol at an OLR of 5.6 g COD/(L·d) (Moralejo-Gárate et al., 2013) and crude glycerol at an OLR of 1.5 g COD/(L·d) (Freches and Lemos, 2017). Respect to TAG, Fig. 6 shows that the accumulation was also independent of the reported OLR, i.e.25% w/w of TAG were obtained at 5 and 1.5 g COD/(L·d), using different carbon source, such as crude glycerol (Fra-Vázquez et al., 2018) or hydrocarbons-rich wastewater (Castro, et al., 2018).

Respect to PHA production, an OLR higher than 3 g COD/(L·d) resulted in PHA accumulation below 10% w/w (Pokój et al., 2019; Fra-Vázquez et al., 2018; Moralejo-Gárate et al., 2013b). While using OLR lower than 3 g COD/(L·d) there is not a clear trend, being reported values in a wide range (Table 1, Fig. 6). For example, Mohamad Fauzi et al. (2019) reported 78% w/w of accumulated PHA using crude glycerol at 2.5 g COD/(L·d), whereas Pokój et al. (2019) reported an accumulated PHA lower than 10% w/w at similar OLR. A tendency to increase the PHA accumulation can be discern when the OLR decreased from 3 to 1 g COD/(L·d) despite of the used carbon sources (Uma and Gandhimathi, 2019; Mohamad Fauzi et al., 2019) (Fig. 6).

High OLR conditions could entail inhibition by substrate, limiting microbial activity and substrate uptake by microorganisms (Li et al., 2019). On the other hand, OLR-limited conditions could lead to a low F/F ratio, thereby microbial growth limitation (Albuquerque et al., 2010). It has been reported that MMC selection is achieved under carbon starvation for long periods, but in these cases, the biomass concentrations are usually low (de Oliveira et al., 2019). Applying high OLRs can increase biomass production, but it can also extend the duration of the feast phase, reducing the MMC selection (Valentino et al., 2015). Hence, F/F culture strategy should be optimally run at the highest possible OLR that still results in stable operation at low F/F ratios, without resulting in substrate inhibition (de Oliveira, et al., 2019).

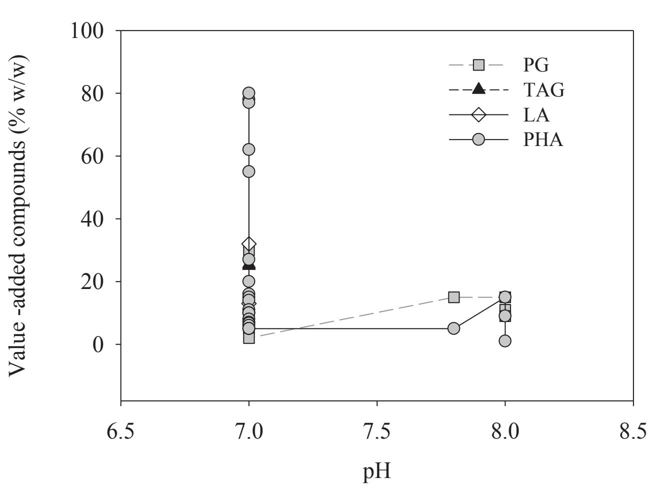

Fig. 5. PG, TAG, PHA and LA production as a function of pH, where PG, Polyglucose; TAG, Triacylglycerides; PHA, Polyhydroxyalkanoates; LA, Levulinic acid.

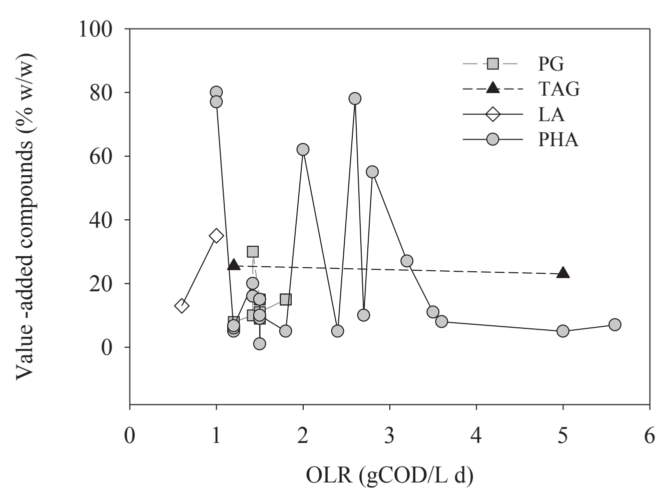

Fig. 6. PG, TAG, PHA and LA production as a function of OLR, where PG, Polyglucose; TAG, Triacylglycerides; PHA, Polyhydroxyalkanoates; LA, Levulinic acid; OLR, organic loading rate.

4.6. Carbon - nitrogen ratio (C/N)

Reviewed literature shows that it was not possible to define a clear tendency about PG, TAG, PHA, and LA accumulations with respect to C/N ratio. PG accumulations of 10 and 30% w/w were reported for the same C/N ratio of 44 (Moralejo-Gárate et al., 2013a, 2011). For TAG, 25% w/w accumulation were reported at a C/N ratio of 7.1 (Tamis et al., 2015) and 17 (Fra-Vázquez et al., 2018). Similarly, PHA accumulations of 10% w/w were reported at very different C/N ratios such as 100 (Heepkaew and Suwannasilp, 2020) or 8 (Pokój et al., 2019) (Table 1). However, according to Mohamad Fauzi et al (2019), higher PHA accumulation was obtained when the C/N ratio decreased, 77 and 27% w/w PHA accumulated at a C/N ratio of 2.6 and 9, respectively. Likewise, the same trend was reported by Uma and Gandhimathi et al, (2019), who reported PHA accumulations of 80%w/w and 55 %w/w at a C/N ratio of 22 and 61, respectively. About LA accumulation, an increment of 19% w/w was reported when C/N ratio decreased from 33 to 22.5 (Pinto-Ibieta et al., 2020).

4.7. Temperature

Reviewed literature shows that PG, TAG, and PHA accumulation have not a clear relation with the operational temperature, although it is worth to note that all the reported temperatures were within the mesophilic range (Table 1). For PG, accumulations of 15% w/w were reported at operation temperatures of 21°C (Freches and Lemos, 2017), 23°C (Moita et al., 2014) and 30°C (Moralejo-Gárate et al., 2013a). For TAG, accumulation around 25% w/w were achieved at 22°C (Castro et al., 2018) and 30°C (Fra-Vázquez et al., 2018; Tamis et al., 2015). For PHA, accumulation higher than 50% were obtained at 20°C (Uma and Gandhimathi, 2019) and 30°C (Mohamad Fauzi et al., 2019). However, Jiang et al (2011) reported that PHA accumulation increased with increasing temperature from 15 to 35°C, while Pittmann & Steinmetz (2014) reported the highest PHA accumulation at 20°C when assessing temperatures from 15°C to 30°C.

The temperature is an essential parameter that critically affect microbial growth and metabolic activities (Inoue et al., 2018). Although the temperature does not have a clear impact on the production of any of the target compounds, temperature is an important parameter to be optimized due to its potential impact on the operational costs.

5. Concluding remark

DO concentration was the variable that most clearly influenced the accumulation of targeted compounds. At DO concentrations higher than 3 mg/L, MMC tend to synthesize PG and TAG, while DO concentrations lower than 3 mg/L favored the production of PHA and LA. In a lesser extent, the OLR and the cycle length were identified to have an impact on the accumulation of PHA, whose accumulation was favored at lower OLR and longer cycle lengths. Further research at DO higher than 3 mg/L would be necessary to have a better understanding of the accumulation of targeted compounds different to PHA.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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