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Production of L-arabinonic acid from L-arabinose by the acetic acid bacterium *Gluconobacter oxydans*

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A R T I C L E I N F O

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A B S T R A C T

L-Arabinonic acid is a five carbon sugar acid valuable for various potential applications. Based on previous observations that *Gluconobacter oxydans* 621H oxidizes L-arabinose in the periplasm by the membrane-bound glucose dehydrogenase GdhM yielding L-arabinonic acid, we tested its ability for production. In fed-batch shake flasks without pH control, 17.4 g/L L-arabinonic acid and 5.7 g/L L-arabino-1,4-lactone were obtained. A large fraction of L-arabinose remained unused since acidification of the medium prevented further substrate oxidation. In pH 6-controlled fed-batch bioreactors, up to 120 g/L L-arabinonic acid and 13 g/L L-arabino-1,4-lactone could be obtained with strain 621H (144 h). Constitutive overexpression of *gdhM* did not increase product titers and resulted in reduced biomass formation, yet the *gdhM* overexpression strain showed higher biomass-specific production (169 g/L/g_{cdw}) compared to 621H (131 g/L/g_{cdw}). The high combined product titer (133 g/L, 814 mM) makes *G. oxydans* a very promising host for high-level production of L-arabinonic acid.

1. Introduction

Arabinonic acid (arabonate) is a five carbon sugar acid (predicted pK_a 3.39) that can serve a variety of purposes. In the patent literature, it is described that arabinonic acid or its lactone could be useful for electrolytic decarboxylation to produce erythrose and erythritol (Genders and Stapley, 2016; Stapley and Genders, 2016), for producing polymer variants for different applications (Ohsumi and Fujii, 2018; Van Es et al., 2017; Weng et al., 2018), for composite cements and semiconductor processing materials (Lee, 2013; Yamazaki, 2007), for medical applications (Okuda and Shimizu, 2016; Sanai and Tanaka, 2010), and for cosmetics (Kawasaki et al., 2005; Maaß et al., 2013). L-Arabinonic acid can also be used to produce L-1,2,4-butanetriol (Niu et al., 2003), which is a precursor of the propellant 1,2,4-butanetriol trinitrate, an important plasticizer for nitrate ester plasticized polyether and useful to improve mechanical properties and reliability of nitroglycerin (Pei et al., 2017).

Arabinonic acid can be formed chemo-catalytically, *e.g.* by oxidation of arabinose on gold and palladium catalysts, by oxidation of trehalose with *N*-bromoacetamide in the presence of suitable rhodium catalysts, by oxidation of lactose with potassium iodate in the presence of suitable iridium catalysts, or by oxidation of glucose with silver(III) periodate in the presence of suitable ruthenium-osmium catalysts (Correia et al., 2019; Kusema et al., 2010; Sataraddi and Nandibewoor, 2013; Singh et al., 2014; Smolentseva et al., 2011).

Enzymatically, arabinonic acid can be formed by arabinose-oxidizing enzymes from L-arabinose-metabolizing bacteria, which typically are intracellular dehydrogenases that use NAD(P)$^+$ as a cofactor. Here, the carbon and energy source L-arabinose is oxidized to L-arabino-1,4-lactone, which then is hydrolyzed in a spontaneous reaction or by a lactonase to yield L-arabinonic acid (Dilworth et al., 1986; Duncan, 1979; Johnsen et al., 2013; Mathias et al., 1989; Novick and Tyler, 1982; Seiboth and Metz, 2011; Watanabe et al., 2006a; Watanabe et al., 2006b; Weimberg, 1959; Weimberg and Doudoroff, 1955). For the microbial production of L-arabinonic acid from L-arabinose, selected L-arabinose dehydrogenases were tested in *Saccharomyces cerevisiae*. With L-arabinose/D-galactose 1-dehydrogenase AraDH from *Rhizobium leguminosarum* expressed in *S. cerevisiae*, a titer of 18 g/L L-arabinonic acid corresponding to a yield 86 of % was achieved within 118 h in a pH 5.5-controlled 0.5 L batch fermenter (Aro-Karkkainen et al., 2014). In an engineered *Escherichia coli* strain with inactivated L-arabinose metabolism, 43.9 g/L was achieved with 40 g/L L-arabinose within 36 h in a pH 7-controlled 5 L batch fermenter by expressing NAD(P)$^+$-dependent

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Table 1
Strains and plasmid used in this study.

Strain	Relevant characteristic(s)	Ref./Source
E. coli S17-1	Δ*recA*, *endA1*, *hsdR17*, *supE44*, *thi*-1, *tra*$^+$	Simon et al. (1983)
G. oxydans 621H	DSM 2343	DSMZ
Plasmid		
pMM4a-mGDH	expression of the membrane-bound glucose dehydrogenase gene (GOX0265, *gdhM*) from the constitutive alcohol dehydrogenase promoter P_{adh}	Mientus et al. (2017)

L-arabinose dehydrogenase AraDH from *Azospirillum brasilense* (Liu et al., 2014).

In contrast to the intracellular NAD(P)$^+$-dependent oxidation of L-arabinose, the periplasmic oxidation of L-arabinose provides some advantages. Substrate import into the cytoplasm and product export out of the cytoplasm, which both may limit the production efficiency, are not required. Periplasmic enzymes oxidizing sugars including arabinose to the corresponding aldonic acids occur in acetic acid bacteria (AAB), such as *Gluconobacter oxydans* (Matsutani and Yakushi, 2018; Peters et al., 2013). *G. oxydans* is well-established in industry for oxidative biotransformations of carbohydrates to produce *e.g.* L-sorbose, a precursor of vitamin C, dihydroxyacetone, a tanning agent, or 6-amino-L-sorbose, a precursor of the antidiabetic drug miglitol (Ameyama et al., 1981; Gupta et al., 2001; Hekmat et al., 2003; Saito et al., 1997; Tkac et al., 2001; Wang et al., 2016). This bacterium catalyzes the regio- and stereoselective periplasmic oxidation of many substrates, including sugars and sugar alcohols, by membrane-bound dehydrogenases with subsequent release of the products into the medium *via* porins in the outer membrane (Mamlouk and Gullo, 2013; Mientus et al., 2017; Pappenberger and Hohmann, 2014).

In *G. oxydans* 621H, L-arabinose is oxidized in the periplasm by the membrane-bound glucose dehydrogenase GdhM (GOX0265) yielding L-arabinonic acid, while the activity of the cytosolic glucose dehydrogenase GdhS (GOX2015) was not relevant for this reaction (Fricke et al., 2020; Mientus et al., 2017; Peters et al., 2013). Recently, the ability of *G. oxydans* for conversion of lignocellulose-derived non-glucose sugars from corn stover, including 10 g/L L-arabinose, into the corresponding sugar acids in pH-controlled bioreactors was also reported (Yao et al., 2017).

In this study, we tested the ability of *G. oxydans* 621H to produce L-arabinonic acid at higher levels from pure L-arabinose stock. Control of the medium pH was crucial to achieve long-term formation of L-arabinonic acid, as it caused a strong acidification of the medium. Plasmid-based overexpression of *gdhM*, although having a negative impact on growth and robustness of the cells, improved the biomass-specific production parameters. Despite, the highest product titers were obtained

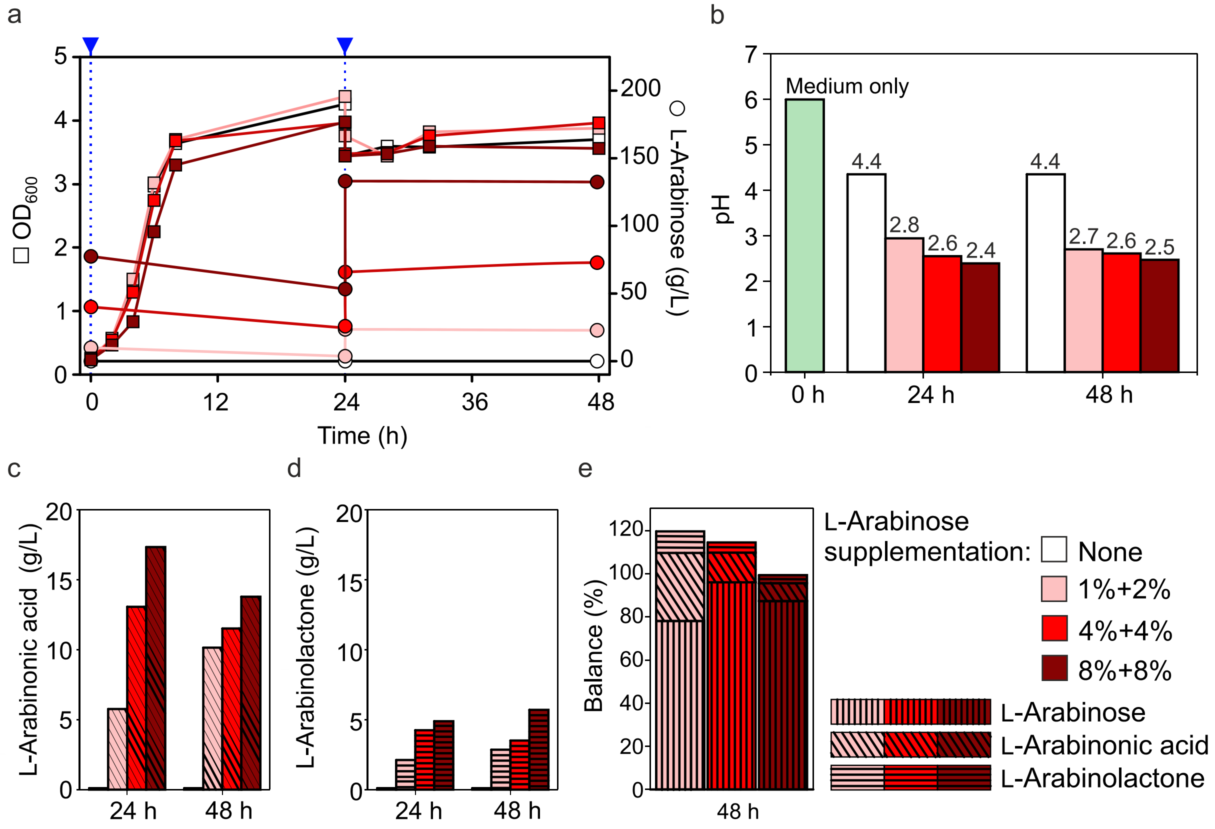


Fig. 1. Shake flasks cultivations of *G. oxydans* 621H grown in D-mannitol medium with supplements of L-arabinose and one feed after 24 h (blue indicator). a) Growth according to OD$_{600}$ and L-arabinose concentrations. b) pH values measured in the culture supernatants after 24 h and 48 h of cultivation. c, d) Concentrations of L-arabinonic acid and L-arabino-γ-1,4-lactone in culture supernatants. e) Carbon balance as stacked relative amounts (%) of the residual substrate L-arabinose and the two formed products L-arabinonic acid and its 1,4-lactone as determined at 48 h and calculated from the concentrations. For each condition, the total amount of the substrate L-arabinose supplied was set to 100%. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

with the *G. oxydans* 621H type strain without *gdhM* overexpression. In pH-controlled fed-batch bioreactors, 120 g/L L-arabinonic acid and 13 g/L of its 1,4-lactone were accumulated, which more than tripled the product titers previously reported for *E. coli* and *S. cerevisiae*.

2. Material and methods

2.1. Bacterial strains, plasmids, medium and shake flasks cultivations

Strains and plasmids used in this study are listed in Table 1. *G. oxydans* was cultivated in D-mannitol medium containing 4% (w/v) D-mannitol, 5 g/L yeast extract, 1 g/L KH_2PO_4, 1 g/L $(NH_4)_2SO_4$, 2.5 g/L $MgSO_4$ x 7 H_2O at 30 °C. As a precaution to prevent bacterial contamination, all media were routinely supplemented with 50 μg mL^{-1} cefoxitin. In cultivations of *G. oxydans* harboring plasmid pMM4a-mGDH, additionally 50 μg mL^{-1} kanamycin was added to the medium (Mientus et al., 2017). For shake flask cultivations, cells were inoculated from pre-cultures to an initial optical density at 600 nm (OD_{600}) of 0.3 (UV-1800, Shimadzu), and grown in 500 mL shaking flasks with three baffles containing 60 mL D-mannitol medium.

2.2. Quantification of L-arabinose, L-arabinonic acid and L-arabino-1,4-lactone

For quantification of L-arabinose, L-arabinonic acid, and L-arabino-1,4-lactone by nuclear magnetic resonance (NMR) spectroscopy, supernatant samples were diluted in a 1:10 ratio with miliQ water. Furthermore, 10% (v/v) D_2O was added to generate an NMR lock signal and 5 mM dimethyl sulfoxide (DMSO) as a reference for quantification of reactants. One-dimensional ^1H NMR spectra were acquired with a Bruker AVANCE III HD 600 spectrometer equipped with a 5 mm HCN TCI cryo-probe operating at 599 MHz (14.1 Tesla). The ^1H NMR data were obtained at 25 °C sample temperature and with the following acquisition parameters: presaturation time of 30 s for water suppressing, 8 transients, 4800 Hz sweep width corresponding to 4 s of acquisition time and 38,362 time domain data points. Spectra were processed and analyzed using Bruker Topspin version 3.6.2. After Fourier transformation, zerofilling to 512 K data points and baseline correction, the nonoverlapping signals of L-arabinose, L-arabinonic acid and L-arabino-1,4-lactone were integrated. The concentration of the three compounds was calculated by using the 5 mM DMSO reference integral.

2.3. Fed-batch in pH-controlled bioreactor cultivation conditions

DASbox® mini-bioreactors were used for cultivations in D-mannitol medium. Bioreactors controlled by DASware software (Eppendorf) were used in combination with two 6-bladed Rushton-type impellers, pH-(EasyFerm Plus K8 120, Hamilton), O_2-(InPro® 6800 series, Mettler-Toledo) and temperature-sensors. For the cultivations, 385 mL glass vessels were filled with 100 mL of 4% (w/v) D-mannitol medium and cells were grown at 30 °C from an initial OD_{600} of 0.3. Starting with 500 rpm agitation frequency and a gas flow rate of 6 sL h^{-1} purged directly into the medium, a three step cascade was applied to maintain the dissolved oxygen tension $\geq$30%. Firstly, agitation was gradually increased to 1200 rpm. Secondly, the percentage of oxygen in the air supply was up-regulated to a maximum of 80% (v/v), and finally the air flow rate was automatically elevated. During the entire cultivation, pH 6 was maintained by automatic titration with a 3 M KOH solution. Samples for off-line monitoring of growth, substrate consumption and product formation were taken in intervals and treated as described above. Supernatants were stored at −20 °C until the NMR analysis of substrates and products. For the calculations of biomass-specific product titers, a correlation factor of 0.32 g cell dry weight (cdw)/L for a culture with an OD_{600} of 1 was used (Richhardt et al., 2012).

Table 2

Total volumes of titrated 3 M KOH stock to maintain pH 6 in fed-batch bioreactor conditions with complex D-mannitol medium with resulting final concentrations of KOH calculated based on total medium volume changes (see Fig. 2a).

Strain and L-arabinose feed	3 M KOH (mL)	mM KOH after 144 h
621H +4%	62 ± 0.5	1016 ± 8
621H +8%	77 ± 15	1156 ± 140
621H/pMM4a-mGDH +4%	47 ± 5	837 ± 64
621H/pMM4a-mGDH +8%	72 ± 0	1119 ± 0

3. Results and discussion

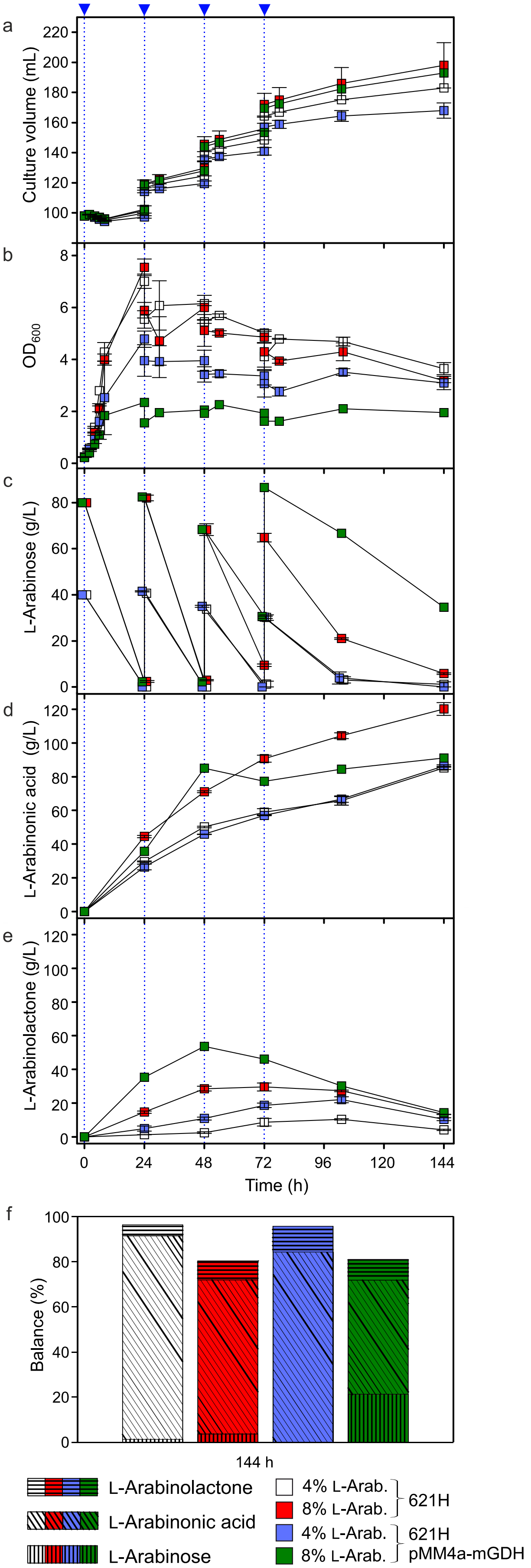
3.1. L-Arabinonic acid formation in fed-batch shake flask is pH-limited

In order to elucidate the potential of *G. oxydans* to form L-arabinonic acid at higher titers in one step from L-arabinose, strain 621H first was cultivated in shake flasks in D-mannitol medium supplemented with 10 g/L, 40 g/L, and 80 g/L L-arabinose. Under all conditions, the strain grew very similar. Even with 80 g/L L-arabinose only a slight growth retardation was observed (Fig. 1a). After 24 h, equal volumes of different L-arabinose stock solutions prepared with D-mannitol-free medium were fed to obtain a supplement of 20 g/L, 40 g/L, and 80 g/L, respectively. For the control (0 g/L L-arabinose), equal volume of D-mannitol-free medium was added. The formation of L-arabinonic acid (pK_a 3.39, https://hmdb.ca/metabolites/HMDB0000539) led to additional acidification of the medium. The L-arabinose left at 24 h before feed and at 48 h indicated that L-arabinose consumption was strongly decreased below pH 3 or even disabled below pH 2.7 (Fig. 1a, b). The maximal L-arabinonic acid concentration was 17.4 g/L after 24 h with 80 g/L L-arabinose (Fig. 1c). The NMR analysis also revealed L-arabino-1,4-lactone. The highest titer of 1,4-lactone was 5.7 g/L after 48 h with 80 g/L L-arabinose (Fig. 1d). The somewhat lower L-arabinonic acid titer at 48 h compared to 24 h resulted from the 10 mL volume increase due to the feed at 24 h and some acid was likely converted in the acidic conditions to 1,4-lactone, since these levels were similar at 24 h and 48 h despite the volume increase. Based on the concentrations measured by NMR and the volume changes, the carbon balance sum of the final amounts of residual substrate and the two products corresponded approximately to 120%, 110% and 100% of the amount of substrate provided in total (Fig. 1e). This suggested that the metabolite levels were somewhat overestimated by NMR. Then, the data of the high L-arabinose condition (80 + 80 g/L) could indicate a carbon gap of 10% to 20% potentially resulting from nonspecific formation of unknown byproducts at higher L-arabinose or product titers. According to the NMR data, no signals suggesting further byproducts could be found. At 48 h, the molar sum of the two products corresponded to approximately 42%, 19%, and 20% of the amount of 10 + 20 g/L, 40 + 40 g/L, and 80 + 80 g/L L-arabinose provided.

For the L-arabinose/D-galactose 1-dehydrogenase AraDH from *R. leguminosarum*, the L-arabino-1,4-lactone was reported to be the stable oxidation product, which was assumed to open slowly at neutral pH to the linear form (Aro-Karkkainen et al., 2014). *Vice versa*, the 1,4-lactone can be formed from the linear form in acidic pH conditions (Aro-Karkkainen et al., 2014). In case of the GdhM reaction, the 1,4-lactone is unlikely to be the direct oxidation product. Under the rapidly acidifying pH conditions in shake flasks, the 1,4-lactone would not open slowly. Therefore, the linear form is likely the direct oxidation product of the GdhM reaction since L-arabinonic acid was the most of the two compounds and the 1,4-lactone was formed rather from the linear form due to the acidic pH conditions.

3.2. Production of L-arabinonic acid in pH-controlled fed-batch bioreactor

Since the acidification below pH 3 limited further product formation,



(caption on next column)

Fig. 2. Fed-batch DASbox fermentation of *G. oxydans* 621H without and with plasmid pMM4a-mGDH grown in D-mannitol medium supplemented and fed with L-arabinose as indicated. a) Initial culture volume (100 mL) and volume increase over time due to fed every 24 h (blue arrows and dotted line indicators), withdrawal of samples, and base titration for pH 6 maintenance. b) Biomass formation according to OD_{600}. c, d, e) Concentrations of L-arabinose, L-arabinonic acid, and L-arabino-1,4-lactone according to NMR analysis. Data are based on two independent biological replicates for each strain. In Fig. 1c, overlapping data points at a time were somewhat shifted for better visibility. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

we next tested production in pH-controlled bioreactors. pH 6 was reported to be optimal for GdhM (Matsushita et al., 1994). Besides *G. oxydans* 621H, we also tested strain 621H transformed with plasmid pMM4a-mGDH for constitutive overexpression of the *gdhM* gene (Mientus et al., 2017). Both strains were grown in pH 6 D-mannitol medium initially supplemented with 40 g/L and 80 g/L L-arabinose. Every 24 h, L-arabinose dissolved in D-mannitol-free medium was fed to add another 40 g/L or 80 g/L (corresponding to the initial culture volume). KOH titrations for maintaining pH 6 and feed volumes increased the culture volumes despite taking samples. Overall, due to higher base consumption in the 80 g/L conditions (Table 2), their final culture volumes were higher than that of the 40 g/L conditions (Fig. 2a). As expected for pH-controlled conditions, strain 621H reached an almost two-fold higher maximal OD_{600} at the end of the exponential growth in both conditions 40 g/L ($OD_{600} = 7.0 \pm 0.3$) and 80 g/L ($OD_{600} = 7.5 \pm 0.3$) compared to shake flasks without pH control (Fig. 2b). In contrast to 621H, biomass formations of strain 621H/pMM4a-mGDH were much lower with both 40 g/L (OD_{600} 4.8 ± 0.3) and 80 g/L (OD_{600} only 2.3). This indicated that constitutive overexpression of *gdhM* and possibly kanamycin in the medium were detrimental for growth. In *E. coli,* detrimental effects of membrane protein overexpression have been attributed to a limiting Sec translocon capacity having a severe impact on the cell envelope and the cytoplasmic proteome (Wagner et al., 2007). Accumulation of cytoplasmic aggregates containing the overexpressed membrane protein as well as chaperones, proteases, many essential cytoplasmic proteins, and many precursors of periplasmic and outer membrane proteins were found. Also, levels of respiratory chain complexes in the cytoplasmic membrane were strongly reduced, resulting in inefficient ATP production in *E. coli* (Wagner et al., 2007). Presumably, in *G. oxydans* similar effects are caused by saturation of the Sec translocon, which mediates both translocation of secretory proteins across and integration of membrane proteins into the cytoplasmic membrane. Furthermore, kanamycin causes abnormal cell morphology suggesting stress to *G. oxydans* (Fricke et al., 2021b). Both, constitutive overproduction of membrane-bound GdhM protein in combination with use of kanamycin seems to be detrimental, especially under osmotic stress conditions. In fact, even without high levels of L-arabinose and KOH from base titration, we observed notable differences when handling the plasmid-free 621H strain and 621H/pMM4a-mGDH. For the overexpression strain, sedimentation of the cells by centrifugation was difficult and cell pellets were much more loose and slimy than for plasmid-free 621H. In this context, we frequently observed lower initial OD_{600} values than expected by calculation when inoculating new cultures from resuspended pre-culture pellets, which suggested some extent of cell lysis of the overexpression strain. As in *E. coli*, conditionally timed and tuned overexpression of a membrane protein could avoid detrimental effects and improve biomass and functional membrane protein formation (Wagner et al., 2008). Recently, two systems became available for tunable induction of target gene expression in *G. oxydans* (Fricke et al., 2021a; Fricke et al., 2021b).

In 40 g/L condition, L-arabinose was always almost fully consumed within 24 h by both strains, while in 80 g/L condition higher levels of residual substrate at the end of day 3 and later were found (Fig. 2c). These residual substrate levels in the later stage (≥72 h) were much higher for the *gdhM* overexpression strain. Since even with 80 g/L substrate there was no residual L-arabinose titer 24 h after a feed until the end of day 2 (48 h), the much lower biomass (OD_{600}) of the *gdhM* overexpression strain was not *per se* limiting L-arabinose oxidation. Rather, some cell instability and/or (osmotic) stress sensitivity of the *gdhM* overexpression strain was likely limiting L-arabinose oxidation from 48 h onward and plasmid-free 621H with a higher biomass finally outperformed the sensitive overexpression strain with respect to absolute product titers. Generally, for both strains the product titers were higher with 80 g/L compared to 40 g/L feed (Fig. 2d, e). In 80 g/L condition, the *gdhM* overexpression strain produced a transiently much higher 1,4-lactone level (54 g/L). Since pH 6 was maintained, the transiently much higher levels of the 1,4-lactone should have resulted from the open acid form by a lactonizing enzyme activity either released from the more sensitive cells of the overexpression strain upon partial cell lysis or due to increased metabolite exchange through the impaired cell membrane. These 1,4-lactone titers peaking from day 2 to 3 in the 80 g/L condition then continuously decreased until the end of the fermentation. For the *gdhM* overexpression strain, this decrease cannot be explained alone by increasing culture volumes caused by base titrations and the third substrate feeding. Slow opening of the lactone at close-to-neutral pH could only be effective if the assumed lactonizing activity became more and more inactive. Moreover, in view of the L-arabinose consumption indicated by residual titers still decreasing after 72 h, the L-arabinonic acid titer is expected to increase accordingly if L-arabinose is still oxidized and if additionally the 1,4-lactone is assumed to open slowly, yet the L-arabinonic acid titer did not. Therefore, the data suggested a loss of substrate or products at higher titers by nonspecific conversions. Balancing the sum of the final amounts of residual L-arabinose substrate and the two products in comparison to the L-arabinose supplied in total revealed a carbon gap of approximately 20% for both strains for the 80 g/L condition while for 40 g/L the carbon gap was only 4% (Fig. 2f). In the NMR analysis, again no signals indicating another byproduct were found. If the carbon gap resulted from nonspecific conversion of L-arabinose, an optimized feeding avoiding too high substrate titers should increase product formation and reduce the carbon gap. The highest combined absolute product titers of L-arabinonic acid plus its 1,4-lactone obtained was approximately 133 g/L for strain 621H, while the *gdhM* overexpression strain showed a higher biomass-specific production (169 $g/L/g_{cdw}$) compared to strain 621H (131 $g/L/g_{cdw}$).

4. Conclusion

The endogenous capability of *G. oxydans* to oxidize L-arabinose in the periplasm by the membrane-bound glucose dehydrogenase GdhM is highly suitable for one-step production of L-arabinonic acid from L-arabinose. Already without strain optimization and further process improvements, the product titer obtained was more than three-fold above the titers reported for engineered *S. cerevisiae* and *E. coli*. The biomass-specific product titer of the *G. oxydans* strains indicated that additional expression of *gdhM* can increase space-time yield. Together with an optimized L-arabinose feeding strategy and process optimizations, further increase in product titer and production rate should be achievable with *G. oxydans*.

Availability of data and materials

Data and materials are available upon request.

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CRediT authorship contribution statement

Philipp Moritz Fricke: Investigation, Formal analysis, Writing – review & editing, Validation. **Rudolf Hartmann:** Formal analysis, Validation. **Astrid Wirtz:** Formal analysis, Validation. **Michael Bott:** Writing – review & editing, Validation. **Tino Polen:** Writing – review & editing, Validation.

Declaration of competing interest

All authors declare that they have no competing interests.

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References

Ameyama, M., Shinagawa, E., Matsushita, K., Adachi, O., 1981. D-fructose dehydrogenase of Gluconobacter industrius: purification, characterization, and application to enzymatic microdetermination of D-fructose. J. Bacteriol. 145 (2), 814–823.

Aro-Karkkainen, N., Toivari, M., Maaheimo, H., Ylilauri, M., Pentikainen, O.T., Andberg, M., Oja, M., Penttila, M., Wiebe, M.G., Ruohonen, L., Koivula, A., 2014. L-Arabinose/D-galactose 1-dehydrogenase of Rhizobium leguminosarum bv. Trifolii characterised and applied for bioconversion of L-arabinose to L-arabonate with Saccharomyces cerevisiae. Appl. Microbiol. Biotechnol. 98 (23), 9653–9665. https://doi.org/10.1007/s00253-014-6039-2.

Correia, L.S., Grenman, H., Warna, J., Salmi, T., Murzin, D.Y., 2019. Catalytic oxidation kinetics of arabinose on supported gold nanoparticles. Chem. Eng. J. 370, 952–961. https://doi.org/10.1016/j.cej.2019.03.241.

Dilworth, M.J., Arwas, R., Mckay, I.A., Saroso, S., Glenn, A.R., 1986. Pentose metabolism in Rhizobium leguminosarum Mnf300 and in cowpea Rhizobium Ngr234. J. Gen. Microbiol. 132, 2733–2742.

Duncan, M.J., 1979. L-Arabinose metabolism in Rhizobia. J. Gen. Microbiol. 113 (Jul), 177–179. https://doi.org/10.1099/00221287-113-1-177.

Fricke, P.M., Link, T., Gatgens, J., Sonntag, C., Otto, M., Bott, M., Polen, T., 2020. A tunable L-arabinose-inducible expression plasmid for the acetic acid bacterium Gluconobacter oxydans. Appl. Microbiol. Biotechnol. 104 (21), 9267–9282. https://doi.org/10.1007/s00253-020-10905-4.

Fricke, P.M., Klemm, A., Bott, M., Polen, T., 2021a. On the way toward regulatable expression systems in acetic acid bacteria: target gene expression and use cases. Appl. Microbiol. Biotechnol. 105 (9), 3423–3456. https://doi.org/10.1007/s00253-021-11269-z.

Fricke, P.M., Lürkens, M., Hünnefeld, M., Sonntag, C.K., Bott, M., Davari, M.D., Polen, T., 2021b. Highly tunable TetR-dependent target gene expression in the acetic acid bacterium Gluconobacter oxydans. Appl. Microbiol. Biotechnol. 105 (18), 6835–6852. https://doi.org/10.1007/s00253-021-11473-x.

Genders, J.D., Stapley, J.A., 2016. Methods for the Simultaneous Electrolytic Decarboxylation and Reduction of Sugars. EP000003033442B1.

Gupta, A., Singh, V.K., Qazi, G.N., Kumar, A., 2001. Gluconobacter oxydans: its biotechnological applications. J. Mol. Microbiol. Biotechnol. 3 (3), 445–456.

Hekmat, D., Bauer, R., Fricke, J., 2003. Optimization of the microbial synthesis of dihydroxyacetone from glycerol with Gluconobacter oxydans. Bioproc. Biosyst. Eng. 26 (2), 109–116. https://doi.org/10.1007/s00449-003-0338-9.

Johnsen, U., Sutter, J.M., Zaiss, H., Schonheit, P., 2013. L-Arabinose degradation pathway in the haloarchaeon Haloferax volcanii involves a novel type of L-arabinose dehydrogenase. Extremophiles 17 (6), 897–909. https://doi.org/10.1007/s00792-013-0572-2.

Kawasaki, Y., Hori, M., Yamamoto, Y., Hiraki, J., 2005. Cosmetic Composition Containing Polyorganosiloxane-containing Epsilon-polylysine Polymer, and Polyhydric Alcohol, and Production Thereof. EP000001604647B1.

Kusema, B.T., Campo, B.C., Maki-Arvela, P., Salmi, T., Murzin, D.Y., 2010. Selective catalytic oxidation of arabinose - a comparison of gold and palladium catalysts. Appl. Catal. A-Gen. 386 (1–2), 101–108. https://doi.org/10.1016/j.apcata.2010.07.037.

Lee, W., 2013. Novel Nitrile and Amidoxime Compounds and Methods of Preparation. EP000002207872B1.

Liu, H., Valdehuesa, K.N.G., Ramos, K.R.M., Nisola, G.M., Lee, W.K., Chung, W.J., 2014. L-arabonate and D-galactonate production by expressing a versatile sugar dehydrogenase in metabolically engineered Escherichia coli. Bioresour. Technol. 159, 455–459. https://doi.org/10.1016/j.biortech.2014.03.056.

Maaß, S., Wagner, R., Sockel, K.-H., Davis, M., Schnering, A., Streicher, K., 2013. UV-photo-protecting Cosmetic Composition. EP000002667947B1.

Mamlouk, D., Gullo, M., 2013. Acetic acid bacteria: physiology and carbon sources oxidation. Indian J. Microbiol. 53 (4), 377–384. https://doi.org/10.1007/s12088-013-0414-z.

Mathias, A.L., Rigo, L.U., Funayama, S., Pedrosa, F.O., 1989. L-Arabinose metabolism in Herbaspirillum seropedicae. J. Bacteriol. 171 (9), 5206–5209. https://doi.org/10.1128/jb.171.9.5206-5209.1989.

Matsushita, K., Toyama, H., Adachi, O., 1994. Respiratory chains and bioenergetics of acetic acid bacteria. Adv. Microb. Physiol. 36, 247–301. https://doi.org/10.1016/s0065-2911(08)60181-2.

Matsutani, M., Yakushi, T., 2018. Pyrroloquinoline quinone-dependent dehydrogenases of acetic acid bacteria. Appl. Microbiol. Biotechnol. 102 (22), 9531–9540. https://doi.org/10.1007/s00253-018-9360-3.

Mientus, M., Kostner, D., Peters, B., Liebl, W., Ehrenreich, A., 2017. Characterization of membrane-bound dehydrogenases of Gluconobacter oxydans 621H using a new system for their functional expression. Appl. Microbiol. Biotechnol. 101 (8), 3189–3200. https://doi.org/10.1007/s00253-016-8069-4.

Niu, W., Molefe, M.N., Frost, J.W., 2003. Microbial synthesis of the energetic material precursor 1,2,4-butanetriol. J. Am. Chem. Soc. 125 (43), 12998–12999. https://doi.org/10.1021/ja036391+.

Novick, N.J., Tyler, M.E., 1982. L-Arabinose metabolism in Azospirillum brasiliense. J. Bacteriol. 149 (1), 364–367. https://doi.org/10.1128/Jb.149.1.364-367.1982.

Ohsumi, K., Fujii, T., 2018. Polymer Bead. EP000003584318A1.

Okuda, T., Shimizu, H., 2016. Immunity Inducer for Saccharide Antigens. EP000002993182A1.

Pappenberger, G., Hohmann, H.P., 2014. Industrial production of L-ascorbic Acid (vitamin C) and D-isoascorbic acid. Adv. Biochem. Eng. Biotechnol. 143, 143–188. https://doi.org/10.1007/10_2013_243.

Pei, L., Dong, K., Tang, Y., Zhang, B., Yu, C., Li, W., 2017. Theoretical studies of the decomposition mechanisms of 1,2,4-butanetriol trinitrate. J. Mol. Model. 24 (1), 6. https://doi.org/10.1007/s00894-017-3541-3.

Peters, B., Mientus, M., Kostner, D., Junker, A., Liebl, W., Ehrenreich, A., 2013. Characterization of membrane-bound dehydrogenases from Gluconobacter oxydans 621H via whole-cell activity assays using multideletion strains. Appl. Microbiol. Biotechnol. 97 (14), 6397–6412. https://doi.org/10.1007/s00253-013-4824-y.

Richhardt, J., Bringer, S., Bott, M., 2012. Mutational analysis of the pentose phosphate and Entner-Doudoroff pathways in Gluconobacter oxydans reveals improved growth of a Δedd Δeda mutant on mannitol. Appl. Environ. Microbiol. 78 (19), 6975–6986. https://doi.org/10.1128/Aem.01166-12.

Saito, Y., Ishii, Y., Hayashi, H., Imao, Y., Akashi, T., Yoshikawa, K., Noguchi, Y., Soeda, S., Yoshida, M., Niwa, M., Hosoda, J., Shimomura, K., 1997. Cloning of genes coding for L-sorbose and L-sorbosone dehydrogenases from Gluconobacter oxydans and microbial production of 2-keto-L-gulonate, a precursor of L-ascorbic acid, in a recombinant G. Oxydans strain. Appl. Environ. Microb. 63 (2), 454–460.

Sanai, K., Tanaka, Y., 2010. Preventive/remedy for urinary calculosis. Patent 20100227923, (Ed.) L.C. United States Godo Shusei Co., JP), Vol. Patent 20100227923.

Sataraddi, S.R., Nandibewoor, S.T., 2013. Oxidation of D-glucose by silver(III) periodate complex in the presence of Ru(III)/Os(VIII) as a homogeneous catalyst: a comparative mechanistic study (stopped flow technique). J. Solut. Chem. 42 (5), 897–915. https://doi.org/10.1007/s10953-013-0002-1.

Seiboth, B., Metz, B., 2011. Fungal arabinan and L-arabinose metabolism. Appl. Microbiol. Biotechnol. 89 (6), 1665–1673. https://doi.org/10.1007/s00253-010-3071-8.

Simon, R., Priefer, U., Pühler, A., 1983. A broad host range mobilization system for in vivo genetic-engineering - Transposon mutagenesis in Gram-negative bacteria. Bio-Technol. 1 (9), 784–791. https://doi.org/10.1038/nbt1183-784.

Singh, A.K., Singh, R.K., Srivastava, R., Rahmani, S., Srivastava, J., Singh, M., 2014. Rh (III)-catalysed oxidation of D(+) trehalose by n-bromoacetamide in acidic medium. A kinetic and mechanistic study. Oxid. Commun. 37 (1), 193–208.

Smolentseva, E., Kusema, B.T., Beloshapkin, S., Estrada, M., Vargas, E., Murzin, D.Y., Castillon, F., Fuentes, S., Simakov, A., 2011. Selective oxidation of arabinose to arabinonic acid over Pd-au catalysts supported on alumina and ceria. Appl. Catal. A-Gen. 392 (1–2), 69–79. https://doi.org/10.1016/j.apcata.2010.10.021.

Stapley, J.A., Genders, J.D., 2016. Methods for the Electrolytic Decarboxylation of Sugars. EP000002971254B1.

Tkac, J., Navratil, M., Sturdik, E., Gemeiner, P., 2001. Monitoring of dihydroxyacetone production during oxidation of glycerol by immobilized Gluconobacter oxydans cells with an enzyme biosensor. Enzyme Microb. Technol. 28 (4–5), 383–388.

Van Es, D.S., Pazhavelikkakath Purushothaman, R.K., Frissen, A.E., Van Haveren, J., Van der Klis, F., 2017. Oxidation of uronic acids to aldaric acids. EP000003204155B1.

Wagner, S., Baars, L., Ytterberg, A.J., Klussmeier, A., Wagner, C.S., Nord, O., Nygren, P. A., van Wijk, K.J., de Gier, J.W., 2007. Consequences of membrane protein overexpression in Escherichia coli. Mol. Cell. Proteomics 6 (9), 1527–1550. https://doi.org/10.1074/mcp.M600431-MCP200.

Wagner, S., Klepsch, M.M., Schlegel, S., Appel, A., Draheim, R., Tarry, M., Hogbom, M., van Wijk, K.J., Slotboom, D.J., Persson, J.O., de Gier, J.W., 2008. Tuning Escherichia coli for membrane protein overexpression. Proc.Natl. Acad. Sci. U. S. A. 105 (38), 14371–14376. https://doi.org/10.1073/pnas.0804090105.

Wang, E.X., Ding, M.Z., Ma, Q., Dong, X.T., Yuan, Y.J., 2016. Reorganization of a synthetic microbial consortium for one-step vitamin C fermentation. Microb. Cell Factories 15, 21. https://doi.org/10.1186/s12934-016-0418-6.

Watanabe, S., Kodaki, T., Makino, K., 2006a. Cloning, expression, and characterization of bacterial L-arabinose 1-dehydrogenase involved in an alternative pathway of L-arabinose metabolism. J. Biol. Chem. 281 (5), 2612–2623. https://doi.org/10.1074/jbc.M506477200.

Watanabe, S., Shimada, N., Tajima, K., Kodaki, T., Makino, K., 2006b. Identification and characterization of L-arabonate dehydratase, L-2-keto-3-deoxyarabonate dehydratase, and L-arabinolactonase involved in an alternative pathway of L-arabinose metabolism. Novel evolutionary insight into sugar metabolism. J. Biol. Chem. 281 (44), 33521–33536. https://doi.org/10.1074/jbc.M606727200.

Weimberg, R., 1959. L-2-Keto-4,5-dihydroxyvaleric acid: an intermediate in the oxidation of L-arabinose by Pseudomonas saccharophila. J. Biol. Chem. 234 (4), 727–732.

Weimberg, R., Doudoroff, M., 1955. The oxidation of L-arabinose by Pseudomonas saccharophila. J. Biol. Chem. 217 (2), 607–624.

Weng, W., Liu, C., Yan, C., Su, H., Zhou, C., 2018. 8-Arm Polyethylene Glycol Derivative, Manufacturing Method and Modified Bio-related Substance Thereby. EP000003315531B1.

Yamazaki, H., 2007. Polycarboxylic Acid Polymer for Cement Admixture and Cement Admixture. EP000001767505A2.

Yao, R.M., Hou, W.L., Bao, J., 2017. Complete oxidative conversion of lignocellulose derived non-glucose sugars to sugar acids by Gluconobacter oxydans. Bioresour. Technol. 244, 1188–1192. https://doi.org/10.1016/j.biortech.2017.08.078.