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A sustainable method for potato side stream valorisation to obtain steroidal glycoalkaloids within a bioeconomic approach

Nina Stadler, ^a Birgit Henßen, ^{a,b} Jörg Pietruszka ^{a,b} and Thomas Classen *^b

This study explores potato side streams as a source of valuable natural products, specifically steroidal glycoalkaloids (SGAs). A bioeconomic approach was envisioned for valorisation. The *E*-factor (environmental factor) was used as a key measurement tool to optimise the extraction of SGAs and to compare the extraction and hydrolysis with the semi synthesis of solanidine starting from diosgenin in a lab scale up to 6 g. In particular, extraction was significantly optimised through the use of a swing mill and cyclopentyl methyl ether (CPME) and dimethyl carbonate (DMC) as 'green' solvents. It was shown that the potato variant Innovator displayed the highest SGA content (~20 mg per g dry weight), and flowers showed higher levels compared to leaves and berries. The results indicate that extraction with hydrolysis is a more environmentally friendly method, particularly when using fresh plant material. The study concludes that potato side streams can be valorised without affecting food streams, providing opportunities for natural products with potential applications in agriculture and beyond.

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1. A side stream valorisation of potatoes to obtain solanidine for further derivatisation was envisioned. Different potato cultivars were analysed for their steroidal glycoalkaloid content and different cell disruption methods were investigated for efficacy and purity.
2. Extractions were improved in terms of energy consumption by the determination and optimisation of their *E*⁺-factors as well as substitution of the solvent system by recommended more sustainable alternatives. For comparison, the total synthesis of solanidine was performed and showed an increased *E*⁺-factor and higher environmental impact than the extraction.
3. Industrial/large scale extractions with swing mill disruption could improve the extractable amount. Established enzyme-based hydrolysis could be adapted for steroidal glycoalkaloids.

Introduction

Tackling sustainability and circular bioeconomy is one way to become less dependent on fossil-based fuels and create a sustainable future. Therefore, pursuing research into the recycling and further processing of unused materials and waste streams of widely used industrial processes is vital.¹ One of these waste streams is the leaves, berries, and flowers from potatoes, which are left on the field after the harvest of their tubers and contain valuable natural products. Potatoes (*Solanum tuberosum* L.) belong to the *Solanaceae* family and are one of the main crops worldwide with over 284 million tons annually; therefore, there is a major accumulation of the leftover plant

material, which can be considered as both green manure and side-stream biomass.^{2,3} Their secondary metabolites are steroidal glycoalkaloids (SGAs), which are mainly α -solanine and α -chaconine in *S. tuberosum* (Fig. 1), while α -solamargine can be found in *S. nigrum*.^{4,5} These are natural plant protection agents and apart from unwanted effects on mammals such as nausea or neurological disorders, they show potential applications against pathogenic trichomonads, snails, or the potato cyst nematode.^{6–9} These predators and pathogens can have a negative impact on total harvest biomass during potato production. While α -solamargine is effective against potato cyst nematodes through prevention of *Globodera pallida* hatching,¹⁰ the most destructive pathogen *Phytophthora infestans* can cause a harvest loss of up to 20% and must be treated with fungicides.¹¹

Since their biological activity is interesting and the extraction of SGAs is well studied, potato by-products are favourable for valorisation of plant material and further semi-synthetic

^aHeinrich Heine University Düsseldorf, Institute for Bioorganic Chemistry, D-52426 Jülich, Germany

^bForschungszentrum Jülich GmbH, Institute for Bio- and Geosciences I: Bioorganic Chemistry, D-52426 Jülich, Germany. E-mail: T.Classen@fz-juelich.de



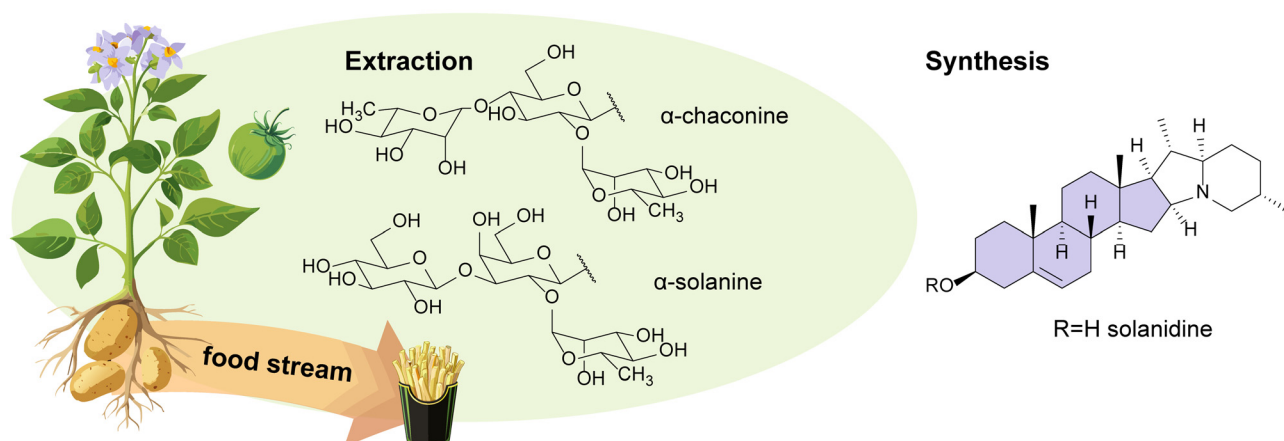


Fig. 1 Extractable glycoalkaloids α -solanine and α -chaconine as well as the aglycon solanidine produced through hydrolysis or total synthesis. Extraction has no effect on the food stream, since the glycoalkaloid rich parts are leftovers on the field and function as side streams from potato production. With courtesy of Irene Küberl, Adobe Firefly is used to generate the potato plant.

derivatisation.^{12,13} As there are not many known derivatives of α -solanine and α -chaconine or their aglycon solanidine, new derivatives would address a research gap.^{13,14}

Several publications highlight the benefits of further processing of existing biomass, including the potential reduction of monetary losses for countries if food wastes were instead utilised than disposed of.⁶ For this side-stream valorisation, different techniques have been applied for the extraction of SGAs from potatoes, most of them for analytical purposes. Wang *et al.* used a bisolvent maceration consisting of methanol and chloroform to extract the glycoalkaloids (27.4–85 mg per 100 g fresh weight).¹⁵ Another method was extraction with pyridine in a Soxhlet apparatus.¹⁶ Bushway also used maceration for his extraction technique but with a solvent system consisting of THF, acetonitrile, water, and acetic acid (4.6–32.0 mg per 20 g freeze-dried).¹⁷ In more recent publications, SGAs were obtained through microwave-assisted (19.9–81.6 mg kg^{−1}) or electro membrane extractions (285 mg kg^{−1} freeze-dried).^{18–20}

In this publication, a bioeconomic approach was envisioned for potato production. The present work presents a screening of different variants and tissues for the highest isolatable steroidal glycoalkaloid content. For this purpose, the extraction method from Bushway *et al.* was used with two different cell disruption techniques, and the results were analysed with respect to purity, SGA, α -solanine and α -chaconine yields, and method of cultivation.¹⁷ As proof of principle, the solvents acetonitrile and tetrahydrofuran were substituted by the greener alternatives dimethyl carbonate and cyclopentyl methyl ether.²¹

Once α -solanine and α -chaconine are successfully isolated, the aglycon solanidine (Fig. 1) is available through hydrolytic cleavage of the sugars or *via* a multi-step synthesis starting from diosgenin (1) as published by Zhang *et al.*, Wang *et al.* and Hou *et al.*^{22–24} A valuable tool for the ecological validation of such processes is the calculation of the *E*-factor, which

describes the waste-to-product ratio of processes. For sustainability purposes, the *E*⁺-factor, which additionally includes the energy consumption of each step and converts the electric energy into carbon dioxide mass equivalents, is relevant.²⁵ As a means of evaluating how sustainable the process of extraction and hydrolysis is, these factors were calculated for the extractions of flowers, leaves, and berries. For comparison, total synthesis was performed according to the procedure of Zhang *et al.* and analysed with regard to the *E*- and *E*⁺-factors.

Results and discussion

Establishment of extraction from potato production side streams

The first goal of this work was the evaluation of potato variants and tissues regarding their isolatable SGA content. Therefore, eight variants from the field and greenhouse were extracted and analysed. Since not all potato cultivars form flowers and berries, there was a limitation in the material available for isolation. Thus, for some cultivars, the SGA levels of the leaves were the only available data.

For the extraction, a modified method from Bushway *et al.* was used.¹⁷ In this approach, the disruption was performed using a blender before the maceration took place in THF, acetonitrile, and glacial acetic acid. After filtration, evaporation and centrifugation, the supernatant was collected, and the SGAs were precipitated with ammonium hydroxide. The precipitated SGAs were centrifuged and the supernatant discarded, while the precipitate was dried through lyophilisation followed by purification.

Since the amounts of flowers and berries (*e.g.*, from Granola) were very small, thus making cell disruption with a blender less effective, the samples were ground with a swing mill before the extraction solvents were added, and the process was continued as before. The SGA content in the samples was



determined by LC/MS analysis. For first insights, the extractable SGAs from the variants and tissues, which were disrupted by both methods, blender and swing mill, were plotted as a bar diagram (Fig. 2). It is obvious that both the variant and the tissue differ significantly in SGA content, ranging from 1.5–12.9 mg per g DW.

Furthermore, this method showed that the extraction of SGAs was improved when using the swing mill, and the swing mill samples displayed a higher purity after lyophilisation even without any purification step ($\sim 58\% \pm 14\%$ purity). In contrast, the disruption employing the blender requires ethanol extraction and chromatographic purification and only led to $\sim 44\% \pm 18\%$ purity (Fig. 3). These data show that the technique used for cell disruption has a major impact on the isolatable SGAs as well as the purity of the samples. The swing mill resulted in time and solvent savings and was therefore the preferable method for this process. The vigorous mixing of the blender can have a detrimental effect on extraction due to the plant tissue matrix.

Factorial analysis

The samples within this study vary in terms of variant (Agria, Granola, Innovator, Laura, Levante, Nixe, Quarta, Record), tissue (berries, flowers, leaves), and the kind of cultivation (greenhouse, field). From a technical point of view, the disruption technique (blender, swing mill) is included. However, not all combinations are available, e.g., Agria provides no berries or flowers. The entire study population is shown in the sparse matrix with respect to these parameters (Table S2). Tubers were omitted in this study, focussing on the side products of the potato harvest.

Hereafter, the evaluation was performed using a factorial analysis to get better insights into the connections between cultivation method, tissue, variant, and disruption technique

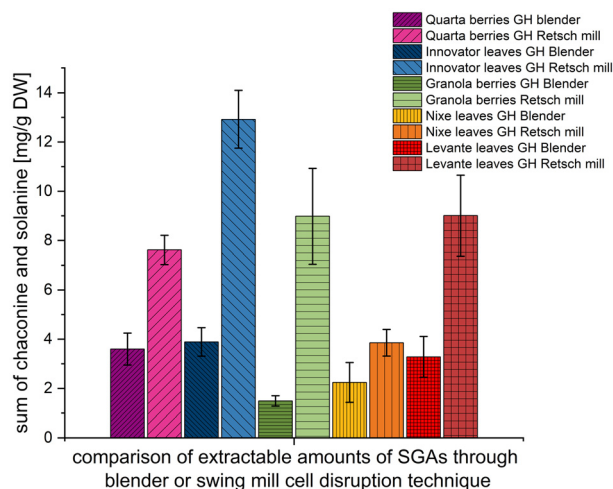


Fig. 2 Comparison of extractable amount of steroidal glycoalkaloids of different potato cultivars and organs, with cell disruption performed by either a blender or a swing mill. Swing mill disruption showed an increase in the obtained mg SGAs per g dry-weight material. All extractions were performed in triplicate from pooled biological samples. All samples were grown in greenhouses, except for Granola, which was a field harvest.

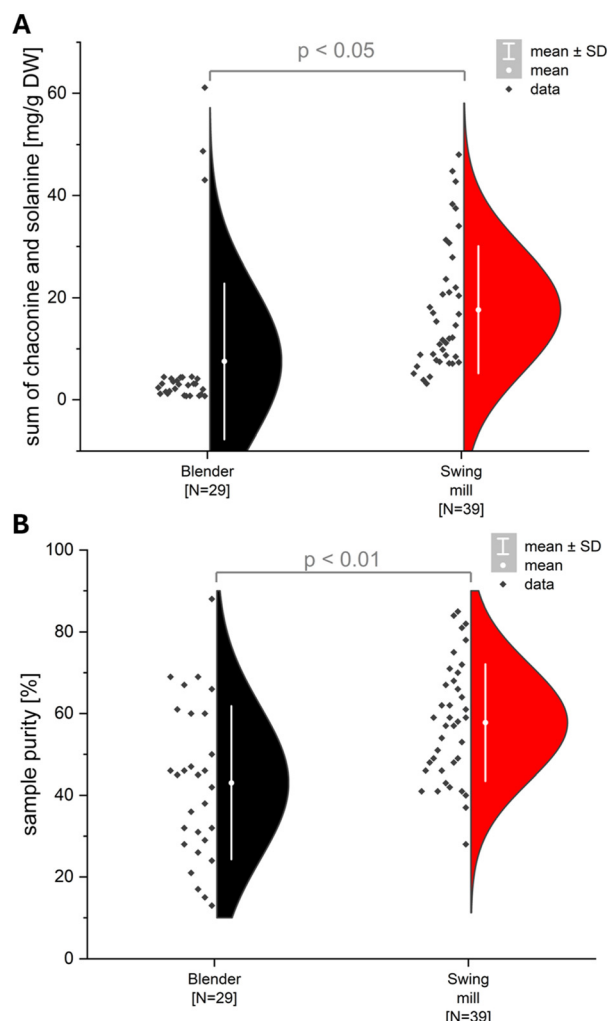


Fig. 3 Total extractable SGA content (A) and sample purity (B) determinations with cell disruption performed by a blender or a swing mill. Significant (t-test, $p < 0.05$) increase of the extractable mg SGAs per g dry-weight material and significant (t-test, $p < 0.01$) increase in sample purity through swing mill disruption. The whole data set includes all organs (flowers, leaves and berries) from different cultivars. Individual samples can be found in Table S1 (number of replicates: blender: $N = 29$ and swing mill: $N = 39$).

with respect to the resulting SGA content, chaconine/solanine ratio and the purity of the samples.

In factorial analysis, the whole dataset is analysed with respect to one parameter only (e.g., the tissue). Variations on other parameters (extraction method, variant, cultivation) are aggregated with respect to this single parameter only. There might be some correlative bias caused, but this method was chosen to obtain initial trends for the limited sample size.

While the analysis of the cultivation method showed it had no impact on the fraction of chaconine, SGA content or sample purity (Fig. S1 and Table S3), the initial results regarding the cell disruption technique (Fig. 3) showed that the purity and the extractable amount of SGAs increased when the technique of cell disruption was changed from blender to swing mill (see above).



Furthermore, the impact of the organ, such as flowers, berries or leaves, was evaluated with respect to amount and purity of SGAs. It is known that the content of SGAs is the highest in flowers; this was validated in this study (Fig. 4A/B blue curve and Table S4). The sum total of chaconine and solanine shows no significant difference in berries and leaves, while the isolatable amount in flowers is significantly higher. The same holds true for the sample purity. One possible explanation could be a bias due to the cell disruption technique. However, three out of nine extractions were performed using a blender instead of a swing mill, ruling out the possibility of a single factor. The content of chlorophyll, which is a major impurity, is low in flowers and high in leaves, with berries showing a medium content.

Only the berry extraction process was hindered by an inability to remove the major fraction of chlorophyll. During the extraction process and the first centrifugation step, which can help to remove the majority of chlorophyll, the berry extracts always exhibited a layer of chlorophyll on top of the supernatant. In contrast, a similar issue was not observed for flowers or leaves, which led to the hypothesis that berry extracts exhibit some different matrix effects, and their separation is more difficult compared to those of other organs. Consequently, there is a minor increase in the mean purity of the leaves visible in the graph.

Finally, the eight variants of this study have been analysed. Six out of eight cultivars show higher chaconine than solanine content; Innovator is the only cultivar producing more solanine (Fig. 5). There seems to be a general preference for one of the two SGAs in the potato plant, given that Laura is the only variant showing an equal distribution of both SGAs. A reason might be the biosynthesis apparatus, namely the glycosyltransferases, differing in the cultivars, but it might be possible that the starting materials, namely UDP-rhamnose or UDP-glucose, have different abundances in every cultivar.

As can be seen in Fig. 5, there is uniform variation of the chaconine fraction over all samples. Thus, the data show that the set of samples does not contain a bias with respect to this parameter. In contrast, looking at the total amount of SGAs (Fig. 6), there is a severe danger of bias. Both Agria and Laura were represented by only three samples. These three samples were leaves and berries only. Other tissues were not sampled and, as was shown, there is a difference in SGA content in different tissues. For the sake of completeness, the data are shown in Fig. 6; however, the results for Agria and Laura are more likely to be due to the tissue rather the variant. Thus, for Fig. 6, all samples were obtained from flowers. The full dataset can be found in Fig. S2 and Table S5.

Without flowers, Granola and Innovator (10.4/11.3 mg per g DW) have the same sum of α -chaconine and α -solanine, Record is slightly higher (15.2 mg per g DW) and Laura has the highest content (25.2 mg per g DW). The German Federal Ministry of Food and Agriculture has published a table of the most planted potato cultivars in Germany.²⁶ In combination with the results of this study, the most favourable variant would be Innovator, which comprises 2.2%²⁶ of the total

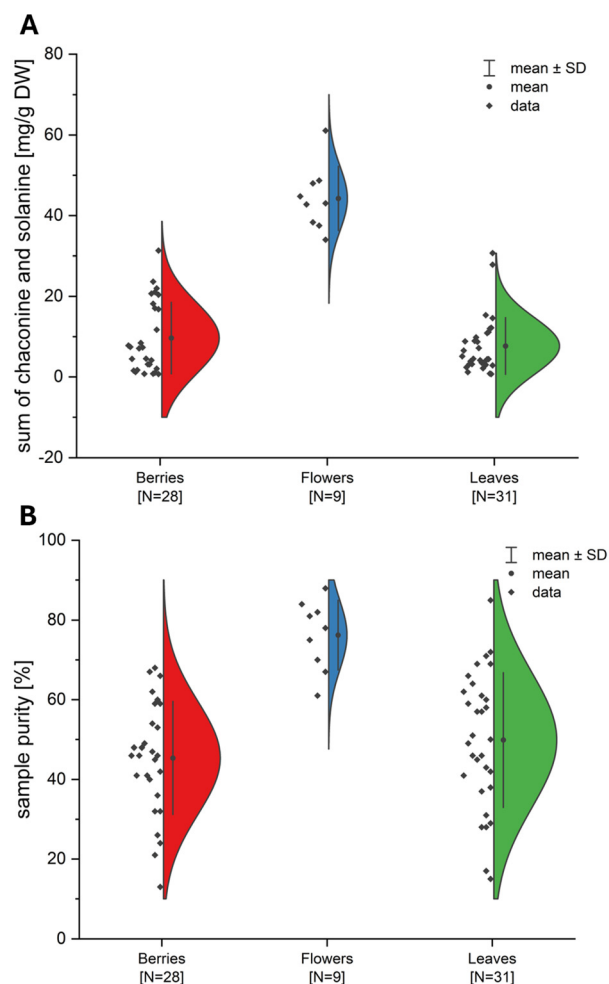


Fig. 4 Factorial analysis of different potato tissues: (A) sum of chaconine and solanine and (B) the purity of the sample. The samples have been aggregated with respect to the tissue; diamonds show the individual sample distribution summarised as Gaussian-curve density in the violin diagram including the mean value (circle) with whiskers being standard deviation of all the samples. The sample sizes are given in the categoric axis with *N*.

potato cultivation on tilled fields in Germany and also has one of the highest extractable amounts of SGAs. As a second option, Laura (1.1%)²⁶ would be useful, while Quarta has only a mediocre SGA content and a fraction of the tilled fields (0.2%).²⁶ Thus, the variant Quarta would not be suitable for an economic production of SGAs.

As mentioned before, the content in flowers is generally greater; however, flowers are not a typical side stream of industrial potato production, because they fade before harvest and their harvest would be manually very laborious.

Determination of the *E*- and *E*⁺-factors for the extraction of potato side-streams

Next, the *E*-factor²⁷ was chosen as a proxy for sustainability analysis. This useful method determines the environmental impact of a process through calculations of how much waste is



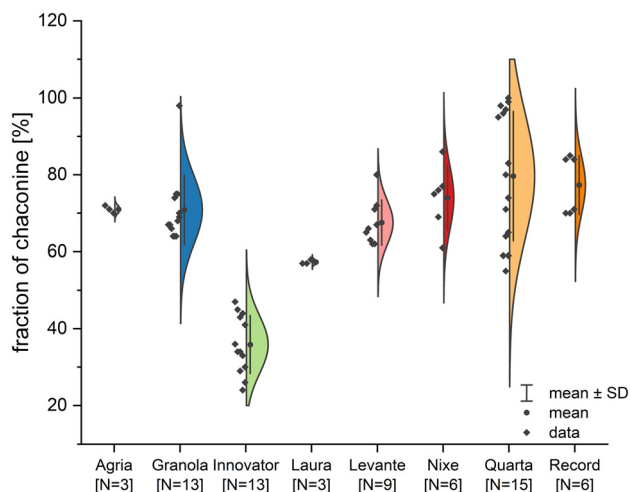


Fig. 5 Factorial analysis of different potato variants with respect to the chaconine fraction within the sum of chaconine and solanine. The samples have been aggregated with respect to the variant; diamonds show the individual sample distribution summarised as Gaussian-curve density in the violin diagram including the mean value (circle) with whiskers being standard deviation of all the samples. The sample sizes are given in the categoric axis with *N*.

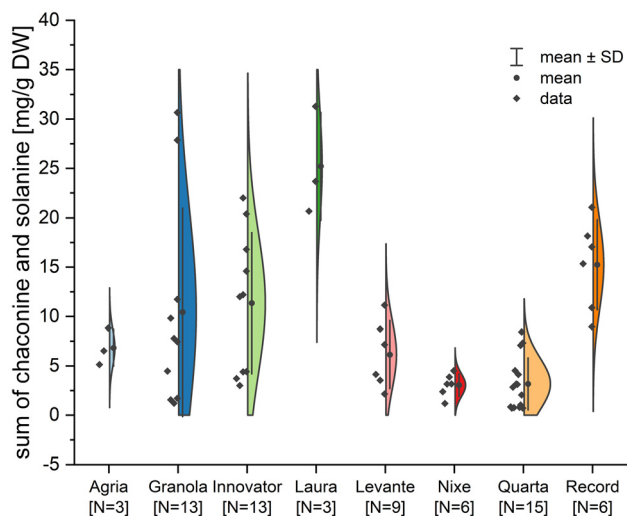


Fig. 6 Factorial analysis of total glycoalkaloid content in each of the analysed cultivars (Agria: *N* = 3, Granola: *N* = 9, Innovator: *N* = 10, Laura: *N* = 3, Levante: *N* = 6, Nixe: *N* = 6, Quarta: *N* = 15 and Record: *N* = 6). The diagrams do not include data from flowers, but from cell disruption by blender and swing mill. Highest contents are extractable in Granola, Innovator, Laura and Record, while the lowest are in Nixe or Quarta.

produced by a process in relation to the obtained product.²⁷ However, this equation does not include the impact that occurs through energy consumption. Therefore, Tieves *et al.* added an energy-term and called it the E^+ -factor.²⁵ The formulas for both the E -factor and E^+ -factor are shown below.

$$E = \frac{\sum m(\text{waste})}{m(\text{product})} (\text{kg kg}^{-1})$$

$$E^+ = \frac{\sum m(\text{waste})}{m(\text{product})} (\text{kg kg}^{-1}) + \frac{W \cdot \text{CI}}{m(\text{product})} (\text{kWh (kg(CO}_2\text{)/kWh)}^{-1} \text{kg}^{-1})$$

W = electrical power, CI = carbon intensity (380 g CO_2 per kWh in Germany).²⁸

In this study, the solvents, silica and filter material were included as waste, which differs from the original description. To avoid confusion, the terms E^* -factor and E^{*+} -factor are used for these data, and, additionally, calculations of the original description were performed. Using these formulas, both factors were calculated for the extraction from tissues (berries and leaves) of the most favourable variant Innovator. Cell disruption was performed with a swing mill (or mortar for fresh leaves). While the E^* -factor was around 3 000–18 000 for all three organs, the E^{*+} -factor was, for most of the extractions, higher than 500 000, with values up to nearly 2 million, which highlights the immense energy consumption used. Since all process steps were measured, the reason for the high value was quickly located. Over 50% of the total consumed energy (47.6/63 kWh for berries and 23.8/39 kWh for leaves) can be attributed to the freeze-drying process. Due to these high values, it was tested whether extraction is possible with fresh plant material. Thus, a normalisation from dry weight to fresh weight was performed to compare the results. A t -test of the extraction results found no significance, which shows that freeze-drying is not necessary (Fig. S3 and Table S6). The new calculation for the E^{*+} -factor without freeze-drying shows a significant decrease (Fig. 7 and Tables S12–15). However, there is an increase in the standard deviation for freeze-dried samples that we cannot explain.

Swing mill cell disruption is limited to the size of its jars, so large scale extractions were performed in a blender to compare the E^* - and E^{*+} -factors for three different protocols:

(1) Extraction of freeze-dried plant material with purification.

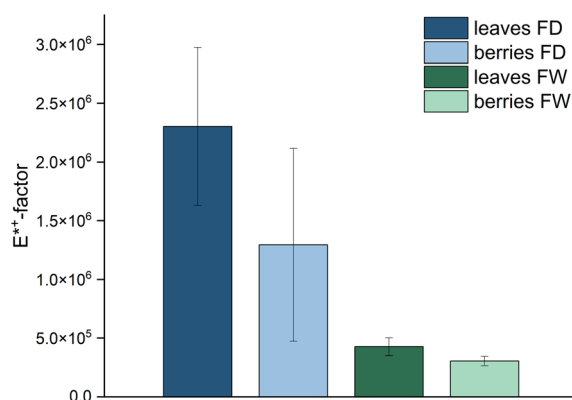


Fig. 7 E^{*+} -Factors for extraction samples from different tissues of Innovator. Fresh samples (FW) are highlighted in shades of green, and freeze dried (FD) samples are highlighted in shades of blue. The samples were measured in triplicate.



(2) Extraction of freeze-dried plant material without purification.

(3) Extraction of fresh plant material without purification.

Fig. 8 shows the differences between the E^* - and E^{*+} -factors for these processes. The amount of waste was higher when purification took place, and the energy consumption increased due to evaporation processes. Furthermore, the process of purification resulted in lower yields. For the second and third processes, the extracted SGA amounts were higher, with no significant differences between fresh and freeze-dried.

Application of green(er) solvents

The extraction process of Bushway *et al.* uses THF and acetonitrile.¹⁷ Neither are recommended for further use because of their environmental impact, waste or life cycle score.²⁹ Thus, substitutions were tested for feasibility. For acetonitrile, the recommended solvent is dimethyl carbonate (DMC), while for THF, the substitution is cyclopentyl methyl ether (CPME). CPME shows favourable properties compared to 2-methyl-THF due to better properties in waste, flammability, and stability.³⁰

The extractions were carried out with fresh Innovator leaves and were tested with three combinations of solvents. First, the acetonitrile was replaced by DMC, while the THF, water, and acetic acid remained the same. Second, the substitution of THF by CPME was tested, and, lastly, the replacement of both THF and acetonitrile (ACN) was performed. Analysis of the extracts with LCMS are shown in Fig. 9.

As shown, in the cases of DMC substitution and the replacement of both solvents, the extraction works in a similar fashion. There is no significance difference (*t*-test, $\alpha = 5\%$) between the replacements and the original extraction of fresh leaves.

With respect to boiling point, heat capacity, and vaporisation energy,³¹ the 'green' solvents seem to have a higher

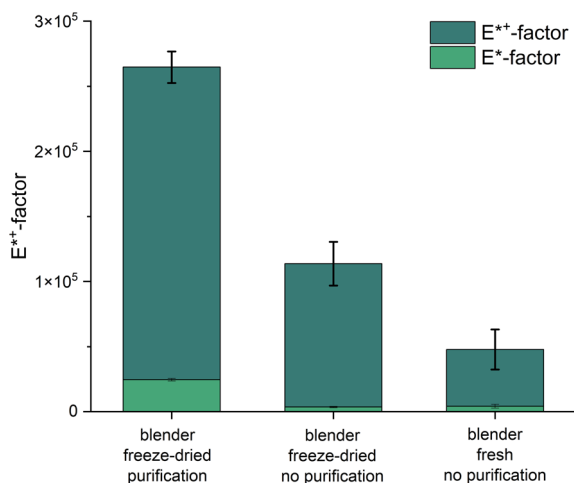


Fig. 8 Comparison of E^* - and E^{*+} -factors for large scale blender extraction with freeze-dried plant material both with and without subsequent purification, and using fresh plant material without purification. The full dataset for the extractions can be found in Tables S16–18.

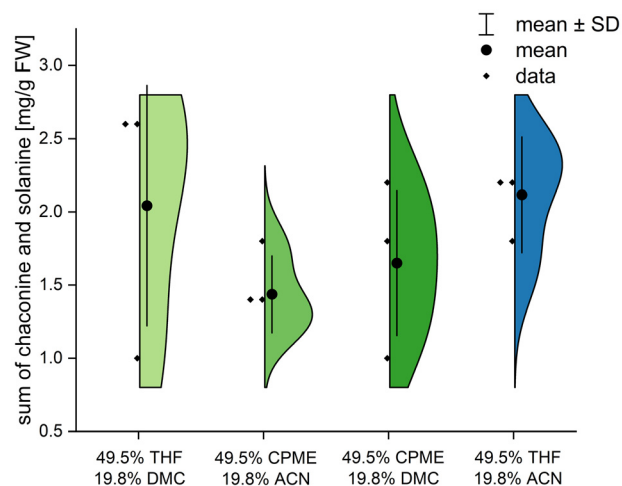


Fig. 9 Violin diagrams for the extraction of fresh Innovator leaves [$N = 3$] with different combinations of solvents. Individual samples are shown as diamonds and the mean values as circles with whiskers in the length of standard deviation. The violins are kernel densities. The foremost right dataset (blue) was the extraction procedure according to Bushway *et al.*¹⁷ in which the extractant contained 29.7% water and 0.01% acetic acid, which remained unchanged. The three left datasets (green) show the extractions in which THF was replaced by CPME and ACN by DMC, individually and simultaneously. The full dataset can be found in Table S7.

energy demand compared to THF and ACN. Thus, the E^{*+} -factors were determined for both the extractions employing THF/DMC and CPME/DMC, which were feasible in terms of natural compound capability. For both extraction mixtures, duplicates of ~76 g of leaves of the Innovator variety were extracted.

This resulted in E^{*+} -factors of $113\,798 \pm 28\,607$ for THF/DMC and $123\,240 \pm 14\,932$ for CPME/DMC, which are indeed higher compared to the values obtained for the standard procedure with THF/ACN ($47\,837 \pm 16\,877$, $N = 3$, $m = \sim 100$ g). This is due to the scaling, namely the limitation to a 76 g sample size. Looking at the energy required for the actual evaporation, it should be noted that those using THF/DMC and CPME/DMC, at 0.42 ± 0.01 kWh and 0.66 ± 0.26 kWh, are comparable to the energy requirement for THF/ACN (0.69 ± 0.11 kWh, $N = 3$). Overall, therefore, the use of 'green' solvents can be considered advantageous.

Determination of E^- and E^{*+} -factors for the total synthesis of solanidine

Since different groups have published the total synthesis of solanidine, we set out to directly compare its extraction from potatoes with the semi-synthetic one.^{22–24} For this purpose, the work of Zhang *et al.* was chosen, which starts from commercially available diosgenin (**1**),²² as the total synthesis of solanidine from Wang *et al.* includes a bulkier protection group (TBDPS).²³ Using the Zhang route,²² an evaluation of every synthetic step was made regarding both chemical and energy consumptions. In the synthetic process, electric energy

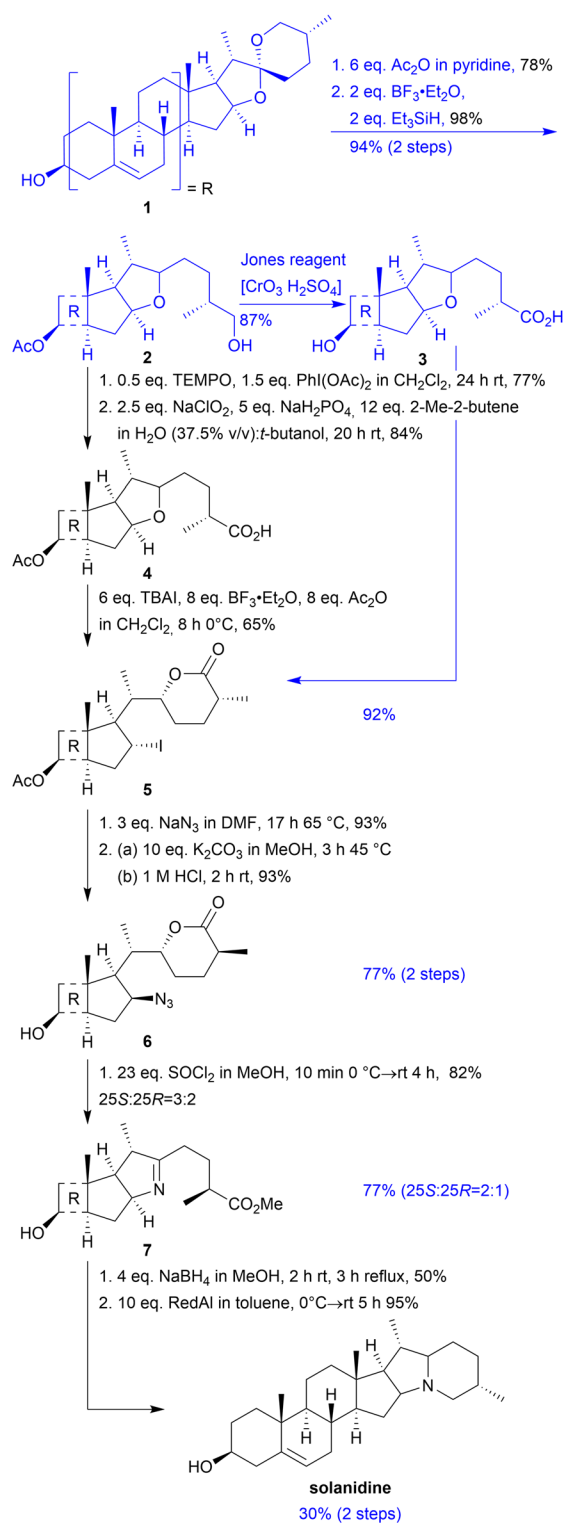
usage was recorded during the reaction and the evaporation process, if technically possible. Otherwise, the electric energy usage was calculated based on the equipments' technical characteristics, as provided from their manufacturers. Additionally, separate values for the reaction and the reaction plus purification were calculated. For a fair comparison, the aim was literature scale or higher. Since data for smaller scale were also evaluated, small and large scales were also compared.

The original publication requires nine steps from diosgenin (1) to solanidine. After the protection of the hydroxy group, a ring-opening reaction took place (2) where it was possible to skip purification, since the raw product had a purity between 85%–90% with a yield of 97%–99%. This saved around 6 kg of waste and energy for evaporation. From this compound on, Zhang *et al.* performed one oxidation step with Jones reagent³² [chromium(vi) oxide and sulphuric acid] to generate the carboxylic acid (3). To avoid this chromium-containing, toxic, and environmentally harmful reagent, the reaction was modified to more benign conditions. First, a TEMPO-mediated (2,2,6,6-tetramethylpiperidinyloxy) oxidation for the generation of the aldehyde was performed and, afterwards, a Pinnick oxidation to get the carboxylic acid (3) (Scheme 1).

While most of the reactions resulted in good yields, the yield of the ring-switching process to generate an iodide (4) after the carboxylic acid is far below the literature reported yield (92%).²² Even after several attempts, the yield was never higher than 65%. Therefore, the yields of two separate synthetic steps had to be combined to reach the required amount for the next step. A purity determination by qNMR was performed for the product of this reaction to ensure an absence of iodide (purity 98%).

However, the follow-up synthesis of the azide resulted in a 93% yield. Epimerisation of the methyl group and deprotection sometimes led to the opened lactone, which was separable by chromatographic purification and was closed again afterwards. While the reaction scale for this step (5) was 500 mg (1.00 mmol), it was 1.35 g (3.00 mmol) for the Schmidt reaction³³ (6). Thus, the yields of three separate batches had to be combined to get at least around 1 g (2.21 mmol) for the next reaction. This reaction step was also the only one which deviated from the literature in terms of a lower scale. After the last two steps of the synthesis of solanidine, all data were combined in one graph to show the increase of the E^{*+} -factor over the course of the synthesis. Additionally, all small-scale data are visualised (Fig. 10).

Both graphs show similar curves for the first seven reaction steps. It is obvious that an increase occurs for (4), which happens because of the lower yield of this reaction and the combination of two synthesis approaches. The small scale reaction has an even higher E^{*+} -factor and comprises 0.96 mmol, while the large scale is 8.69 mmol. This effect is also noticeable for compounds 6 and 10 and solanidine, where the small scale differs even more. The significant increase in the last two reaction steps can be explained by the yield of only 50% for the amide formation within the ring-closure reaction



Scheme 1 Semisynthesis of solanidine starting from diosgenin (1). The route was modified according to Zhang *et al.*²² For comparison, the results of the Zhang publication are shown in blue. TEMPO: 2,2,6,6-tetramethylpiperidinyloxy; TBAI: tetra-*n*-butylammonium iodide; DMF: dimethylformamide; RedAl: sodium bis(2-methoxyethoxy)aluminium hydride.



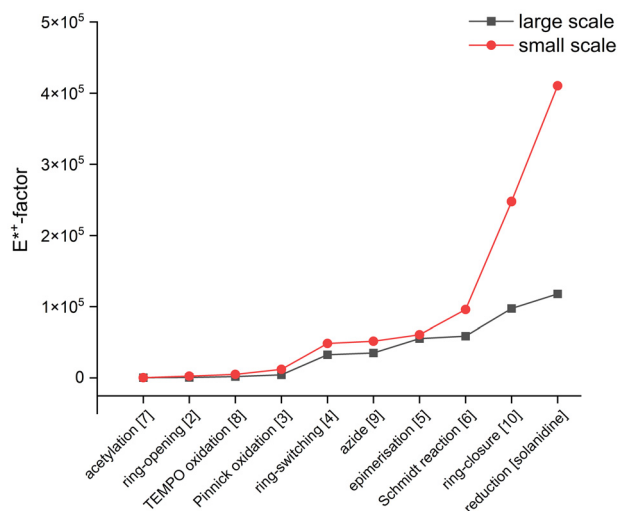


Fig. 10 Accumulated development of the E^* -factor of the sequence of the semisynthesis. Details on experimental conditions and scale can be found in the Experimental section and Tables S8–S10. *E.g.*, for the TEMPO mediated oxidation, small scale used 1 g of the starting material while large scale used 6 g.

and the general small reaction scale for the reduction. Specifically, the reaction yield has the highest impact on the increasing E^* -factor. While for the reduction to solanidine the small and large scale are similar (0.12/0.15 mmol), the yield differs between 0.03 mmol for small scale and 0.14 mmol for large scale, which explains the high difference for the last synthesis step. As shown in Fig. 11, the purification process increased the E^* -factor from 76 028 to 123 706. Without purification, large amounts of solvents, silica and energy would not be used. All this led to an increasing E^* -factor, which is

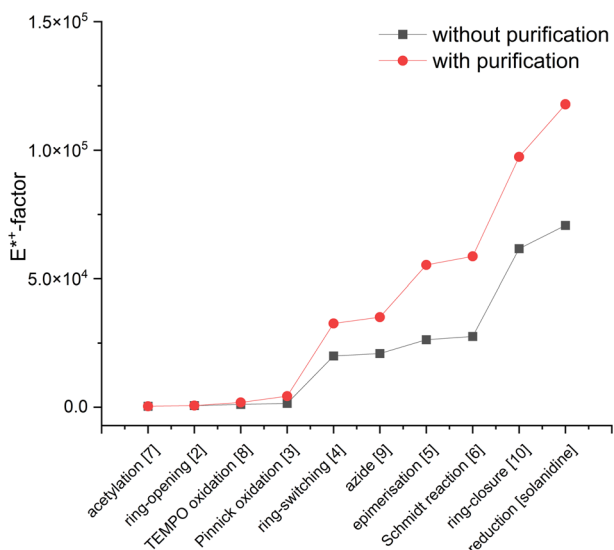


Fig. 11 Accumulated development of the E^* -factor of the sequence of the semisynthesis with and without purification. Details on experimental conditions and scale can be found in the Experimental section and Table S8.

visible in the difference between the red and black curves of Fig. 11. Another high impact is the evaporation process itself. Depending on which rotary evaporator was used, the electric power consumption was higher and, in turn, the mass of carbon dioxide. In general, the purification process increases the E^* -factor by a factor of 1.6.

Finally, after analysis of the entire dataset for extraction and synthesis, a direct comparison was possible (Fig. 12). Since the extraction does not produce solanidine, it is necessary to perform hydrolysis of the SGAs, and this E^* -factor was added on top of the extractions.

The graph shows differences between the accumulated E^+ -factor (without solvents) and E^* -factor (with solvents) for the synthesis and extraction with hydrolysis in three different protocols. In all cases in which no purification was performed (bars 5/6 and 7/8), the effect of exclusion of solvents is low. For the synthesis (bar 1/2), this effect is high, since most of the steps were purified by column chromatography, and this can also be seen for blender extraction with purification (bar 3/4). A significant decrease of the factors between bar 3/4 and 5/6 can be attributed to not performing purification, which not only saves solvent and silica, but also energy due to missing evaporation processes. This analysis also visualises the difference between freeze-dried and fresh samples. The E^* -factor is 123 800 for the extraction of freeze-dried plant material, and it decreases to 57 866 for fresh potato waste.

Obviously, extraction with hydrolysis was an environmentally better option in large-scale compared to synthesis in large-scale, if no freeze-drying was performed (synthesis: 123 706; extraction with hydrolysis: 57 866). Even when calculated with the exclusion of solvents, the extraction was a better option without freeze-drying (synthesis: 76 141; extraction with hydrolysis: 31 335). Since the experiments showed that no freeze-drying was necessary, this method is recommended.

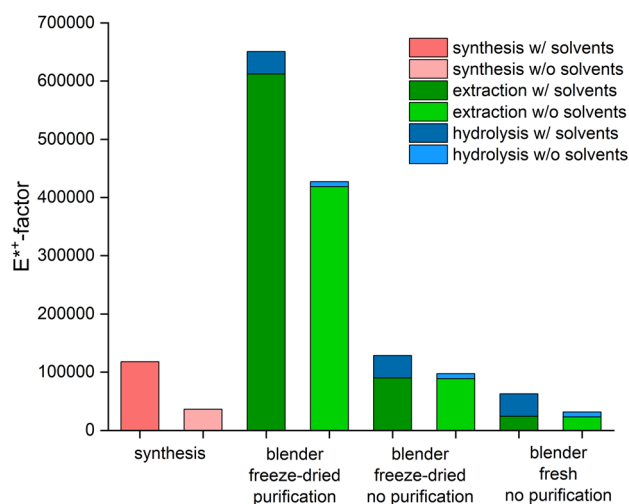


Fig. 12 Accumulated E^* -factors for the optimised synthesis and different extraction protocols along with the hydrolysis of the sugar moiety. The bars in lighter shades do not include solvents and thus are closer to the original definition of E^+ -factor.



Furthermore, it must be considered that the semi synthesis already started with diosgenin (1) extracted from *Dioscoreaceae* (yam), and the *E*-factor burden of this extraction is unknown to us and might be of similar scale as the solanidine extraction from potato. In both cases, the *E*-factor burden from the farm site is not considered. Taking time constraints into account, extraction is faster than the total synthetic approach. Extraction and hydrolysis are performed in 4 days, including analysis and purification, while the total synthesis, even optimised, is estimated to take 20 days.

Experimental section

Potato samples were collected from Moers, Germany (51°25' 08.0"N 6°38'38.0"E) or from the greenhouses of IBG-4 at Forschungszentrum Jülich.

Extraction of steroidal glycoalkaloids α -solanine and α -chaconine

Extractions were performed as described below. All sample purities were determined by LC/MS with calibration curves prepared in triplicates of triplicates from commercially available samples from Sigma-Aldrich (SI).

Blender extraction

Method A: in accordance with Bushway *et al.*,¹⁷ freeze-dried plant material (50 g) was ground with water (300 mL) in a blender for 10 min. For the extraction, 300 mL of THF : acetonitrile : acetic acid (5 : 2 : 0.1) was added and stirred 30 min at rt (room temperature). The mixture was filtered through Celite®, rinsed with 100 mL extraction solvent and evaporated until ~20 mL was left. Then, 2 mL of glacial acetic acid was added, and the extract was ultrasonicated for 2 min and finally centrifuged for 10 min (4 °C, 11 515 rcf). SGAs were precipitated from the supernatant with ammonium hydroxide (~10 mL, pH 10). The mixture was heated for 30 min to 70 °C to complete the precipitation. The mixture was cooled to room temperature and centrifuged again. The precipitate was lyophilised. Dried samples were dissolved in 100 mL ethanol and filtered through Celite® (1st purification) and the filtrate was kept and evaporated. Flash column chromatography on silica gel has been performed with CH₂Cl₂ : MeOH + NH₄OH (75 : 25 + 0.5%; 2nd purification).

Method B: the procedure was similar to method A, except that fresh or freeze-dried plant material was disrupted within a blender without water. The ground plant particles were macerated with extraction solvent (THF : water : acetonitrile : acetic acid; 5 : 3 : 2 : 0.1, 300 mL) and stirred for 30 min at rt. Further processing was the same as in method A but without purification steps.

Swing mill extraction

The freeze-dried or fresh plant material was disrupted with a swing mill (30 s⁻¹, 4 min). An extraction solvent consisting of THF : water : acetonitrile : acetic acid (5 : 3 : 2 : 0.1, 100 mL) was added, then maceration took place for 30 min. The mixture was

filtered through Celite®, rinsed with 50 mL extraction solvent and evaporated until ~5 mL was left. Then, 2 mL glacial acetic acid was added, and the extract was ultrasonicated for 2 min and finally centrifuged for 10 min (4 °C, 11 515 rcf). SGAs were precipitated from the supernatant with ammonium hydroxide (~10 mL, pH 10). The mixture was heated for 30 min to 70 °C to complete the precipitation. The mixture was cooled to room temperature and centrifuged again. The precipitate was lyophilised.

Mortar extraction

Fresh leaves were ground in a mortar for 10 min with 10 mL of extraction solvent (ratio 5 : 3 : 2 : 0.1, solvent systems listed below). Plant particles were extracted with further extraction solvent (total amount 100 mL) for 30 min at rt. The mixture was filtered through Celite®, rinsed with 50 mL extraction solvent and evaporated until ~5 mL was left. Then, 2 mL glacial acetic acid was added and the extract was ultrasonicated for 2 min and finally centrifuged for 10 min (4 °C, 11 515 rcf). SGAs were precipitated from the supernatant with ammonium hydroxide (~10 mL, pH 10). The mixture was heated for 30 min to 70 °C to complete the precipitation. The mixture was cooled to room temperature and centrifuged again. The precipitate was lyophilised.

Solvent systems:

THF : water : acetonitrile : acetic acid

THF : water : dimethyl carbonate : acetic acid

Cyclopentyl methyl ether : water : acetonitrile : acetic acid

Cyclopentyl methyl ether : water : dimethyl carbonate : acetic acid

Hydrolysis of α -solanine and α -chaconine

The steroidal glycoalkaloids (59.2 mg, 0.07 mmol) were mixed with HCl (1 M in ethanol, 6.20 mL) and stirred for 3.5 h at 75 °C. Afterwards, dH₂O (20 mL) was added and the aq. phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (EtOAc : MeOH 80 : 20) to obtain solanidine as a white solid (21.7 mg, 0.05 mmol, 80%).

*E**- and *E**⁺-factor determination

The calculations of *E**- and *E**⁺-factors include all chemicals, solvents, Celite® and silica gel. Energy consumption was determined by an electricity meter during the process. Exact equipment information can be found in Table S11.

Total synthesis of solanidine

All data regarding the synthetic procedure from diosgenin to solanidine are part of the SI. *E**- and *E**⁺-data are listed below the analytical data for each step.

Conclusions

In this study, a detailed analysis of the extraction of steroidal glycoalkaloids from side streams of potato production was per-



formed. Different cell disruption techniques, cultivation methods, organs and cultivars were compared to determine the potato cultivar with the highest SGA content and the extraction method that showed the highest extractable amount per gram of raw material (12.9 mg per g DW). While the cultivation methods showed no differences, the cultivar itself had an impact. The Innovator cultivar had the highest SGA content in general, and cell disruption with a swing mill was the most efficient process for mg g⁻¹ and purity after extraction. Of the organs, flowers were significantly better producers but also constitute a smaller side stream amount when compared to leaves and berries. Additionally, the substitution of acetonitrile (life cycle assessment, volatile, toxic)^{34,35} and THF (life cycle assessment, stability, explosivity)^{30,35,36} was tested with the more sustainable alternatives dimethyl carbonate (sustainable production through CO₂ or CO, >90% biodegradability)^{37–39} and cyclopentyl methyl ether (production with great atom economy from cyclopentene and methanol, low peroxide formation).^{40,41} Both performed in a similar manner and can replace the originally used solvents.

A complete determination of the E -, E^* -, E^+ -, and E^{*+} -factors was performed. The final factor also includes solvents and filter materials. The E factor might be correct for industrial scale, while the extended factor (E^{*+}) more realistically reflects laboratory scale reality. In contrast to other measures (e.g., impact of population growth,⁴² impact of climate change on the marine eco systems⁴³ or the human-induced species losses⁴⁴) the E -factor is rather simple to record. This allowed us to identify critical paths regarding waste savings during extraction and synthesis and then initiate optimisation. Comparatively, the total synthesis is apparently environmentally more benign, if the plant parts are freeze-dried beforehand. For extractions from fresh material, the environmental impact is lower and even under the original description of the E^+ -factor completely ignoring the solvents, extraction with hydrolysis led to a lower E^+ -factor and would be the recommended method. No final statement can be given for extractions in which the cell disruption was performed with a swing mill. Because of the limitation of jar size, no large-scale extraction is possible and no proper comparison for this method could be performed. The envisioned bioeconomic approach showed that potato side streams can be used for valorisation purposes without affecting the food stream. The added value of such natural substances could lie in their utilisation as active ingredients.

There have been endeavours to utilise potato natural compounds, especially from potato peels, as they are the most abundant waste stream in the potato agroindustry. Such endeavours have been summarised recently in Vescovo *et al.*⁴⁵ Two points are noteworthy here. Firstly, the polyphenols and their extraction are very much in the foreground, which is due to the localisation of glycoalkaloids in other parts of the plant. For breeding reasons, the peel contains only a low alkaloid content. The median value for 18 varieties was only 1.5 mg per g DW (0.3–3.6 mg per g DW).^{46–49} Comparing this with the data collected here, significantly higher values are found in

the other organs (median 7.4 mg per g DW, 0.7–61.1 mg per g DW, $N = 68$). It is also striking that the extraction methods are mostly limited to determining the total glycoalkaloid content and that preparative methods are hardly ever used.

It stands to reason that potato by-products offer solanidines, which protect potatoes from predators, and that this ability could also be exploited in the form of a herbicide for other crops, as some nature-based herbicides have already shown.^{50,51} It is often the case that it is not the original natural substances that are used as active ingredients, but derivatives with improved storage stability, reduced metabolism or even an altered spectrum of activity.^{52–54} This work includes the hydrolysis of the sugar groups, which then provide the aglycone with a hydroxyl group, which can be a very good docking point for derivatisation. The obtained semi-synthetic derivatives need to be tested regarding their biological activity.

Author contributions

Investigation: N. S., methodology: B. H., writing original draft: N. S., and review & editing: N. S., B. H., J. P., T. C.

Conflicts of interest

There are no conflicts to declare.

Data availability

Raw data and spectral information are available at <https://doi.org/10.26165/JUELICH-DATA/QTS90W>.

Supplementary information (SI): detailed experimental and analytical information. See DOI: <https://doi.org/10.1039/d5gc03072b>.

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