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A benign process for the recovery of solanesol from tomato leaf waste

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Abstract

Solanesol, the precursor for the synthesis of coenzyme Q10, is currently recovered from tobacco leaves by conventional extraction techniques that require multiple purification steps and a large amount of organic solvents. We recently identified tomato leaves as an alternative source of solanesol and hypothesized that a high-pressure CO₂ extraction could be used as a clean extraction process. The effect of CO₂ pressure and temperature on the extraction of solanesol was determined to achieve high yield and purity. It was found that solanesol could be extracted efficiently by subcritical CO₂ at 25 °C from tomato leaves. The extract contained 40% solanesol and other active compounds such as vitamin K1. A higher level of purity of 93% was achieved using a secondary purification step. Different conventional methods for solanesol extraction was compared to determine the most efficient technique for production of solanesol from tomato leaf. The highest yield of solanesol was achieved at nearly 1% dry weight with using subcritical CO₂, which was superior to conventional methods.

Keywords: Food science, Agriculture, Chemical engineering, Food analysis

1. Introduction

Solaneseol is a polyisoprenoid alcohol found in the lamina and stems of some plant species, particularly the *Solanaceae* family [1, 2]. The biosynthetic pathway for solanesol is via the 2-C-methyl-derythritol4-phosphate (MEP) pathway in plant plastids [3]. Solanesol is a bioactive compound and a precursor used for the synthesis of high-value compounds including vitamins K analogs and coenzyme Q10 [4, 5, 6]. Both vitamin K and coenzyme Q10 consist of quinone rings joined to an isoprenoid tail. As a long-chain terpene alcohol incorporating nine isoprene units, *de novo* chemical synthesis of this compound is challenging and poorly cost effective. Thus in commercial scale, solanesol are currently extracted from tobacco leaves [5]. In recent years, demand for high-purity solanesol has grown from 4,000 tonnes in the early 2000s, to an estimated international demand exceeding 66,000 tonnes by 2022 [7]. High-purity solanesol is the main intermediate for the pharmaceutical manufacturing of coenzyme Q10 and vitamin K2. In addition, high purity solanesol is used clinically to treat heart failure and cancer [2].

Solaneseol is a valuable secondary metabolite and is abundant in the lamina and stems of solanaceous crops, including potatoes, tomatoes, eggplants, and peppers [8]. The content of solanesol varies from 0.3 to 3 % dry weight, and it depends on plant variety, duration of growth, and method of postharvest treatment [9].

Historically, solanesol has been extracted from tobacco leaf using solvent-based methods including heat reflux and Soxhlet extraction [10, 11]. These methods produce relatively large volumes of waste, which can be costly to dispose of and represent an environment hazard. Heating can also result in thermal decomposition of some bioactive compounds in the leaf. Microwave assisted extraction (MAE) and ultrasound assisted extraction (UAE) [6], as well high-speed counter-current chromatography (HSCCC) are alternative techniques for solanesol purification, however all still involve organic solvents [12].

Supercritical fluid extraction (SFE) utilizes a solvent such as carbon dioxide at a temperature and pressure above its critical point where distinct liquid and gaseous phases do not exist [13, 14, 15]. SFE is a rapid process, selective, and minimizes the risk of degradation of thermally labile or easily oxidized compounds [16, 17]. In particular, high-pressure supercritical CO₂ is efficient and commonly used for the extraction of high value compounds from natural products due to its moderate critical temperature (31 °C) and pressure (73.8 bar) [17]. The solvation power of supercritical CO₂ can be influenced by modulating pressure and temperature [18]. Moreover, CO₂ is gaseous at room temperature and thus can be easily removed from purified compounds [19].

Alternatively, subcritical fluid extraction (SCFE) has been used for the extraction of non-polar compounds such as essential oils [20, 21]. Subcritical CO₂ has lower

solvation power, but can be extremely efficient in extracting temperature-sensitive non-polar compounds [22, 23]. While high-pressure supercritical CO₂ has been suggested as a promising technique for extracting solanesol from tobacco leaves [24, 25, 26], subcritical liquid CO₂ may be a practical alternative. High pressure CO₂ extraction is an alternative method to traditional extraction process using organic solvents, and it is well known as an effective technique (environmentally-friendly) for the extraction of lipids. This process is typically carried out at room temperature and in the absence of air, which reduces energy expenditure, and avoids thermal and oxidative damage of active compounds, meeting all legal safety requirements.

In the context of tobacco, the co-extraction of nicotine with solanesol led to potential health concerns [24]. It was speculated that this would not be a concern for tomato leaf waste and that the purification conditions could be further optimised. Tomato is a highly consumed crop with an annual production of 106 million tons [27]. The glasshouse tomato industry produces large amounts of vegetative waste streams such as leaves and stems; these are regularly removed from the vines to improve the fruit development [28] and end up primarily as landfill. This vegetative waste is a potential source of inexpensive, renewable and abundant bioactive compounds, in particular solanesol [29].

In this paper, we describe optimisation of the subcritical CO₂ extraction of solanesol from tomato leaf waste. The goals were to decrease the operating temperature, reduce or eliminate the use of organic solvents, reduce the number of steps and enhance yield compared to prior approaches. Such an environmentally friendly method would be beneficial for the food industry to improve the sustainability of the food chain. Prior to extraction by high pressure CO₂, we screened a variety of tomato leaves and tested conventional methods for extraction to compare the results. Ultimately however, such a technology will need to be analysed in terms of process engineering and economic modelling to determine whether the operational effort and the high investment costs are justified.

2. Experimental

2.1. Materials

Eight varieties of tomato leaf waste were provided by Perfection Fresh Pty Ltd from South Australia. Acetonitrile (HPLC grade), isopropanol (HPLC grade), ethyl acetate and hexane were purchased from Merck (Australia). Food grade carbon dioxide (CO₂) with a purity of >99% was supplied from BOC company (Australia). Solanesol standard ≥90% HPLC grade, potassium hydroxide, and magnesium sulfate were purchased from Sigma-Aldrich Australia.

2.2. Preparation of tomato leaf powder

Tomato leaf waste was dried in a dehydration oven (Thermocline Australia) at 65 °C for 4 h. The dried leaves were ground with an IKA[®] A11 Basic Lab-Tek grinder to a particle size less than 1 mm. The ground powder was stored at 4 °C in an airtight amber glass jar to avoid exposure to light and humidity prior to further characterization and application.

2.3. Alternate methods for recovering solanesol from tomato leaf powder

2.3.1. Maceration

A maceration extraction process was developed and optimised for the recovery of solanesol, dried tomato leaf (Kumato variety) powder (10 g) was macerated in hexane (100 mL) at room temperature (23–25 °C) for 4 h. The mixture was filtered through a filter paper (Whatman qualitative filter paper, Grade 1), the extract was concentrated with a rotary evaporator (IKA RV10 Basic) at 60 °C.

2.3.2. Soxhlet extraction

Dried tomato leaf (Kumato variety) powder (10 g) was placed in a 250 mL soxhlet system and fitted with 250 mL round bottom flask containing 100 mL hexane and refluxed at 60 °C for 2 h [4]. The extract was concentrated with a rotary evaporator (IKA RV10 Basic) at 60 °C.

2.3.3. Ultrasound-assisted extraction (UAE)

Dried tomato leaf (Kumato variety) powder (3 g) was placed in a falcon tube and fitted with 50 mL hexane at 25 °C and sonicated (Ultrasonic Cleaner Elma TIH500MF2) for 1 h. The extract centrifuged (Falcon 6/300) for 10 min with 5000 RPM. The extract was concentrated with a rotary evaporator (IKA RV10 Basic) at 60 °C.

2.3.4. High pressurized solvent extraction (HPSE)

The solanesol was extracted by a HSE method with a BÜCHI speed extractor (E-916/914). The extraction cells were prepared by inserting cellulose filter and metal frit at the bottom of each 10 ml stainless steel cell to prevent entering particles to the solvent lines and collection vials. A total of 3 g of tomato leaf (eg Kumato variety) powder was mixed with 5 g of dispersing (sand) before loading to the extraction cells. The void volume of the cell was filled with sand and the solvent injection needle protected using a circular cellulose filter. The extraction condition was 100 bar,

100 °C, 1 h and n-hexane (95%) as extraction solvent. The extract was concentrated with a rotary evaporator (BÜCHI Multivapor P-6) at 60 °C.

2.3.5. Saponification of solanesol-containing residue

Solanesol in the leaves can be released by saponification [30]. Adhesive residues from prior extraction methods was saponified with 100 mL (0.2% w/v) ethanolic (purity 95%) potassium hydroxide solution with heat reflux for 2 h at 60 °C [30]. This extract was washed with water, after which magnesium sulfate was added and the solution concentrated with a rotary evaporator. The final product was achieved by solubilizing the resultant solution with acetonitrile and filtering through a 0.22 µm HPLC nylon syringe filter.

2.3.6. High-pressure CO₂ extraction

The experiments were carried out using the high-pressure system schematically shown in Fig. 1. The setup consists of an ISCO 500D syringe pump; a custom made high-pressure extraction vessel, a water bath, and a sample collection vial. The temperature was controlled by a Thermoline (TU1 Unistat) heater/circulator. In each experiment, three grams of dry leaf powder was mixed with glass beads to increase the surface area and improve mass transfer. This mixture was loaded into the extraction vessel (Jerguson Flat Glass Gage Series RL-10). To avoid blockage of the sample in the pipe lines, glass wool was placed at the top and bottom of the vessel. The temperature was adjusted, and the system was left for 30–40 min to reach thermal equilibrium. During this period the syringe pump was filled with liquid CO₂ by circulating cold water around the pump head and condensing CO₂ in the extraction vessel was then purged with CO₂ to remove the air and the system was pressurized to a predetermined pressure for extraction. The system was then isolated for a certain period of time (soaking the sample in liquid CO₂ for 0.5–1 h).

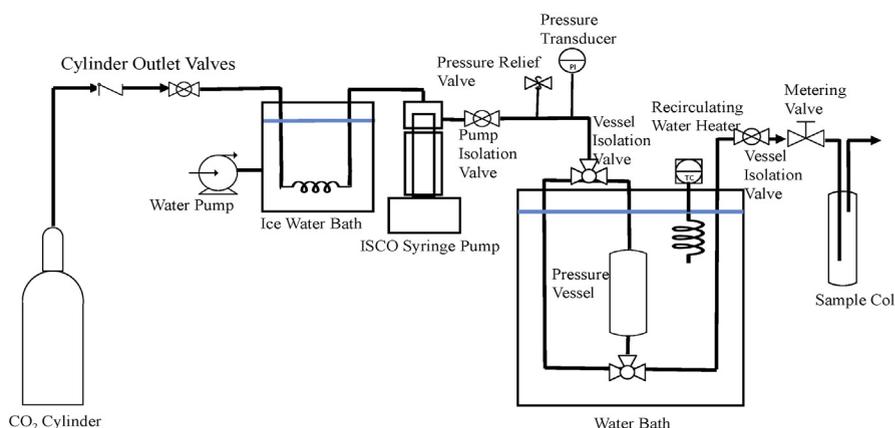


Fig. 1. Schematic diagram of the apparatus for the extraction of phylloquinone using high pressure CO₂.

After this period the sample was collected at constant temperature and pressure by connecting the extraction vessel to the pump at run at constant pressure mode and gradually opening the metering valve to control the flow rate at 1 mL/min and pressure of the system to ensure collecting the sample at equilibrium. In each batch commonly three gram of dry tomato leaf and 120 gram CO₂ were used. The optimum extraction condition was 180 bar, 25 °C, 2 h dynamic at 1 mL/min flow rate. After collecting the extract, the system was depressurized and the sample was analyzed by HPLC.

2.4. Solid phase purification of solanesol

The solanesol was purified by Solid phase extraction method (Restek™ Normal Phase Cartridges). Hexane was used to prepare the column as equilibration solvent. The extract (23–40% purity) was diluted with hexane (1:10 v/v) and was loaded on the equilibrated silica bed. Further, the washing step was conducted by hexane, and after that, the elution was optimised by using 0.5–1 % (v/v) ethyl acetate concentration in hexane [31].

2.5. HPLC analysis of solanesol purity

High-performance liquid chromatography (HPLC) is a useful and robust technique for the isolation of natural products [32]. HPLC is the main choice for fingerprinting for the quality control of natural products [33]. Solanesol was analyzed and quantified using a HPLC instrument (Agilent Technologies 1200 Series) equipped with a vacuum degasser, quaternary pump, standard autosampler and variable wavelength detector (VWD).

A Luna C₁₈ (2) (250 × 4.6 mm, 5 μm) reversed phase column was used. Analysis was conducted under isocratic conditions using an injection volume of 20 μL, and a flow rate of 0.7 mL/min. The mobile phase was acetonitrile: isopropanol (80:20). All chromatographic operations were carried out at room temperature (25 °C), detection was performed at a wavelength of 210 nm. Solanesol stock solutions prepared by dissolving 10 mg solanesol standard in 10 mL acetonitrile and the standard working solutions at the concentration of the calibration range (0.01–2 mg/mL), prepared by serial dilutions of stock solutions with acetonitrile.

The effective concentration range for testing was examined using 8 standard solutions with concentrations ranging between (0.01 and 2 mg/mL). Regression analysis confirmed a linear relationship within this concentration range with a high correlation coefficient ($y = 8 \times 10^{-5}x = 0.771$; $R^2 = 0.9998$). The assay's accuracy and precision were assessed by 6 repeated injections of standard solutions at different days. The relative standard deviation (RSD) values for peak area was 1.2%, and it showed an acceptable repeatability of the method. The Limit of Quantification (LOQ) and Limit of Detection (LOD) values were 0.1 and 0.03 mg/mL, respectively.

2.6. Statistical analysis

All values were expressed as the mean \pm standard deviation (SD) of triplicate experiments. One-way analysis of variance (ANOVA) and *post hoc* multiple comparison testing (Tukey HSD) was used to determine the significant differences ($p < 0.05$) between the means values for solanesol content.

3. Results and discussion

3.1. Solanesol refinement using maceration

The amount of solanesol content in the tomato leaves is gradually increased until the leaf maturation and it also depends on the variety and conditions that plants grow [34]. The result of our preliminary studies and previous studies showed that the amount of solanesol in the leaves was nearly 6-fold higher than other parts of the plant [35, 36]. Therefore, in this study we assessed the effects of extraction period and solid to solvent ratio on the recovery of solanesol from tomato leaves. We also observed that the amount of solanesol in Kumato tomato leaves was significantly higher than other variety. Therefore, these leaves were used for the rest of experiments. Tomato leaves were macerated at 25 °C using 100 mL hexane, then solanesol was extracted by saponification and the concentration was measured by HPLC analysis.

The results in Fig. 2 demonstrate that the amount of solanesol recovered from leaf was increased from 0.7 wt% (dry weight of inserted tomato leaves) to 0.9 wt% by increasing the processing time from 2 hours to 4 hours. Increasing the processing time further did not increase the yield and in fact, decrease the yield to 0.65 wt% ($p < 0.001$). Similar results were observed in previous studies in which the amount of solanesol extracted was decreased by extending maceration period more than 4 hours [4, 5, 37]. This effect might be due to degradation or complexation of solanesol in the solution.

3.2. The effect of solid to solvent ratio on solanesol content

To examine the effect of solid to solvent ratio on the yield of solanesol a series of extractions were conducted at 25 °C for a period of 4 hours using hexane as a solvent. As shown in Fig. 3 by increasing the solid to solvent ratio from 1:5 g mL⁻¹ to 1:20 g mL⁻¹ the yield of solanesol was significantly increased from 0.4 wt% to 1.7 wt%. These data demonstrate that at a lower amount of solvent the solution approached an equilibrium and more solanesol could not be dissolved in hexane. Increasing the amount of solvent to 20 mL per gram tomato leaves resulted in shifting the solution from equilibrium and dissolving more solanesol in hexane at 25 °C.

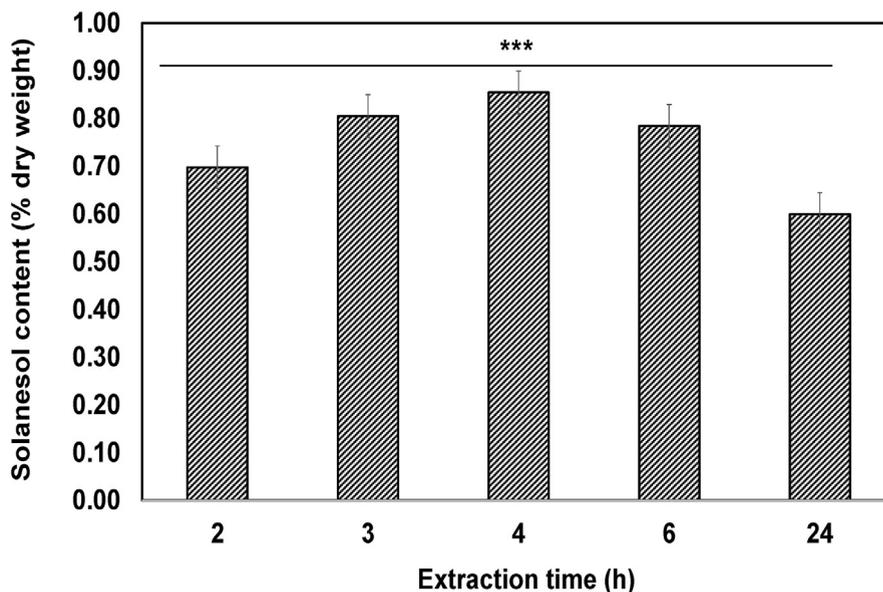


Fig. 2. Mean solanesol content (% dry weight) using different extraction time ($n = 3$) ($p < 0.001$) (***)
Maceration (25 °C, 4 h).

3.3. Recovery of solanesol with different extraction techniques

Different extraction methods, such as Soxhlet, UAE (Ultrasound assisted extraction), maceration, HPSE (High pressurized solvent extraction), and high-pressure CO₂ extraction were compared for the recovery of solanesol from tomato leaf.

The results in Table 1 demonstrate a significance effect of process on the recovery of solanesol from tomato leaves. The yield for recovery of solanesol from tomato leaves was higher when using high-pressure CO₂ extraction (180 bar, 25 °C, 2 h) ($p < 0.001$).

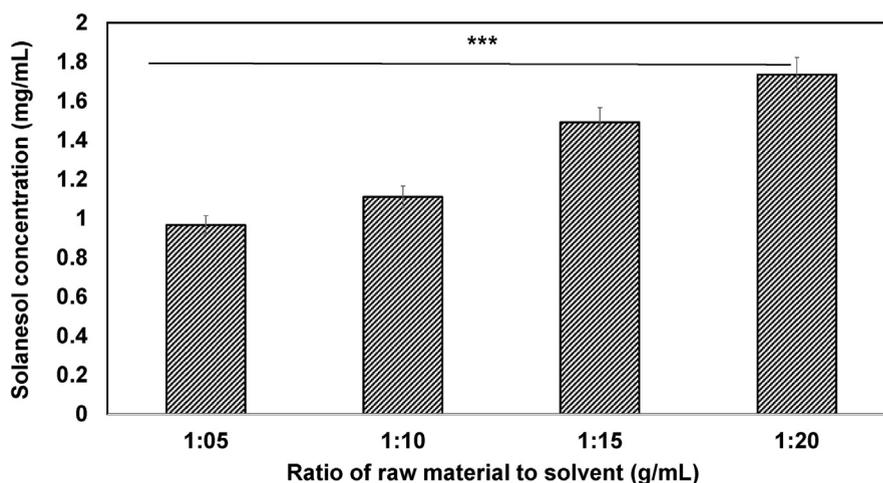


Fig. 3. The effects of solid to liquid ratio on solanesol content (% dry weight) ($n = 3$) ($p < 0.001$) (***)
Maceration (25 °C, 4 h).

Table 1. Comparison of different extraction processes for the recovery of solanesol.

Extraction method	Optimum condition	Solanesol content (% dry weight)	Purity (%)
Maceration ^a	4h, 25 °C	0.86 ± 0.01	34.01
Ultrasound- assisted extraction ^a	1h, 25 °C	0.18 ± 0.01	31.11
Soxhlet ^a	2h, 60 °C	0.78 ± 0.02	27.66
High pressurized solvent extraction ^a	1h, 100 °C, 100 bar	0.97 ± 0.02	23.44
High pressure CO ₂ extraction	3 h, 25 °C, 180 bar	1.00 ± 0.07	40.05

^aHexane was used as a solvent, saponification was conducted for 2 hours at 60 °C using 100 mL (0.2% w/v) ethanolic potassium hydroxide solution with heat reflux [30].

This process is rapid, eliminate the consumption of organic solvent and operate at lower temperatures compared with other methods attempted. In addition, the degree of purity of solanesol extracted by CO₂ was 40%, which was at least 15% higher than other techniques used such as soxhlet and high pressure solvent extraction.

3.4. Optimising the duration of subcritical high-pressure CO₂ solanesol extraction

In this study, we used an iterative approach where individual variables were sequentially optimised rather than a factorial approach. This was primarily due to the practicalities of running multiple extraction experiments for direct comparison. Ultimately however, this iterative approach yielded a highly efficient process with high yield.

The effect of temperature, pressure, and time on the recovery of solanesol from tomato leaves were determined. The process was conducted in two steps: (1) a static extraction mode, which involved soaking the sample in high-pressure liquid CO₂ for the desired period of time from 0.5 to 24 h; and (2) a dynamic mode to pass high-pressure liquid CO₂ through the vessel to leach out the compound of interest out of the system at constant pressure from 80 or 180 bar at three different temperatures (10, 25, and 50 °C).

The results in Fig. 4 demonstrate that one hour static mode is sufficient to achieve a good yield for recovering solanesol from tomato leaves. In fact, further increases of static mode from 2 hours to 24 hours gradually decreased the yield from 0.8 wt% to 0.7 wt% ($p < 0.05$). However, periods shorter than one hour were not sufficient to achieve equilibrium in this system and the yield was decreased to nearly 0.5 wt% ($p < 0.05$). Therefore, the optimum processing conditions was 1 h static followed by 2 h dynamic mode. The decrease in the content of solanesol after 24 h might be solanesol decomposition due to the longer time of extraction. According to Fick's second law of diffusion, after a certain time the final equilibrium will be between the

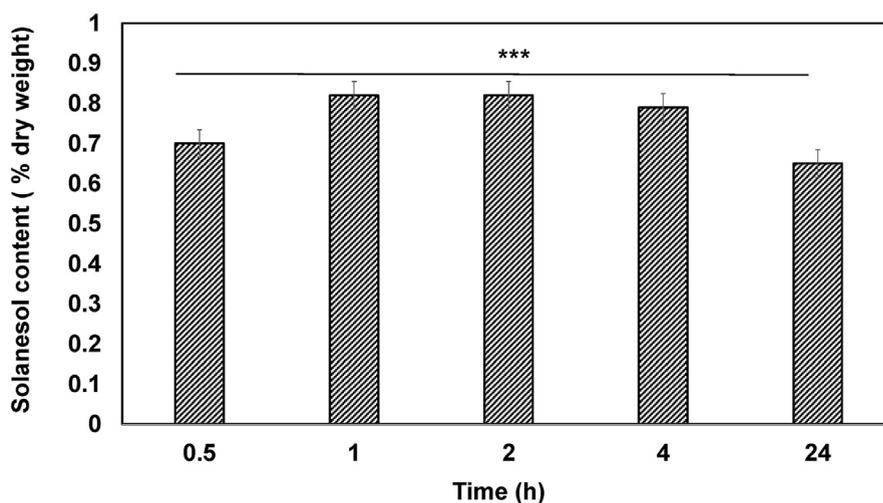


Fig. 4. Effect of static extraction time on solanesol yield (180 bar, 25 °C, 2 h dynamic). Error bars indicate standard error (n = 3) ($p < 0.001$) (***)

solute in the plant sample (solid matrix) and in the bulk solution (extraction solvent) [38].

3.5. Optimising pressure and temperature for subcritical CO₂ solanesol extraction

Huang et al. used supercritical CO₂ modified with ethanol for the extraction of solanesol from tobacco leaves at 45 °C, 380 bar and 2.6 hours [24, 25]. Their method included an additional saponification step where ground tobacco leaves were saponified with 10% ethanolic potassium hydroxide overnight at room temperature. They reported 0.96 wt % solanesol recovery with 52.3 % purity. Wang et al. applied supercritical CO₂ for solanesol extraction from tobacco leaf waste [26]. A pretreatment with a solvent of n-hexane:95% ethanol was used and the extraction condition was 3000 bar (300 MPa) at 40 °C. At these conditions the solanesol yield from tobacco leaf was 0.44%. Zhou et al. also used supercritical carbon dioxide at 20 MPa, and 45 °C to extract solanesol from potato leaves using 95% ethanol as a co-solvent [39]. The solanesol purity in the extract was 93.4% [39].

In this study, we employed subcritical CO₂ at moderate temperatures and pressures for the extraction of solanesol from tomato leaves. The effect of pressure and temperature on solanesol extraction from tomato leaves (Kumato variety) was studied at multiple pressures (80, 120, 150, 180 bar) and temperatures (10 °C, 25 °C, 50 °C) using 1 hour static and 2 hours dynamic mode at 1 mL/min CO₂ flow rate.

As demonstrated in Fig. 5, at both temperatures of 10 and 25 °C the pressure had a positive impact on the extraction efficiency of solanesol ($p < 0.001$). By increasing

the operating pressure from 80 bar to 180 bar the yield for solanesol extraction was increased from 0.7 to 1.01 wt% ($p < 0.001$) at 25 °C. This effect was attributed to enhancing the solvation power of CO₂ at higher pressures due to increasing the density. Furthermore, the results in Fig. 6 demonstrate that at 180 bar by increasing the temperature from 10 °C to 50 °C the yield for recovery of solanesol from tomato leaves was reduced from 0.94 to 0.73 wt% ($p < 0.001$).

The effect of temperature on yield was governed by two factors: CO₂ solvation power (that is directly associated with density) and the vapor pressure of extracted compound. The CO₂ density decreases by increasing the temperature, hence the solvation power drops, while the vapor pressure of a compound increases by elevating the temperature. The slight enhancement of yield from 10 °C to 25 °C can be attributed to having vapor pressure as a dominant factor for recovery of solanesol, while the significant drop in yield by increasing the temperature to 50 °C can be attributed to impact of lowering the CO₂ density, hence its solvation power ($p < 0.001$). The highest yield of solanesol was achieved at nearly 1 wt% with solanesol purity of 40 % when using subcritical CO₂ at 25 °C, 180 bar for 1 hr static and 2 hours dynamic (using total 120 g CO₂). It is important to note that at this operating conditions, vitamin K1 was also co-extracted with the concentration of $29.17 \pm 0.96 \mu\text{g g}^{-1}$ from tomato leaf. The combination of these two extracts can, therefore, be used as nutraceuticals with various health benefits [40].

3.6. Secondary purification of solanesol extract using solid phase chromatography

The resultant extract contained 30–40 % solanesol was further purified by normal phase chromatography [41]. The column was eluted using hexane and two different

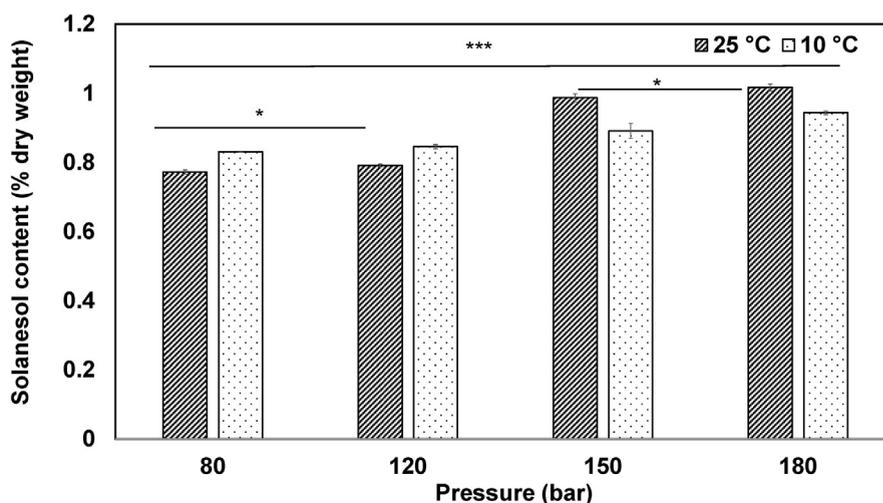


Fig. 5. Effect of pressure on solanesol content at 25 °C and 10 °C. Error bars indicate standard error ($n = 3$) ($p < 0.001$) (***) ($p < 0.05$) (*) (180 bar, 2 h dynamic).

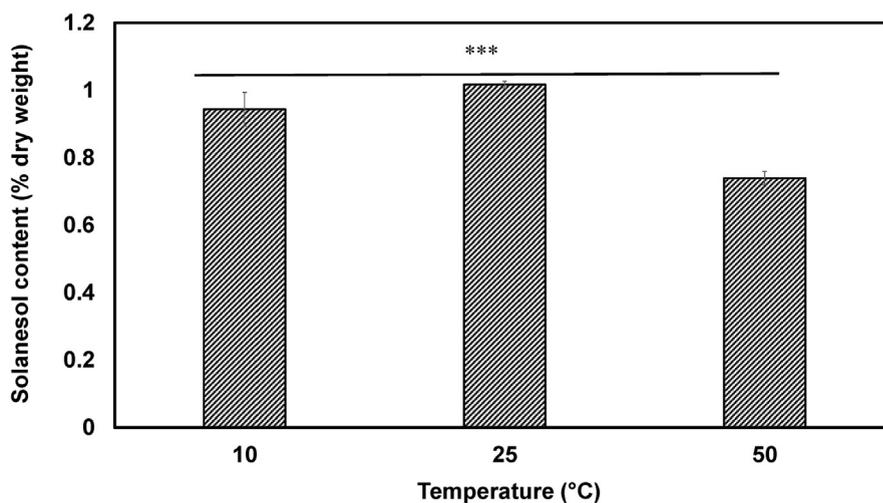


Fig. 6. Effect of temperature on the solanesol content. Error bars indicate standard error ($n = 3$) ($p < 0.001$) (***) (180 bar, 2 h dynamic).

concentrations of ethyl acetate (0.5–1 % v/v). The results of HPLC analysis in Fig. 7 indicated that a maximum purity of 93 % was achievable at 0.5 % (v/v) concentration of ethyl acetate in hexane. It is important to note that this level purity was achieved in only two steps that is more convenient than previous studies that involved multiple steps such as saponification, crystallization and chromatography followed by another step of recrystallization [31, 41].

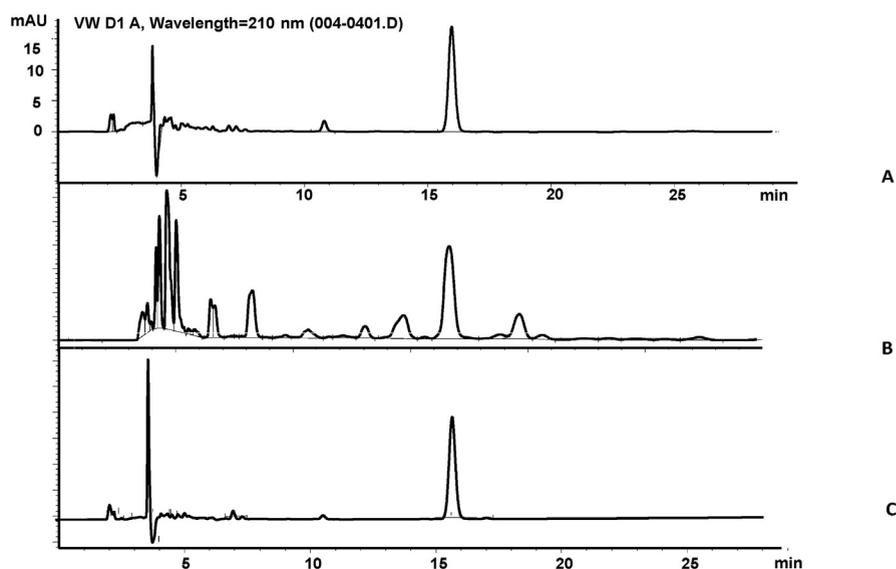


Fig. 7. A) HPLC chromatogram of the purified solanesol B) HPLC chromatogram of the unpurified solanesol C) HPLC chromatogram of the solanesol Standard.

4. Conclusions

In this study, we demonstrated that tomato leaves that are considered as agricultural waste are a rich source of solanesol, an active compound that can be used for the synthesis of co-enzyme-Q10. Furthermore, we developed a benign process for the recovery of solanesol in which subcritical CO₂ was efficiently extracted a large amount of this compounds at room temperature in absence of using any organic solvent. The purity of solanesol extracted by this method was nearly 40% and could be increased to above 93% by an additional purification step. This clean technology also has the potential for extracting other high-value compounds from tomato leaves as well as solanesol from other sources of agricultural waste. Different extraction methods, such as Soxhlet, UAE, maceration, HPSE were compared for the recovery of solanesol from tomato leaf. The yield for recovery of solanesol for tomato leaves was higher when using high-pressure CO₂ extraction (180 bar, 25 °C, 2 h) ($p < 0.001$). This process eliminates the consumption of organic solvent and operates at lower temperatures compared with other methods. In addition, the degree of purity of solanesol extracted by CO₂ was at least 15% higher than other techniques used such as soxhlet and high pressure solvent extraction.

Declarations

Author contribution statement

Marjan Arab: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Bahareh Bahramian, Ali Fathi: Conceived and designed the experiments; Analyzed and interpreted the data.

Aaron Schindeler: Analyzed and interpreted the data; Wrote the paper.

Peter Valtchev: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Robyn McConchie: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Fariba Dehghani: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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