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Ultrasound assisted lycopene extraction from tomato skin waste by volatile natural deep eutectic solvent

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ABSTRACT

In this work, a completely green method was applied for the extraction of lycopene from tomato skins waste. The combination of the ultrasound-assisted technique (UAE) and the use of volatile natural deep eutectic solvent (VNADES) menthol: thymol 1:1 allowed to obtain a green extraction process. Lycopene content was assessed by HPLC-DAD and compared with the lycopene extraction yields obtained using α-pinene and *n*-hexane as extraction solvents. The evaporation of the DES menthol:thymol was conducted using a Vacuum Vortex Evaporator. The highest concentration of extracted lycopene was obtained with *n*-hexane (735.9 mg/g of dried extract (DE)) compared to terpene-based solvents; 468.1 mg/g and 358.7-484.2 mg/g DE were recovered from *α*-pinene and DES menthol/thymol as azeotropic mixture and as such, respectively.

1. Introduction

The valorisation of food waste is one of the main challenges of recent years. Numerous researchers have investigated new methods to extract lycopene from industrial waste in a proper and efficient way using conventional or green solvents and techniques. The obtained extracts could be used to develop nutraceuticals, cosmetics, and dietary supplements.

Tomatoes and tomato products are abundantly consumed in Italy. Tomato skins discarded during the production of peeled tomatoes, tomato purée, concentrates and sauces, represent a rich source of lycopene ($C_{40}H_{56}$), a carotenoid responsible for the red color of the vegetable. The lycopene content in skins is up to 5 times higher than the pulp. From a structural point of view this carotenoid, located in the chloroplasts, is an acyclic terpenoid composed of 13 carbon-carbon double bonds of which 11 are linearly conjugated (Fig. 1); this feature renders lycopene a powerful antioxidant (Papaioannou & Karabelas, 2012; Barreiro & Barredo, 2018).

In nature lycopene can exist in *cis*- and *trans*-isomeric configurations, however almost 90% is all-*trans*-isoform referred to as all-E-lycopene, while the remaining 10% is Cis/Z-isomeric form, namely 5Z, 9Z, and 13Z.

Among the various geometric configurations, about 72 are structurally favored. Notable isomers of lycopene are all-E-lycopene, 5Z-lycopene, neolycopene A (6-*cis*-lycopene), prolycopene (1-, 3-, 5-, 7-, 9-, 11-*cis*-lycopene), and *cis*-lycopene (1-, 3-, 5-, 6-, 7-, 9-, 11-*cis*-lycopene). These isomers show the best thermodynamic stability, following this trend: 5-cis > all-trans>9-cis>13-cis>15-cis>7-cis>11-cis. (Lambelet et al., 2009). Mono- and poly-isomerization reactions can affect the *trans*-isoform of lycopene; the presence of light irradiation, strong thermal energy, chemical transformations during processing and storage can promote *cis*-isomerization, improving the bioavailability of lycopene and its antioxidant capacity (Wang et al. 2023).

Previous studies have shown that it has anticancer effects against prostate cancer due to its ability to inhibit cell proliferation, promote apoptosis, block cell cycle and diminish DNA damages (Holzapfel et al., 2013; Ivanov et al., 2007; Mirahmadi et al., 2020).

Different techniques and solvents have been used for lycopene extraction (Eh & Teoh, 2012; Strati & Oreopoulou, 2011; Poojary & Passamonti, 2015; Madia et al., 2021). Due to the difficult solubilization

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of pigment (Harris' & Spurr, 1969; Papaioannou & Karabelas, 2012), extractions with non-ionic surfactants were carried out after enzymatic pre-treatment aimed at hydrolyzing the pectin in which the pigments accumulate (Papaioannou & Karabelas, 2012). Conversely other works described the extraction processes of lycopene from tomato peel through pH modification-based techniques and subsequent enzymatic hydrolysis using a green approach (Cuccolini et al., 2013). It is well established that the food industry should use non-toxic, food-grade and reusable solvents.

An example of emerging green extraction solvents are NADESs (Natural Deep eutectic solvents) which are environmentally friendly, generally biodegradables, and composed of non-toxic and low cost components which physic-chemical properties can be finely tuned by changing one of them (Dai et al., 2014; Ling et al., 2020; Ling & Hadinoto, 2022). For example the mixture DL menthol/lactic acid was recently used for the extraction of carotenoids from tomato pomace (Lazzarini et al., 2022).

With the aim to extract lycopene from tomato skins waste in a sustainable way with a straightforward procedure, we investigated the lycopene extraction efficiency by ultrasound-assisted extraction (UAE) involving the DES menthol:thymol 1:1 (both terpene compounds), α-pinene, a terpene hydrocarbon derived from gum turpentine (Dejoye Tanzi et al., 2012; Yatagai et al., 1985), and *n*-hexane. Terpenes are biosolvents recognized as environmentally safe, they are slightly more polar than *n*-hexane, less flammable and hazardous (Lizárraga-Velázquez et al., 2020). The main disadvantages of terpenes are their strong energy consumption during evaporation, viscosity and density (Dejoye Tanzi et al., 2012, 2013). The mixture menthol/thymol belongs to the type V of DESs, which are non-ionic and show low viscosities, are chloride free and mostly hydrophobic (Abranches et al., 2019; Busato et al., 2023; Van Osch et al., 2015, 2020). DES menthol/thymol shows a non-ideal behavior where the polar hydrogen of thymol interacts preferentially with the oxygen of menthol forming a hydrogen bond stronger than the other possible intermolecular interactions among the single molecular substances (Abranches et al., 2019; Schaeffer et al., 2021); the hydrophobic properties of the mixtures make this VNADES suitable for the extraction of lipophilic bioactive substances such as lycopene. Regarding the extraction technique, the UAE is described as a simple and economical technique that can promote a reduction of extraction time, energy and solvent always leading to an improvement of the extraction yield of bioactive compounds compared to other techniques (Naseem et al., 2021b, 2021a). The mechanism of UAE is based on the cavitation effect that generate strong shear forces in the matrix. This phenomenon produces micro-jetting on the natural product surface inducing effects such as surface peeling, erosion and particle breakdown. Depending on the nature of the media, other possible effects could be macro-turbulences and micro-mixing for liquid (Chemat et al., 2017). Toma et al. (2001) reported fragmentation of vegetable substrates during irradiation and improved hydration following this technique, also leading to an increase of the extraction index.

In our work the use of UAE can accelerate the extraction procedure. The involvement of a VNADES represents an added value since most of NADESs have high viscosity that impedes the correct separation of the matrix from the extract (Strzemski et al., 2022). HPLC-DAD analysis was performed for each dried extract obtained by UAE performed with *n*-hexane, α-pinene and thymol/menthol mixture. Lycopene content was measured pre- and after evaporation of DES with and without the azeotropic mixture formation. To the best of our knowledge, this is the first report on the application of the selected system thymol-menthol for the extraction and recovery of lycopene from tomato waste.

2. Materials and methods

2.1. Sample preparation

Ice-dried tomatoes skins waste was gently furnished by the local food industry S.A.L.P.A. (Società Abruzzese Lavorazione Prodotti Agricoli, Roseto Degli Abruzzi, Teramo, IT) on 27th September 2022. Soon after the production of tomatoes sauce, tomato skins were stored packed in two plastic bags containing 5 kg each in a freezer at -4°C until extraction. Then freeze-dried material was lyophilized in a Büchi Lyovapor L-200 apparatus for 48 h, powdered in blender and sieved to 1.08 ± 0.10 mm. The obtained dried powder (7.861 g) was used as such for the extracts' preparation. Tomato samples have been weighted in a flask and the solvent added in a ratio 1:2 mass/volume.

2.2. Materials

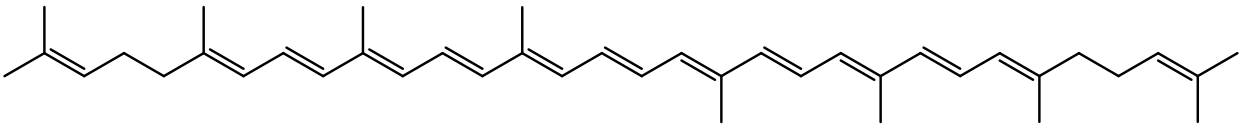
The analytical grade solvents *n*-hexane (99.0%), α-pinene (98.0%), crystal solids menthol (99.0%) and thymol (98.5%) were purchased by Sigma-Aldrich, USA (now Millipore Sigma). Acetonitrile, methanol and tetrahydrofuran were all for HPLC (≥ 99.9%) and used as such for analytical purposes. Lycopene analytical standard ≥85.0% (HPLC) was purchased by Sigma-Aldrich (Milano), shipped in dry ice and stored in an amber glass at -65°C before its use. Ice-dried tomatoes skins waste was lyophilized for 48 h, ground in blender and conserved at -20°C until the extraction.

2.3. Extraction instrumentation

UAE was performed with a Lab-scale ultrasound sonicator (Cole-Parmer, Illinois, USA) with frequency, power and amplitude of 20 kHz, 400 W and 70 %, respectively; centrifugation with an Eppendorf centrifuge 5702; evaporation of α-pinene and *n*-hexane by rotavapor Büchi Vac V-513 followed by high vacuum removal, while total evaporation of DES mixture was done by vacuum vortex evaporator (Buchler Instrument).

2.4. Preparation of VNADES thymol/menthol

An equimolar solution of thymol:menthol (1:1) was prepared adding 10.0 g of menthol to 9.6 g of thymol in a round bottom flask, shaking with a magnet at r.t. for 1 h to obtain a total volume of 20 mL (Fig. 2). The purification step is not required for DES, which means low production cost and environmental sustainability (Dai et al., 2014; Ling & Hadinoto, 2022). The physical properties of menthol/thymol mixture have been previously investigated in literature (Strzemski et al., 2022) and are reported in Table 1 along with those of the other extraction solvents used in this work (Li et al., 2014).



Lycopene

Fig. 1. Lycopene chemical structure.

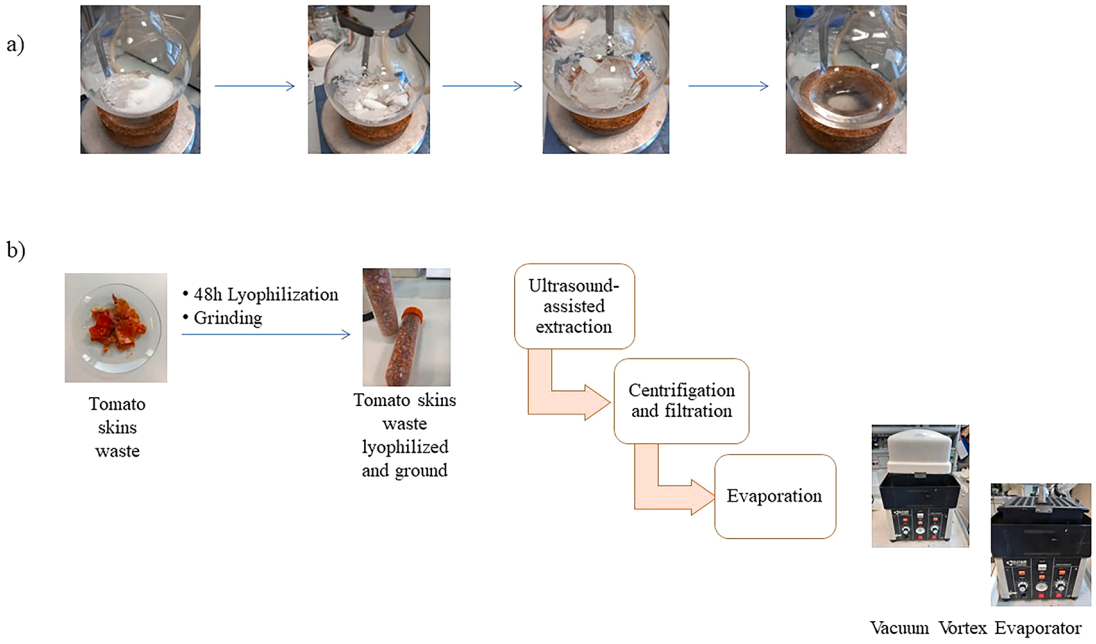


Fig. 2. (a) Preparation of DES menthol/thymol (b) **S**chematic representation of the extraction procedure.

Table 1
Physicochemical properties of solvents for UAE extraction (Li et al., 2014; Strzemski et al., 2022).

solvent	*n*-hexane	α-pinene	Thymol/menthol mixture
Molecular formula	C_6H_{14}	$C_{10}H_{16}$	$C_{10}H_{20}O$
Molecular weight	86.17	136.23	156.26
Density 25°C ($g \cdot cm^{-3}$)	0.675	0.879	0.890 (menthol) 0.96 (thymol) 0.93 (mixture)
Boiling point (°C)	69	155	232 thymol 212 menthol
Viscosity 25°C (Cp)	0.31	1.32	17.36 mPa·s at 40°C menthol
Surface tension	19.28 ($mN \cdot m^{-1}$)	25.87 dynes/cm at 25°C	30 (J/m^2)

2.5. Extraction method

2.5.1. UAE of lycopene using n-hexane

1.0156 g of tomato skins powder was located in a flask within 20 mL of *n*-hexane, and then sonicated at 36°C for 20 min. The suspension was centrifuged at 4400 rpm for 20 min, then filtered on a mesh filter to remove the solid. The supernatant was evaporated by rotary evaporation (boiling point 69°C) followed by high vacuum giving 12.1 mg of dried extract (DE).

2.5.2. UAE of lycopene using α-pinene

1.0057 g of tomato skins powder was treated as reported in 2.5.1. Being α-pinene more viscous than *n*-hexane, the solid remained wet, so a further centrifugation for 5 min at 4400 rpm was required. The supernatant was evaporated by rotary evaporator connected to high vacuum (boiling point 156°C), giving 28.5 mg of dried extract (DE).

2.5.3. UAE of lycopene using VNADES

1.0112 g of tomatoes skins powder was treated as above. Due to the viscosity of the VNADES, the wet solid was centrifuged again for 5 min at 4400 rpm. 1 mL of the supernatant was evaporated by vacuum vortex evaporator (80°C, under agitation, 1 mBar) giving 1.1 mg of dried extract (DE) in 3h. 1.0140 g of tomatoes skins powder was dissolved in 20 mL of DES menthol: thymol following the procedure described above. 1 mL of the extract was evaporated after formation of an azeotrope by adding 2.5 mL of water. The evaporation was conducted by vacuum vortex evaporator (60°C, under agitation, 1 mBar) obtaining 2.5 mg of dried extract after 1.5 h (Fig. 2).

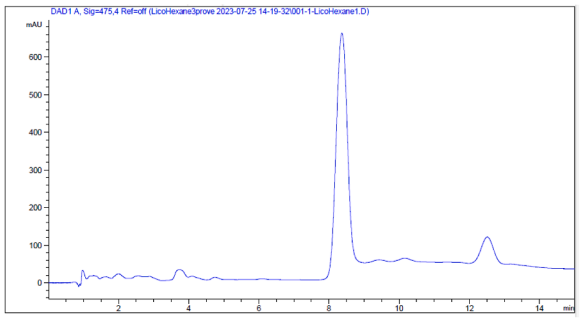
2.6. HPLC-DAD analysis

Quantification and identification of lycopene in the extracts were performed by Reversed-Phase-High-Performance Liquid Chromatography (RP-HPLC) equipment (Agilent Technologies, 1100 Infinity, Germany) with a binary pump, degasser, automatic injector, and diode array detector (DAD) (G1315D 1260 DAD VL), with the following characteristics: C18 column (ZORBAX Eclipse Plus, C18 3.5 μm, 4.6 × 100 mm, USUXR42236, USA), dimethyl-*n*-octadecylsilane stationary phase packing (ultra-high purity >99.995 % SiO_2), ZORBAX Rx-SIL on porous silica support; T = 30°C; 100 μL injected volume for each sample, following the methodology described by Olives Barba et al. (2006) with slight modifications; mobile phase of MeOH/ACN 9:1 + 0.125% TEA filtered on 0.2 μm PTFE filters and sonicated for 15 min. This solution was run through isocratic mode to achieve better identification of lycopene peak in 15 min at a flow rate of 1.2 mL/min. For the determination of the lycopene content in each extract, an analytical standard of lycopene was used (475 nm). The calibration curve was built plotting peak area *versus* concentration considering a range of 0.5-500 mg L^{-1} ($y=28.80x+75.65$; $R^2=1$). Approximately 1 mg of dried extracts were dissolved in 1 mL of THF/ACN/MeOH (1.5:3:5.5) and filtered through a 0.45 μm filters. The extracted compound was identified in a range of retention time of 8.1-8.4 min. depending on the different extracts at 475 nm by comparison with the analytical standard (Fig. 3). The concentration of lycopene was evaluated considering its relative calibration curve.

2.7. Statistical analysis

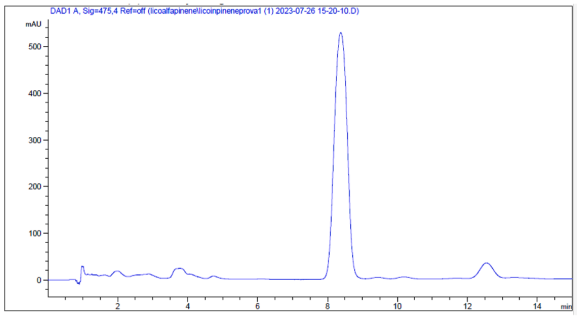
Analysis of variance (ANOVA) by SPSS software was used for statistical analysis, applying Duncan test at 95% confidence. The experimental analysis was done in triplicates and data expressed as mean ± SD (standard deviation).

a



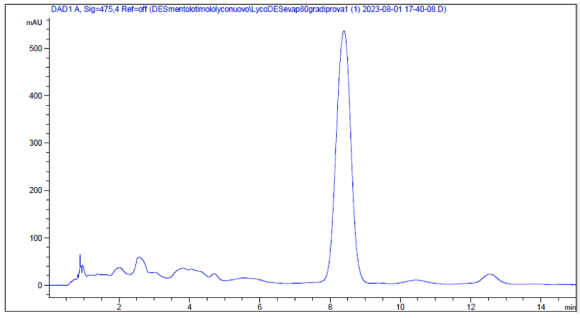
Time (min)	Area	Height	Width	Area %	Symmetry
8.369	15098.7	653.1	0.3853	79.125	0.937

b



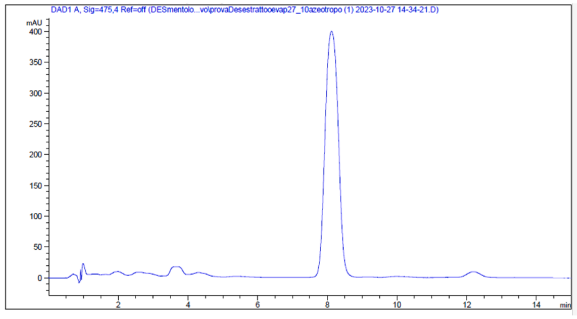
Time (min)	Area	Height	Width	Area %	Symmetry
8.380	13513.3	528.6	0.3652	86.676	0.968

c



Time (min)	Area	Height	Width	Area %	Symmetry
8.398	15499.1	533.1	0.4682	78.685	1.105

d



Time (min)	Area	Height	Width	Area %	Symmetry
8.122	10406.6	399.6	0.3633	89.503	0.902

Fig. 3. Chromatograms obtained by HPLC analysis of the UAE in *n*-hexane (a), *α*-pinene (b), DES menthol:thymol (c) and DES menthol:thymol as azeotropic mixture (d).

3. Results and discussion

In this work we investigated the extraction efficiency of the DES menthol: thymol 1:1 for the recovery of lycopene from tomato skins waste, comparing it to the extraction efficiency of *α*-pinene and *n*-hexane. The physical properties, like density and surface tension, influence the extraction efficiency as previously reported in literature (Strzemski et al., 2022).

Also raw material pre-treatment is crucial to improve the yield of lycopene extraction, considering that drying and grinding processes influence its physical properties and quality; in general the recovery of lycopene increases with decreasing particle size, because of the low mass transfer resistance.

An UAE was performed followed by centrifugation and filtration. The collected supernatant was evaporated. The time of ultrasound treatment is crucial in determining the yield of bioactive compounds, in fact it can accelerate the extraction kinetics and mass transfer as well as the biomass to solvent *ratio*. The setting of high temperature beyond the optimum one, can induce the degradation of bioactive compounds due to the cavitation bubbles and shear stress. In this study the extraction time was set at 20 min. at 36°C temperature for all the procedures, considering the thermal stability of lycopene. The evaporation technique was chosen in light of the type of solvent obtaining dried extracts that makes the comparison of the lycopene content among the preparations more accurate. To remove the deep eutectic solvent menthol/thymol, particular conditions were required. The vacuum vortex evaporator allowed us to operate combining a temperature of 80°C, mechanical agitation and high vacuum (1mBar), obtaining the dried extract in 3 h. However since lycopene could be degradable at high temperature above 100°C (Gheonea (Dima) et al., 2020), we prepared an azeotropic mixture with water in order to reduce the boiling point of the mixture (60°C, 1mBar and mechanical agitation), leading to a dried extract in 1.5 h. Each extract was analysed by reversed-phase-HPLC (see Section 2.6). The lycopene content of each extract was expressed as mg of lycopene per gram of dried extract, as shown in Table 2. The highest content of lycopene was found for the *n*-hexane extract, being an organic solvent with lower viscosity than the terpene-based mixtures; the increased efficiency of lycopene recovery in *n*-hexane may be also attributed to better solubilisation of lycopene compared to other solvents.

The lycopene extraction yields for *α*-pinene and DES menthol/thymol are sensibly high, however the extract obtained through the evaporation of the azeotropic mixture DES-water showed a minor content of lycopene compared to that prepared by the sole use of VNADES.

Furthermore, we analysed by HPLC the lycopene content of the extracts obtained by DES menthol/thymol before and after the evaporation in two different evaporation methods, *e.g.* with or without the aid of an azeotropic mixture with water. For the DES extract, the lycopene content before the evaporation was 1.19 ± 0.01 mg/mL, while post-evaporation we had 0.533 ± 0.002 mg/mL. Thus, we recorded a reduction of the lycopene content in the dried extract of approximately 55%. A decrease of lycopene content was assessed also for the DES-water azeotropic mixture extract. The pre-evaporation lycopene content was 2.32 ± 0.01 mg/mL DES ± SD that become 0.9 ± 0.01 mg/mL DES ± SD after evaporation, leading to a reduction of about 61%.

Thus, the use of the azeotropic mixture did not give any advantage in term of lycopene yield, but allows to obtain a faster recovery of the

Table 2
Lycopene extraction yields of UAE for tomato skins waste using *n*-hexane, α-pinene and DES menthol: thymol 1:1. The results are the media of three different experiments ± standard deviation (SD); DE= dried extract.

UAE-n-hexane (mg/g DE ± SD)	UAE-*α*-pinene (mg/g DE ± SD)	UAE-DES menthol:thymol (mg/g DE ± SD)	UAE-DES menthol:thymol (azeotropic mixture) (mg/g DE ± SD)
735,9 ± 8,8	468,1 ± 1,4	484,2 ± 2,4	358,7 ± 1,2

bioactive molecule by the evaporation process.

4. Conclusion

An easy and straightforward UAE technique based on the use of VNADES menthol/thymol coupled with HPLC-DAD method of analysis was developed for lycopene in tomatoes skins waste. The extraction process was completely green, easy and no time consuming. Type V DES mixture menthol/thymol was successfully enrolled as green solvents for the extraction of lycopene after optimized operating conditions, resulting in good limits of detection, linearity and reproducibility by HPLC analysis. α-pinene and DES menthol/thymol extraction solvents exhibit a good extraction efficiency compared to the conventional extraction using *n*-hexane. We envisaged the possibility to evaporate the DES to recover the dried extract similarly to other solvents like *n*-hexane and α-pinene. Despite a partial degradation, the content of lycopene in the dried extract was found during the evaporation process. The application of this deep eutectic solvent mixture is relatively unexplored, thus it could be successfully applied to the extraction of other hydrophobic molecules less sensible to temperature. To sum up this preliminary work aims to identify an efficient extraction method for retrieval of lycopene from tomato skins using VNADES, which represents an unexpected alternative for waste management based on greener technologies.

CRediT authorship contribution statement

Lorenza Marinaccio: Visualization, Software, Investigation. **Gokhan Zengin:** Software, Resources. **Onur Bender:** Resources, Project administration. **Angelo Cichelli:** Resources, Project administration. **Ettore Novellino:** Software, Resources. **Azzurra Stefanucci:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Adriano Mollica:** Supervision, Conceptualization.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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References

Abranches, D. O., Martins, M. A. R., Silva, L. P., Schaeffer, N., Pinho, S. P., & Coutinho, J. A. P. (2019). Phenolic hydrogen bond donors in the formation of non-ionic deep eutectic solvents: The quest for type V DES. *Chemical Communications, 55*, 10253–10256. https://doi.org/10.1039/C9CC04846D

Barreiro, C., & Barredo, J. L. (2018). Carotenoids production: A healthy and profitable industry. in C. Barreiro, & J.-L. Barredo (Eds.). *Microbial carotenoids* (pp. 45–55). New York: Springer.

Busato, M., Mannucci, G., Rocchi, L. A., Di Pietro, M. E., Capocefalo, A., Zorzi, E., Casu, P., Veclani, D., Castiglione, F., Mele, A., Martinelli, A., Postorino, P., & D'Angelo, P (2023). The complex story behind a deep eutectic solvent formation as revealed by L-menthol mixtures with butylated hydroxytoluene derivatives. *ACS Sustainable Chemistry & Engineering, 11*, 8988–8999. https://doi.org/10.1021/acssuschemeng.3c01209

Chemat, F., Rombaut, N., Sicaire, A. G., Meullemiestre, A., Fabiano-Tixier, A. S., & Abert-Vian, M. (2017). Ultrasound assisted extraction of food and natural products. Mechanisms, techniques, combinations, protocols and applications. A review. *Ultrasonics Sonochemistry, 34*, 540–560. https://doi.org/10.1016/j.ultsonch.2016.06.035

Cuccolini, S., Aldini, A., Visai, L., Daglia, M., & Ferrari, D. (2013). Environmentally friendly lycopene purification from tomato peel waste: Enzymatic assisted aqueous extraction. *Journal of Agricultural and Food Chemistry, 61*, 1646–1651. https://doi.org/10.1021/jf3027815

Dai, Y., Verpoorte, R., & Choi, Y. H. (2014). Natural deep eutectic solvents providing enhanced stability of natural colorants from safflower (*Carthamus tinctorius*). *Food Chemistry, 159*, 116–121. https://doi.org/10.1016/j.foodchem.2014.02.155

Dejoye Tanzi, C., Abert Vian, M., & Chemat, F. (2013). New procedure for extraction of algal lipids from wet biomass: A green clean and scalable process. *Bioresource Technology, 134*, 271–275. https://doi.org/10.1016/j.biortech.2013.01.168

Dejoye Tanzi, C., Abert Vian, M., Ginies, C., Elmaataoui, M., & Chemat, F. (2012). Terpenes as green solvents for extraction of oil from microalgae. *Molecules, 17*, 8196–8205. https://doi.org/10.3390/molecules17078196

Eh, A. L. S., & Teoh, S. G. (2012). Novel modified ultrasonication technique for the extraction of lycopene from tomatoes. *Ultrasonics Sonochemistry, 19*, 151–159. https://doi.org/10.1016/j.ultsonch.2011.05.019

Gheonea (Dima), I., Aprodu, I., Enachi, E., Horincar, G., Bolea, C. A., Bahrim, G. E., Râpeanu, G., & Stănciuc, N. (2020). Investigations on thermostability of carotenoids from tomato peels in oils using a kinetic approach. *Journal of Food Processing and Preservation, 44*. https://doi.org/10.1111/jfpp.14303. Article e14303.

Harris, W. M., & Spurr, A. R. (1969). Chromoplasts of tomato fruits. II. The Red Tomato. *American Journal of Botany, 56*, 380–389. https://doi.org/10.1002/j.1537-2197.1969.tb07547.x

Holzapfel, N. P., Holzapfel, B. M., Champ, S., Feldthusen, J., Clements, J., & Hutmacher, D. W. (2013). The potential role of lycopene for the prevention and therapy of prostate cancer: From molecular mechanisms to clinical evidence. *International Journal of Molecular Sciences, 14*, 14620–14646. https://doi.org/10.3390/ijms140714620

Ivanov, N. I., Cowell, S. P., Brown, P., Rennie, P. S., Guns, E. S., & Cox, M. E. (2007). Lycopene differentially induces quiescence and apoptosis in androgen-responsive and -independent prostate cancer cell lines. *Clinical Nutrition, 26*, 252–263. https://doi.org/10.1016/j.clnu.2007.01.002

Lambelet, P., Richelle, M., Bortlik, K., Franceschi, F., & Giori, A. M. (2009). Improving the stability of lycopene (Z)-isomers in isomerized tomato extracts. *Food Chemistry, 112*, 156–161. https://doi.org/10.1016/j.foodchem.2008.05.053

Lazzarini, C., Casadei, E., Valli, E., Tura, M., Ragni, L., Bendini, A., & Gallina Toschi, T. (2022). Sustainable drying and green deep eutectic extraction of carotenoids from tomato pomace. *Foods, 405*, 11. https://doi.org/10.3390/foods11030405. Article.

Li, Y., Fine, F., Fabiano-Tixier, A. S., Abert-Vian, M., Carre, P., Pages, X., & Chemat, F. (2014). Evaluation of alternative solvents for improvement of oil extraction from rapeseeds. *Comptes Rendus Chimie, 17*, 242–251. https://doi.org/10.1016/j.crci.2013.09.002

Ling, J. K. U., Chan, Y. S., Nandong, J., Chin, S. F., & Ho, B. K. (2020). Formulation of choline chloride/ascorbic acid natural deep eutectic solvent: Characterization, solubilization capacity and antioxidant property. *LWT - Food Science and Technology*, 133. https://doi.org/10.1016/j.lwt.2020.110096. Article 110096.

Ling, J. K. U., & Hadinoto, K. (2022). Deep Eutectic solvent as green solvent in extraction of biological macromolecules: A review. *International Journal of Molecular Sciences, 23*, 3381. https://doi.org/10.3390/ijms23063381. Article.

Lizárraga-Velázquez, C. E., Leyva-López, N., Hernández, C., Gutiérrez-Grijalva, E. P., Salazar-Leyva, J. A., Osuna-Ruíz, I., Martínez-Montaño, E., Arrizon, J., Guerrero, A., Benitez-Hernández, A., & Ávalos-Soriano, A. (2020). Antioxidant molecules from plant waste: Extraction techniques and biological properties. *Processes, 8*. https://doi.org/10.3390/pr8121566. Article 1566.

Madia, V. N., De Vita, D., Ialongo, D., Tudino, V., De Leo, A., Scipione, L., Di Santo, R., Costi, R., & Messore, A. (2021). Recent advances in recovery of lycopene from tomato waste: A potent antioxidant with endless benefits. *Molecules*, 26. https://doi.org/10.3390/molecules26154495. Article 4495.

Mirahmadi, M., Azimi-Hashemi, S., Saburi, E., Kamali, H., Pishbin, M., & Hadizadeh, F. (2020). Potential inhibitory effect of lycopene on prostate cancer. *Biomedicine & pharmacotherapy*, 129. https://doi.org/10.1016/j.biopha.2020.110459. Article 110459.

Naseem, Z., Iqbal, J., Zahid, M., Shaheen, A., Hussain, S., & Yaseen, W. (2021a). Use of hydrogen-bonded supramolecular eutectic solvents for eco-friendly extraction of bioactive molecules from *Cymbopogon citratus* using Box–Behnken design. *Journal of Food Measurement and Characterization, 15*, 1487–1498. https://doi.org/10.1007/s11694-020-00744-2

Naseem, Z., Zahid, M., Hanif, M. A., & Shahid, M. (2021b). Green extraction of ethnomedicinal compounds from *Cymbopogon citratus* Stapf using hydrogen-bonded supramolecular network. *Separation Science and Technology, 56*, 1520–1533. https://doi.org/10.1080/01496395.2020.1781894

Olives Barba, A. I., Hurtado, M. C., Sánchez Mata, M. C. S., Fernández Ruiz, V. F., & López Sáenz de Tejada, M. (2006). Application of a UV–vis detection-HPLC method for a rapid determination of lycopene and β-carotene in vegetables. *Food Chemistry, 95*, 328–336. https://doi.org/10.1016/j.foodchem.2005.02.028

Papaioannou, E. H., & Karabelas, A. J. (2012). Lycopene recovery from tomato peel under mild conditions assisted by enzymatic pre-treatment and non-ionic surfactants. *Acta Biochimica Polonica, 59*, 71–74. https://doi.org/10.18388/abp.2012_2174

Poojary, M. M., & Passamonti, P. (2015). Extraction of lycopene from tomato processing waste: Kinetics and modelling. *Food Chemistry, 173*, 943–950. https://doi.org/10.1016/j.foodchem.2014.10.127

Schaeffer, N., Abranches, D. O., Silva, L. P., Martins, M. A. R., Carvalho, P. J., Russina, O., Triolo, A., Paccou, L., Guinet, Y., Hedoux, A., & Coutinho, J. A. P. (2021). Non-ideality in thymol + menthol type V deep eutectic solvents. *ACS Sustainable*

Chemistry & Engineering, 9, 2203–2211. https://doi.org/10.1021/acssuschemeng.0c07874

Strati, I. F., & Oreopoulou, V. (2011). Effect of extraction parameters on the carotenoid recovery from tomato waste. *International Journal of Food Science & Technology, 46*, 23–29. https://doi.org/10.1111/j.1365-2621.2010.02496.x

Strzemski, M., Dresler, S., Podkościelna, B., Skic, K., Sowa, I., Załuski, D., Verpoorte, R., Zielińska, S., Krawczyk, P., & Wójciak, M. (2022). Effectiveness of volatile natural deep eutectic solvents (VNADESs) for the green extraction of *Chelidonium majus* isoquinoline alkaloids. *Molecules*, 27. https://doi.org/10.3390/molecules27092815. Article 2815.

Toma, M., Vinatoru, M., Paniwnyk, L., & Mason, T. J. (2001). Investigation of the effects of ultrasound on vegetal tissues during solvent extraction. *Ultrasonics Sonochemistry, 8*, 137–142. https://doi.org/10.1016/S1350-4177(00)00033-X

Van Osch, D. J. G. P., Dietz, C. H. J. T., Warrag, S. E. E., & Kroon, M. C. (2020). The curious case of hydrophobic deep eutectic solvents: A story on the discovery, design, and applications. *ACS Sustainable Chemistry & Engineering, 8*, 10591–10612. https://doi.org/10.1021/acssuschemeng.0c00559

Van Osch, D. J. G. P., Zubeir, L. F., Van Den Bruinhorst, A., Rocha, M. A. A., & Kroon, M. C. (2015). Hydrophobic deep eutectic solvents as water-immiscible extractants. *Green Chemistry, 17*, 4518–4521. https://doi.org/10.1039/C5GC01451D

Wang, X., Dong, L., Ma, C., Wang, Z., Hu, X., & Chen, F. (2023). Impact of high-hydrostatic pressure and thermal processing on the antioxidant profiles and capacity of tomato juice during storage. *Food Innovation and Advances, 2*, 124–134. https://doi.org/10.48130/FIA-2023-0016

Yatagai, M., Sato, T., & Takahashi, T. (1985). Terpenes of leaf oils from Cupressaceae. *Biochemical Systematics and Ecology, 13*, 377–385. https://doi.org/10.1016/0305-1978(85)90081-X