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A metal sieve-linked double-syringe sugaring-out liquid-liquid microextraction as a new analytical system for the accurate and sensitive determination of pyrimethanil in GC-MS

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Abstract

Pyrimethanil is a widely used fungicide and its residues in carbohydrate rich foods require vigilant monitoring for consumer protection and regulatory compliance. In this study, a metal sieve-linked double-syringe sugaring-out liquid-liquid microextraction (MSLDS-SULLME) method coupled to GC-MS is presented for pesticide-residue determination in sugar-rich matrices exemplified by grape molasses. Endogenous sugars induce phase separation, while syringe-driven passage through a perforated metal sieve sustains interfacial renewal in a closed configuration, minimizing operator-dependent variability and avoiding disperser additives. In grape-molasses extracts, linear working range of 9.39–481.6 μg kg^{-1} was obtained with R^2 as 0.9989. The limit of detection (LOD) and limit of quantification (LOQ) values were determined as 4.31 and 14.37 μg kg^{-1}, respectively. Under identical GC-MS conditions, 79.66-fold sensitivity enhancement was observed relative to direct instrumental analysis. Using matrix-matching calibration strategy, recoveries of 83.00–129.16% were achieved with low within-set variability, thus confirming applicability in the authentic sugar-rich matrix. Overall, the

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developed approach offers a practical route for improving pesticide-residue analysis in viscous, sugar-rich matrices where conventional sample preparation may be limited by matrix effects and phase-handling difficulties. Therefore, it can be useful for analytical chemists, food-control laboratories and authorities involved in residue monitoring.

Keywords: Pyrimethanil; Sugaring out; Syringe assisted microextraction; Grape molasses; GC-MS

1. Introduction

Since the mid-twentieth century, thousands of pesticides have been introduced into various consumer product and used worldwide (Hernández et al., 2005). They can improve the yield and the quality of both crops and food while contributing to the control of numerous human illnesses that are spread by insect and rodent-borne vectors (Fenik et al., 2011). However, the use of these chemicals (e.g., fungicides, organophosphorus pesticides, insecticides, and herbicides) may lead to environmental pollution during long-term application (Rial-Otero et al., 2007). Additionally, they can persist in vegetables and fruits which can create an emerging threat to consumers (El-Sheikh et al., 2022). Click or tap here to enter text.To address these concerns, several legislative authorities such as the European Union have set maximum residue limits (MRLs) for pesticides in different food samples (Gilbert-López et al., 2009). Among these pesticides, pyrimethanil, N-(4,6-dimethylpyrimidin-2-yl)aniline is a synthetic anilinopyrimidine fungicide that is highly active against an extensive array of plant pathogenic fungi (Garrido et al., 2016). It is employed for the management of leaf scab and grey mold on tomatoes, grapes, strawberries and other fruits as well as landscape plants and vegetables (Navalón et al., 2004). Furthermore, the major effect of this pesticide is the ability to inhibit the generation or release of external hydrolytic enzymes which prevents the spread and growth of fungi (Gikas et al., 2022), (R. Chen et al., 2024). Since it can be relatively persistent and may accumulate in agricultural products, regular monitoring of pyrimethanil residues in food and environmental samples is important for regulatory

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compliance and public health protection. To meet these monitoring needs, sensitive and selective analytical platforms capable of trace-level quantification in complex matrices are required.

In the recent years, several analytical techniques including electrochemical sensor (Hsu et al., 2024), high performance liquid chromatography (HPLC) (Liu et al., 2013), liquid chromatography-tandem spectrometry (LC-MS/MS)(Fan et al., 2014) and gas chromatography-mass spectrometry (GC-MS)(Aquino & Navickiene, 2009) has been widely used for the detection of pyrimethanil residues. Nonetheless, these techniques have some drawbacks such as high instrument cost, challenging sample treatment, and restricted capability for in situ detection (Supchocksoonthorn et al., 2021). GC-MS is one of the most frequently applied analytical techniques for the determination of pesticide residues in a broad spectrum of matrices related to food quality assurance and to assessment of biological exposure (Shendy et al., 2019). It also offers both qualitative and quantitative measurements even in complex matrices which supports accurate and precise analysis for the extensive detection of contaminants (Han et al., 2025).

Sample preparation serves as a key factor in the accurate and reliable determination of pesticide residues, particularly when dealing with food matrices due to their complexity and the presence of trace level analytes (L. Zhang et al., 2012), (Lambropoulou & Albanis, 2007). Among various extraction techniques, the sugaring-out assisted liquid-liquid microextraction (SULLME) method has become highly important due to its cost-effectiveness, simplicity, and suitability for high-sugar matrices like royal jelly (Tu et al., 2018), honey (W. Chen et al., 2019), fruit juice (Timofeeva et al., 2017), and beeswax (Tu et al., 2024), (Sun et al., 2024). Compared with conventional liquid-liquid microextraction (LLME) methods, SULLME takes advantage of the high sugar content in the mixture containing acetonitrile and water, to generate phase separation which facilitates effective extraction of target analytes into the organic phase without additional separation agents (J. Zhang et al., 2013). For the SULLME technique, grape molasses, honey, royal

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jelly and fruit juice inherently supply the sugars needed for phase separation. Grape molasses typically contains 50 to 80% total sugar with glucose and fructose as the main constituents (Salameh et al., 2024), (Korkmaz, 2023; Tu et al., 2018). To harness this matrix-driven phase separation while advancing practicality, sugaring-out was coupled with an in-syringe, metal sieve-linked double-syringe (MSLDS) operated in a closed, pump-actuated system. Constant back-and-forth motion and passage through a perforated metal sieve maintain continuous interfacial renewal and finely controlled solvent dispersion without disperser additives (Gösterişli et al., 2022). Operator-dependent variability is reduced, and mass transfer is intensified, which strengthens the sugaring-out step and improves extraction performance in viscous, sugar-rich matrices such as grape molasses.

In this study, a sugaring-out based MSLDS-SULLME method is firstly introduced for the determination of pyrimethanil in grape molasses matrices. The novelty of this approach is the integration of metal sieve-linked double-syringe mixing with matrix-driven sugaring out phase separation. This separation is driven by endogenous sugars, and the acetonitrile phase is dispersed by back-and-forth syringe transfer through a perforated metal sieve, which increases interfacial area and accelerates mass transfer. The procedure is coupled with GC-MS for the determination of target pesticide residues and is positioned as a greener and more practical alternative to conventional liquid–liquid microextraction and stand-alone sugaring-out. As a whole, the combination of sugaring out based MSLDS-LLME method offers an eco-friendly, rapid, highly effective and reliable sample pre-treatment strategy for trace pesticide determination in challenging sugar-rich matrices.

2. Materials and methods

2.1. Instrumentation

Gas-chromatographic measurements were performed on an Agilent 6890N gas chromatograph coupled to an Agilent 5973N mass spectrometry system fitted with an HP-5MS capillary column (5% phenyl-methylpolysiloxane, 30 m

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× 0.25 mm i.d., 0.25 µm film). Helium served as the carrier at 1.6 mL min^{-1} under constant flow. Injections were made in splitless mode with an injection volume of 1.0 µL through the front inlet at 290 °C with 16.03 psi inlet pressure, the purge was set to 45.0 mL min^{-1}, and the gas saver engaged after 2.0 min at 20.0 mL min^{-1}. The MS ion source, quadrupole and interface temperatures were set at 230 °C, 150 °C and 280 °C. The temperature program was 90°C for 0.00 min followed by 20 °C min^{-1} to 190°C with a 1.00 min hold and then 25 °C min^{-1} to 300 °C with a 1.60 min hold, giving a total run time of 12.00 min with 0.50 min equilibration. The mass spectrometer operated with electron-impact ionization at 70 eV in selected-ion monitoring and pyrimethanil was quantified at 198 m/z with characteristic ions recorded for confirmation. Extracts were prepared using a hybrid liquid-phase setup that coupled sugaring-out with a metal-sieve-linked double-syringe transfer, where two syringes were joined by a stainless-steel mesh adaptor and three-way fittings. All solutions were handled in PTFE-lined autosampler vials while using a calibrated analytical balance with ±0.1 mg readability.

2.2. Chemicals, standards and reagents

All chemicals were analytical or GC-MS grade and used as received. The pyrimethanil reference standard with 99.00% purity was obtained from Ehrenstorfer (Augsburg, Germany). The stock solution in acetonitrile was prepared gravimetrically at a nominal concentration of 990.84 mg kg^{-1} with density correction when required. Working standards were prepared gravimetrically in water containing 2.5% w/w acetonitrile to match the solvent composition used during extraction and GC-MS measurements throughout method development and optimization. Chloroform, dichloromethane, 1,2-dichloroethane, methanol, and acetonitrile were obtained from Merck (Germany). Deionized water produced by an Elga FLEX 3 system was used in all preparations and rinsing steps. All procedures were carried out in the real matrix that is grape molasses rather than in model solutions. Grape molasses used for development optimization and recovery

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experiments was purchased from retail markets in Istanbul, Türkiye across multiple lots and stored at 4 °C until analysis.

2.3. Extraction procedure

Initially, 0.50 g grape molasses was weighed into a 15 mL polypropylene tube, and 7.5 mL of a standard or sample solution containing 2.5% (w/w) acetonitrile was added. The resulting suspension was transferred into a 10 mL syringe to enable closed handling and controlled mixing. Subsequently, 200 µL 1,2-dichloroethane (DCE), preloaded in a 2 mL syringe as the extraction solvent, was injected into the sample syringe to form a distinct organic phase and promote efficient partitioning of the analyte within the sugar-rich medium. Afterwards, a second clean 10 mL syringe was connected via a stainless-steel mesh adaptor with three-way fittings, and the biphasic mixture was cycled back and forth for 15 cycles across the mesh to generate a fine transient dispersion that increases interfacial area and accelerates mass transfer. Thereafter, the mixture was centrifuged at 3000 rpm for 2.0 min to sharpen the phase boundary, aided by the intrinsic sugaring-out effect of the carbohydrate matrix. Finally, the analyte rich DCE phase was collected with a calibrated microliter syringe, transferred to PTFE-lined autosampler vials, and submitted to GC-MS under the specified instrumental conditions.

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3. Results and discussion

3.1. Grape molasses amount

In acetonitrile-water systems employing sugaring out, the carbohydrate content of the sample governs phase disengagement and enrichment efficiency. Increased sugar content dehydrates the aqueous domain and promotes formation of an acetonitrile-rich phase, which favors transfer of moderately polar analytes into the organic layer (Wang et al., 2008). Using metal sieve-linked double-syringe pressurization to achieve rapid dispersion, grape molasses charges of 0.50, 0.75, 1.00 and 1.50 g were examined under

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identical conditions. Although 1.00 g yielded the highest mean signal, the responses at 0.50, 0.75 and 1.50 g were statistically indistinguishable from 1.00 g within experimental uncertainty as demonstrated in Figure 1, indicating response saturation once the threshold sugar content for reproducible phase separation was achieved. The 0.50 g preserved response while lowering viscosity, shortening dispersion and settling, and limiting co extracted saccharides. To support throughput and routine handling while maintaining response, 0.50 g was selected as the optimum for subsequent work.

3.2. **Extraction solvent type and volume**

Selection of the extraction solvent is decisive in sugaring-out assisted LLME because solvent identity governs immiscibility with the acetonitrile-water system, interfacial behavior, disengagement time and solvation of the target analytes (Sadeghi & Coutinho, 2024). Under identical SULLME-MSLDS conditions, chloroform, dichloromethane and 1,2-dichloroethane were examined by GC-MS. Dichloromethane produced the largest peak areas but with higher signal variability and a less stable boundary, as shown in Figure 2. In contrast, 1,2-dichloroethane gave comparable responses with lower variability and a consistently sharp two-phase boundary while chloroform yielded lower signals. Considering response, precision, boundary stability and routine operability together, 1,2-dichloroethane was selected as the extraction solvent for subsequent experiments. Additionally, since DCE is a toxic solvent, all experimental steps were carried out in a fume hood, and the waste was collected separately. In future applications, greener extraction solvents may be evaluated to improve the environmental compatibility of the method.

Extraction solvent volume was then assessed as it governs the phase ratio and attainable enrichment. At fixed sample volume and organic content, 1,2-dichloroethane volumes of 200, 300, 400 and 500 µL were examined. As shown in Figure 3, 200 µL provided the highest mean signal while maintaining a well-defined, recoverable layer, whereas larger volumes led to

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lower responses due to dilution of the extract and slower disengagement. Lower volumes of DCE were not included because even at 200 µL, the collection of the organic phase was required careful handling due to small volume of the DCE layer in the viscous grape-molasses matrix. A further decrease in the DCE volume was expected to make phase recovery less reliable, increase the risk of organic phase loss during collection, and compromise repeatability. Accordingly, 200 µL of 1,2-dichloroethane was adopted as the extraction-phase volume to support throughput and routine handling while maintaining response.

3.3. **Mixing cycle**

Aligned with the solvent and volume optimizations, mixing was evaluated because hydrodynamic dispersion governs interfacial renewal, diffusion distance and mass transfer in sugar-rich media (Torkaman et al., 2024; Yarahmadi et al., 2025). A cycle was defined as one complete back-and-forth transfer between the two syringes through the metal-sieve connector. Pressurized shuttling through the perforated sieve fragments and redistributes the organic phase within the viscous matrix, which shortens diffusion paths and accelerates mass transfer. With all other parameters fixed, 0, 10, 15, 30 and 60 cycles were examined. At 60 cycles the mean signal was the highest, but variability increased, and transient emulsions were observed, while 30 cycles produced a slightly lower response with variability that remained elevated as illustrated in Figure 4. At 15 cycles, a high signal was obtained with lower variability, a consistently sharp phase boundary and a shorter extraction time. Conditions without external mixing by the syringe system, or with limited syringe mixing (10 cycles), constrained dispersion and reduced response. Considering precision, response, boundary stability and overall analysis time together, 15 cycles were selected as the mixing condition for subsequent experiments.

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3.4. **Evaluation of analytical figures**

Under the optimized conditions summarized in the Table 1, analytical performance was evaluated for both the stand-alone GC-MS system and the developed MSLDS-SULLME method coupled to GC-MS. In grape-molasses extracts, the extraction-assisted system provided a linear dynamic range of 9.39 to 481.6 µg kg^{-1} with a determination coefficient (R^2) of 0.9989. The calibration curve used for analytical performance evaluation was constructed using non-matrix-matched standards. Method sensitivity was estimated from the calibration plot using the 3 s/m and 10 s/m criteria. Here, s was calculated as the standard deviation of four replicate responses obtained at the lowest calibration level while m corresponded to the slope of the same calibration curve. The resulting limit of detection and quantification were determined as 4.31 and 14.37 µg kg^{-1}, respectively. Compared with direct GC-MS analysis under identical instrumental settings, the developed MSLDS-SULLME method provided a calibration-sensitivity enhancement of 79.66, reflecting a substantive gain in response per unit concentration in the sugar-rich matrix. The calibration plot and full numerical characteristics for MSLDS-SULLME system are presented in Figure 5.

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Table 1. Optimized conditions of the developed MSLDS-SULLME method.

Optimized parameter	Optimum value
Grape molasses amount	**0.5 g**
Extraction solvent type / volume	**1,2-dichloroethane / 200 µL**

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Mixing cycle	**15**

3.5. **Comparison of previous literature studies**

The previously reported MSLDS-LPME system (Gösterişli et al., 2022) is based on the same metal sieve-linked double-syringe configuration and provides efficient phase dispersion through syringe-assisted mixing without the use of disperser solvents. In the present study, this method is extended by integrating SULLME, enabling matrix-assisted phase separation in addition to mechanical dispersion. Compared with the MSLDS-LPME system, the proposed approach introduces sugar-induced phase separation, which enhances applicability to high-sugar, viscous matrices. This extension improves practical performance in complex sugar-rich samples.

Previous studies have demonstrated the applicability of sugaring-out assisted liquid–liquid extraction (SULLE) in different analytical applications. Zhang et al. (2013) developed a SULLE-LC-MS/MS method for the determination of antiviral drugs in human plasma, highlighting the feasibility of sugar-induced phase separation in acetonitrile-water systems for LC-MS/MS analysis (J. Zhang et al., 2013). Shishov et al. (2017), developed an automated solid sample dissolution coupled with sugaring-out homogeneous liquid–liquid extraction system for pharmaceutical analysis in throat lozenges, enabling on-line sample preparation (Shishov et al., 2017). Timofeeva et al. (2017), developed a fully automated in-syringe SULLE (IS-SULLE) system coupled with HPLC-MS/MS for the determination of pesticides in fruit juices, achieving rapid extraction and high analytical efficiency, but requiring a dedicated flow-injection setup and instrument integration (Timofeeva et al., 2017). In contrast, the present study employs a simpler and more flexible sugaring-out LLE strategy, avoiding complex on-line configurations while still

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ensuring efficient phase separation, good selectivity, and compatibility with chromatographic analysis.

3.6. **Recovery studies**

Recovery studies were performed in two distinct grape-molasses samples from the same commercial brand, each corresponding to a different expiry lot. Samples were spiked at multiple levels of pyrimethanil from 49.34 to 216.05 μg kg^{-1} using gravimetric preparation using a sensitive balance and were processed under the optimized method parameters with the GC-MS temperature program. Calibration plots were constructed separately for each lot to implement matrix matching calibration strategy so that each lot's calibration was applied to the other lot's spiked samples to determine calculated concentration of the spiked samples and probe potential matrix effects. The percentage recovery (REC%) value was calculated using Eq. 1. Under these conditions, recoveries were obtained in the range of 83.00–129.16%, with low within-set variability and close agreement between lots, as shown in Table 2.

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$$\%REC = \frac{\text{Mean value}_{\text{Calculated concentration of analyte for spiked sample}}}{\text{Mean value}_{\text{Theoratical concentration of analyte for spiked sample}}} \text{ X } 100 \qquad \text{(Eq. 1)}$$

These findings support the suitability of the developed MSLDS-SULLME-GC-MS method for accurate determination of pyrimethanil residue in grape molasses and other sugar-rich matrices and identify matrix matching as the preferred calibration strategy for routine application.

Table 2. Percent recoveries for grape molasses using the MSLDS-SULLME-GC-MS method with matrix matching strategy.

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	Spiked concentration, µg/kg	Calculated concentration, µg/kg	%Recovery	±Standard deviation
Grape-molasses (expiry date: 20.03.2028)-Grape-molasses (expiry date: 20.05.2028)	49.35	56.35	114.17	1.54
	99.12	128.02	129.16	7.38
	149.44	173.41	116.04	2.40
	216.05	240.04	111.10	7.26
Grape-molasses (expiry date: 20.05.2028)-Grape-molasses	49.34	45.93	93.10	12.52
	99.04	100.58	101.56	12.45
	149.45	135.32	90.55	0.21
	216.02	179.30	83.00	4.58

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4. **Conclusion**

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An MSLDS-SULLME-GC-MS strategy was established that couples matrix-driven phase separation with syringe-mediated, sieve-assisted mixing in a closed system, enabling controlled dispersion, clean phase disengagement, and improved handling in sugar-rich media. A linear working range of 9.39–481.6 µg kg^{-1} was obtained with R^2 as 0.9989, and LOD and LOQ values were determined as 4.31 and 14.37 µg kg^{-1}, respectively. Under identical GC-MS conditions, a 79.66-fold sensitivity enhancement was observed relative to direct instrumental analysis. Using a matrix-matching calibration strategy, recoveries of 83.00–129.16%, were achieved across two expiry lots, supporting accurate quantification in grape molasses. The method may still be affected by analyte properties and matrix composition. In particular, differences in viscosity and sugar profile among sugar-rich foods can influence phase separation and extraction efficiency. Therefore, further validation is needed for other pesticides and matrices. Owing to its controlled dispersion, robust phase disengagement, and compatibility with matrix-matching calibration, this method can serve as a foundational and guiding procedure for subsequent studies in sugar-rich matrices, informing extensions to other commodities, development of multi-residue applications, evaluation of greener extraction solvents and implementation of syringe assisted systems.

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Declarations

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CRediT authorship contribution statement

Ayça Girgin: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft.

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Olcaytu Çetiner: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft.

Tuğçe Unutkan Gösterişli: Conceptualization, Data curation, Investigation, Methodology, Visualization, Validation, Writing– original draft.

Sezgin Bakırdere: Conceptualization, Data curation, Investigation, Methodology, Visualization, Supervision, Writing– review & editing.

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Figure Legends

Figure 1. Effect of grape molasses amount on the MSLDS-SULLME method.

Figure 2. Effect of extraction solvent type on the MSLDS-SULLME method.

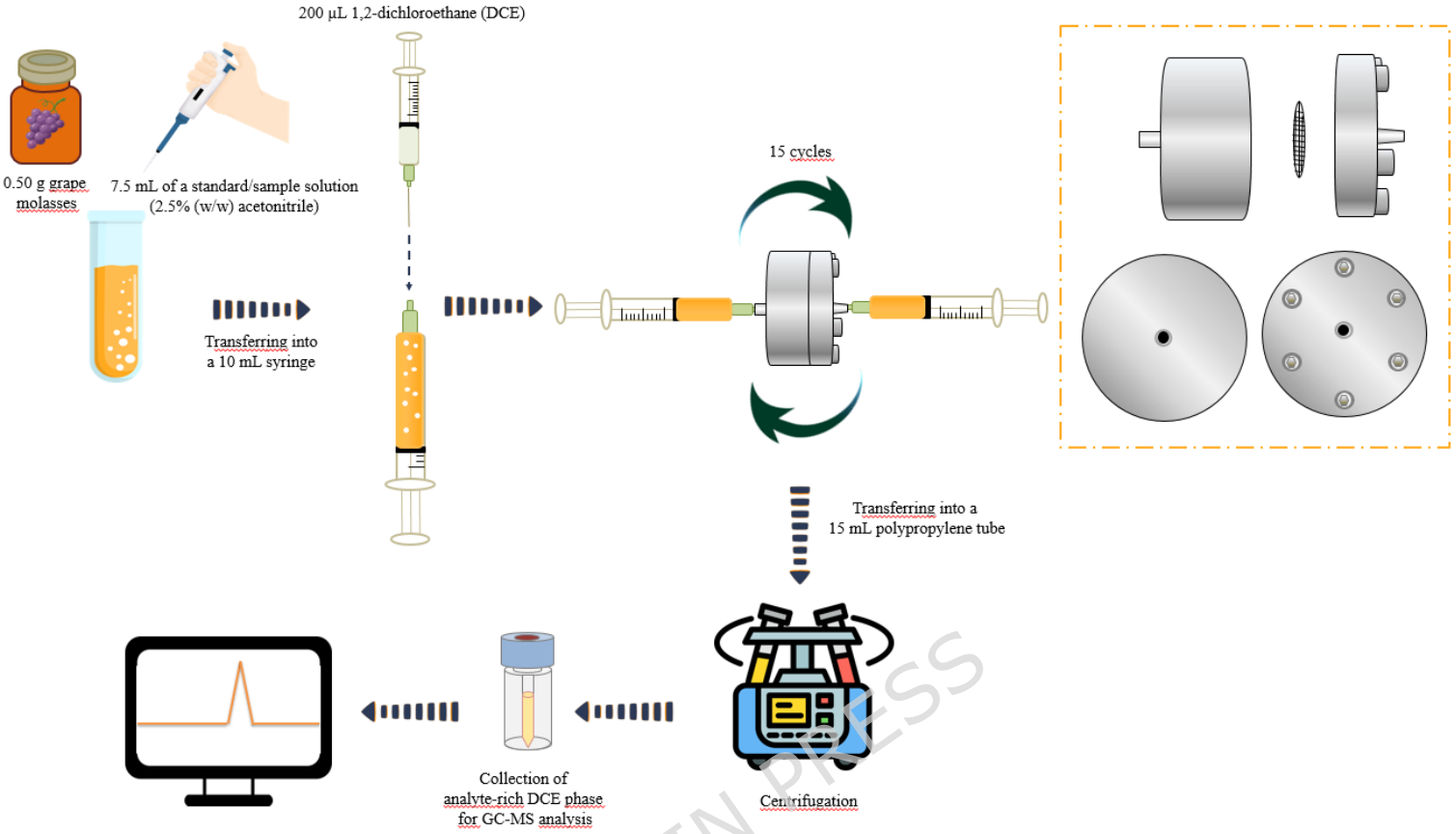
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Figure 3. Effect of extraction solvent volume on the MSLDS-SULLME method.

Figure 4. Effect of mixing cycle on the MSLDS-SULLME method.

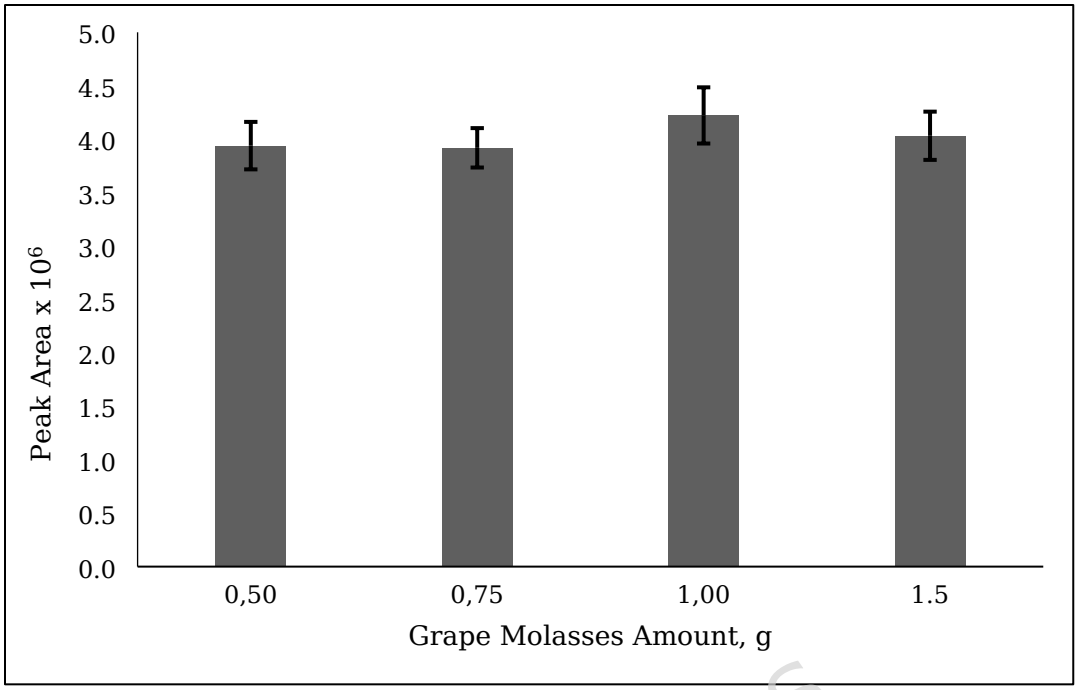
Figure 5. The calibration curve of the MSLDS-SULLME method.

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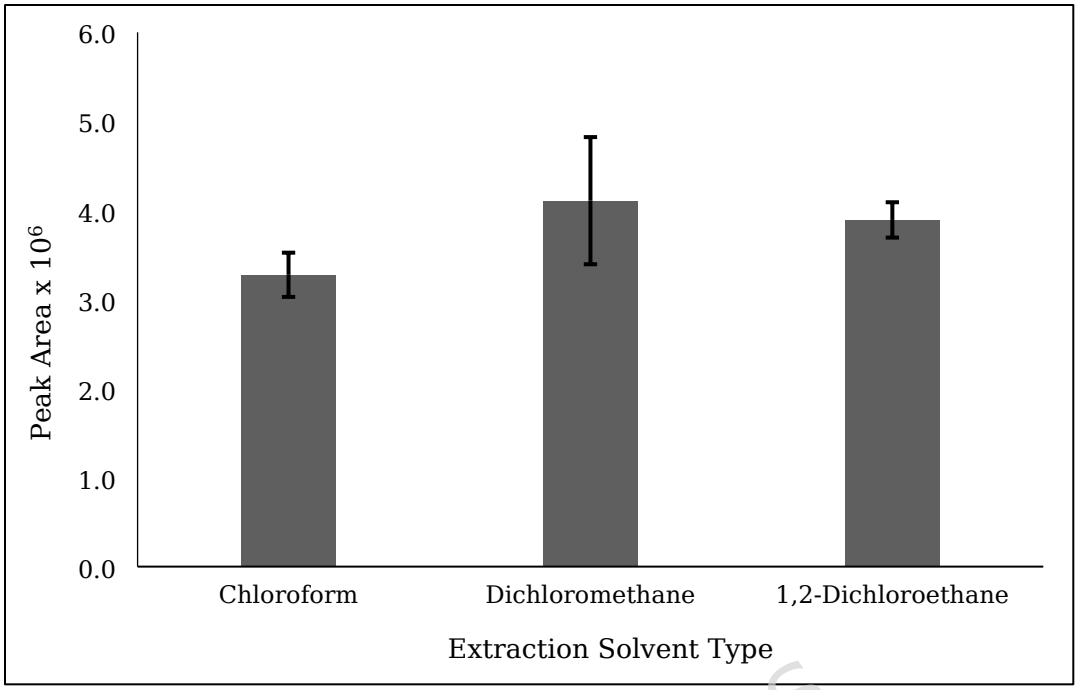
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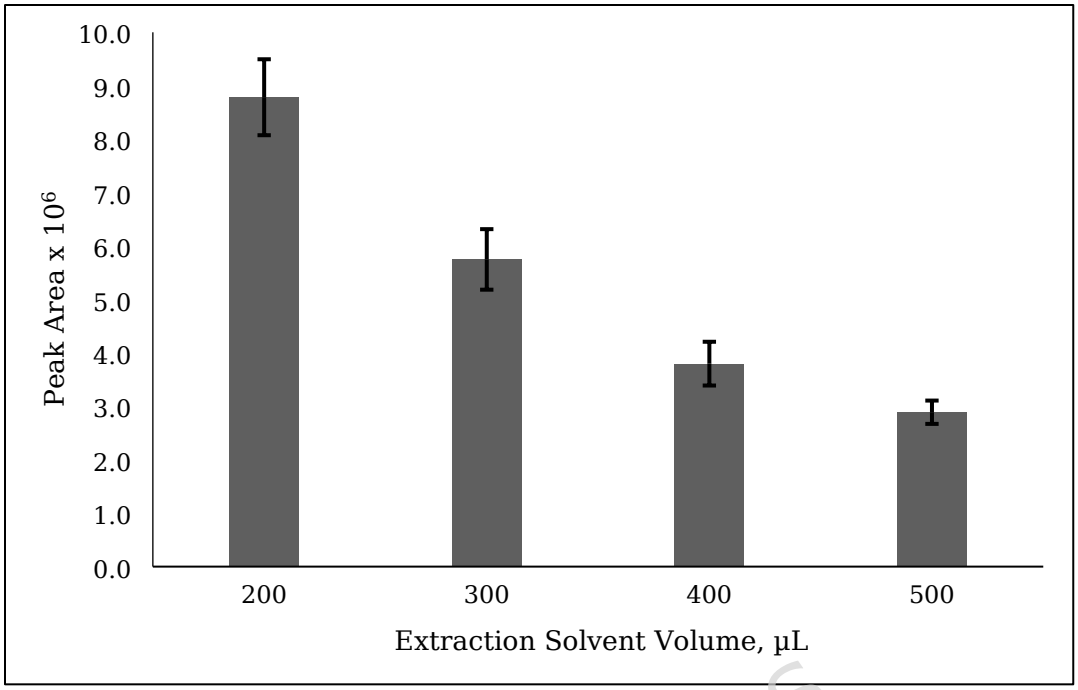
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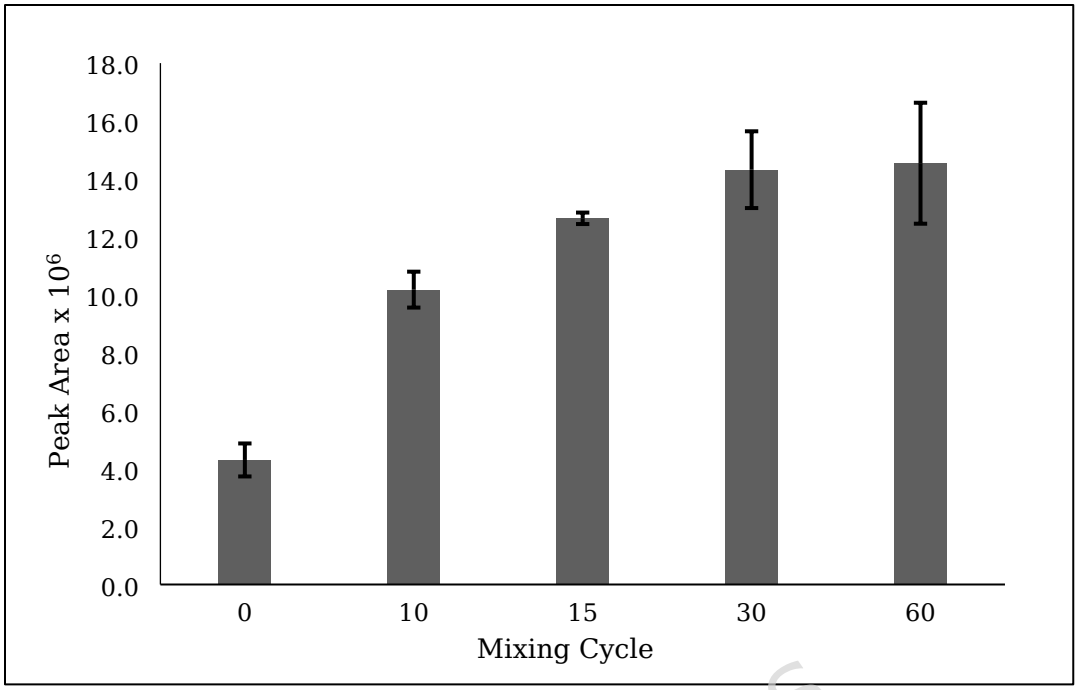
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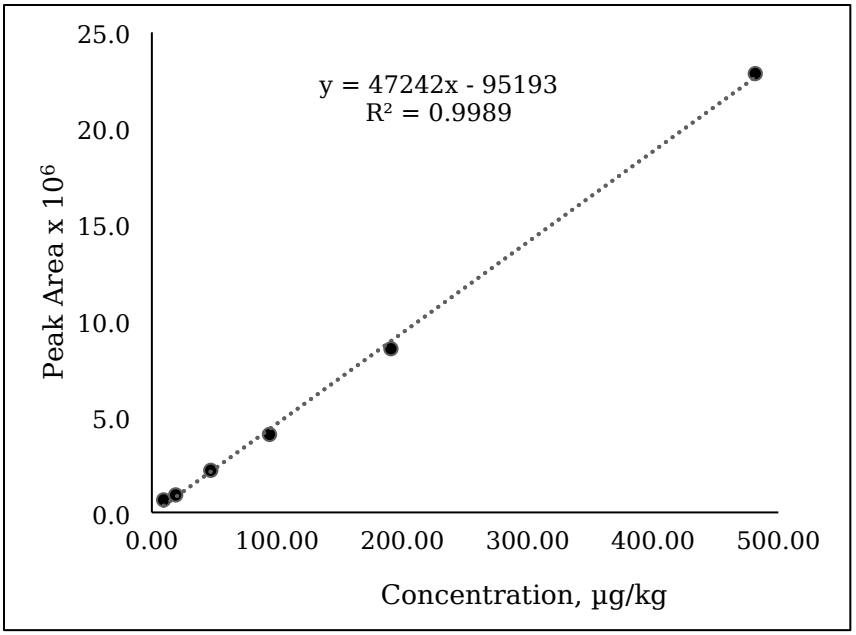
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