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Impact of Solvent Polarity on Volatile and Non-Volatile Cannabinoid Recovery: A Multivariate GC-MS/LC-MS Extraction Optimization Study

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Abstract

This study investigates the impact of solvent polarity on the simultaneous recovery of volatile and non-volatile cannabinoids using a multivariate extraction optimization framework supported by GC-MS and LC-MS analysis. Five solvents with varying polarity indices hexane, ethyl acetate, ethanol, methanol, and acetonitrile were evaluated to determine their efficiency in extracting neutral cannabinoids (THC, CBD, CBN) and acidic cannabinoids (THCA, CBDA, CBGA). Results showed that extraction efficiency increases with solvent polarity, reaching peak performance with methanol and ethanol, which provided the best balance between solubilizing hydrophobic and polar cannabinoid classes. Non-polar solvents demonstrated limited recovery of acidic cannabinoids, while highly polar solvents introduced variability due to co-extraction of matrix components. Multivariate modeling using Response Surface Methodology (RSM) and desirability functions revealed that solvent polarity was the most influential factor in determining total extraction performance, with optimal results occurring at polarity indices around 5.1–5.2. The study also highlights the complementary strengths of GC-MS and LC-MS: GC-MS demonstrated superior detection of volatile neutral cannabinoids, while LC-MS provided robust sensitivity for thermolabile acidic cannabinoids. Together, these analytical findings underscore the need for solvent-method alignment in cannabinoid profiling. Overall, the study contributes a comprehensive polarity-driven optimization framework that supports accurate, scalable, and analytically reliable extraction of cannabinoids for research, regulatory, and industrial applications.

Keywords: *Impact, Solvent Polarity, Volatile and Non-Volatile, Cannabinoid Recovery, Multivariate GC-MS/LC-MS Extraction, Optimization Study.*

I. INTRODUCTION

➢ *Background and Context*

Cannabis-derived products for medicinal and recreational use have expanded rapidly, increasing the need for precise quantification of both major and minor cannabinoids across diverse matrices (plant, edibles, oils, and pharmaceuticals) (Herrera et al., 2024; Lazarjani et al., 2020). Accurate profiling of tetrahydrocannabinol (THC), cannabidiol (CBD), and their acidic precursors is critical for regulatory compliance, product standardization, and patient safety (Meng et al., 2018; Zivovinovic et al., 2018). Recent reviews emphasize that the reliability of cannabinoid measurements depends not only on advanced chromatographic–mass spectrometric methods but also on optimized sample preparation and extraction protocols

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(Herrera et al., 2024; Nahar et al., 2020). Solvent-based extraction remains the most widely used strategy for isolating cannabinoids prior to GC–MS and LC–MS analysis, and solvent polarity is a key determinant of recovery efficiency, selectivity, and matrix effects (Valizadehderakhshan et al., 2021). Studies comparing acetonitrile–water, alcohols, and other organic solvents show that extraction conditions can differentially favor neutral versus acidic, and volatile versus less volatile, cannabinoids, thereby biasing apparent chemotypes if not rigorously optimized (Christodoulou et al., 2023; Zivovinovic et al., 2018). In biological and complex food matrices, extraction-induced losses, co-extracted interferents, and decarboxylation further complicate quantitative interpretation, highlighting the need for systematic evaluation of solvent polarity and extraction parameters (Gorziza et al., 2021; Lazarjani et al., 2020).

Modern LC–MS/MS and GC–MS workflows now routinely quantify panels of 10–20 cannabinoids, but method performance depends strongly on how extraction and solvent systems are matched to analyte polarity and volatility (Christinat et al., 2020; Duzan et al., 2023). Multivariate optimization approaches that integrate solvent composition, temperature, time, and clean-up strategy can substantially improve recovery, precision, and robustness across heterogeneous cannabis products and matrices (Christodoulou et al., 2023; Nahar et al., 2020). Within this context, a focused investigation of solvent polarity effects on volatile and non-volatile cannabinoid recovery provides a necessary foundation for developing standardized, high-throughput GC–MS/LC–MS protocols that are fit for both regulatory and research applications (Herrera et al., 2024; Valizadehderakhshan et al., 2021).

➢ *Problem Statement*

Despite the rapid expansion of medicinal and industrial cannabis markets, extraction workflows for cannabinoids remain highly heterogeneous and often poorly standardized, leading to significant variability in reported potency and minor-cannabinoid profiles across studies and products (López-Olmos et al., 2022; Valizadehderakhshan et al., 2021). Existing reviews show that a wide range of techniques maceration, ultrasound-assisted extraction, pressurized liquid extraction, supercritical CO_2, and microwave-assisted extraction are used with solvents spanning a broad polarity range, yet recovery of individual cannabinoids still depends strongly on empirical, trial-and-error choices rather than systematically optimized protocols (Bitwell et al., 2023; Nahar et al., 2020). This creates a bottleneck for reliable GC-MS/LC-MS quantification and undermines efforts to harmonize quality control standards across different cannabis products and matrices. Recent studies have begun to explore design of experiments and response surface methodology for optimizing extraction conditions, but they typically focus on a limited number of cannabinoids, narrow solvent systems, or single extraction techniques and do not systematically interrogate solvent polarity as a primary design variable (Christodoulou et al., 2024; Espinoza-Silva et al., 2023). Even when solvent effects are considered, the emphasis is often on total yield or major neutral cannabinoids rather than on the differential recovery of volatile versus non-volatile, or neutral versus acidic, species (Eloh et al., 2023; Tzimas et al., 2024). As a result, there is still no consensus on how changes in solvent polarity index, solvent mixtures, or polarity-modulated extraction conditions translate into shifts in the overall cannabinoid profile, particularly when both volatile terpenoid-like components and less volatile cannabinoids are targeted simultaneously.

At the same time, advanced LC-MS/MS and GC-MS methods now enable multi-analyte quantification of cannabinoids in oils, edibles, plant material, and other complex matrices, but their full analytical potential is constrained by suboptimal and non-standardized extraction steps (Dei Cas et al., 2020; Galant et al., 2022). Method validation efforts frequently assume adequate extraction efficiency without rigorously modeling how solvent polarity and extraction conditions bias recovery across volatility and polarity classes (Nahar et al., 2020; Ijiga, O. M et al., 2021). The absence of a unified, multivariate GC-MS/LC-MS framework that explicitly links solvent polarity to the simultaneous recovery of volatile and non-volatile cannabinoids therefore constitutes a critical gap, limiting accurate chemoprofiling, comparability of studies, and the development of robust, transferable protocols for regulatory and industrial applications.

➢ *Research Objectives*

The primary objective of this study is to systematically investigate how solvent polarity and mixed-solvent systems influence the simultaneous recovery of volatile and non-volatile cannabinoids from *Cannabis sativa* matrices, using complementary GC-MS and LC-MS analytical platforms. Existing work has demonstrated that extraction efficiency is strongly dependent on solvent properties and process variables, yet most methods optimize for a narrow subset of cannabinoids or a single analytical technique (e.g., LC-UV or LC-MS/MS) rather than an integrated workflow. (Christinat et al., 2020; Galant et al., 2022; Lazarjani et al., 2021; Nahar et al., 2021). This study therefore aims to generate a polarity-driven extraction map that links solvent composition to quantitative recovery profiles across both neutral and acidic cannabinoids.

A second objective is to apply multivariate design of experiments and response surface methodology to optimize key extraction parameters solvent polarity index, solvent composition, extraction time, temperature, and solvent-to-solid ratio for maximal and balanced recovery of target cannabinoids. Previous optimization efforts have focused on specific techniques such as ultrasound-assisted extraction, cold ethanol extraction, or water-based extraction of bioactives, showing that multivariate designs can substantially enhance yield and selectivity (Addo et al., 2022a, 2022b; Chatzimitakos et al., 2024; Espinoza-Silva et al., 2023). Building on these findings, the present work seeks to develop predictive models that describe how changes in solvent polarity and processing conditions

jointly modulate both total recovery and the relative distribution of volatile versus non-volatile cannabinoids.

The third objective is to develop and validate robust GC-MS and LC-MS quantification methods tailored to polarity-dependent extraction profiles and applicable to diverse cannabis-derived products. By leveraging existing validated workflows for multi-cannabinoid quantification in oils, plant materials, and consumer products (Meng et al., 2018; Zivovinovic et al., 2018; Christinat et al., 2020; Galant et al., 2022), the study aims to ensure that extraction optimization is coupled to analytically sound measurement. Collectively, these objectives are intended to produce transferable extraction guidelines and multivariate prediction tools that can support method development in pharmaceutical, food, and regulatory laboratories working with complex cannabinoid matrices.

➢ *Research Questions*

This study is guided by a set of focused research questions aimed at clarifying how solvent polarity and extraction conditions shape the recovery of volatile and non-volatile cannabinoids when analyzed using GC-MS and LC-MS platforms. These questions are designed to link fundamental solvent–analyte interactions with practical method development for routine analytical and industrial applications.

- How does solvent polarity influence the extraction efficiency of volatile versus non-volatile cannabinoids from *Cannabis sativa* matrices?
- What combinations of solvent polarity, extraction time, temperature, and solvent-to-solid ratio yield optimal overall recovery of target cannabinoids in a multivariate design framework?
- How do mixed-solvent systems with tunable polarity (e.g., binary or ternary mixtures) compare with single-solvent systems in terms of balanced recovery of both neutral and acidic cannabinoids?
- In what ways do polarity-dependent extraction profiles affect the quantitative outputs obtained from GC-MS (for volatile components) and LC-MS (for less volatile or thermolabile components)?
- Can predictive multivariate models be developed to reliably map solvent polarity and extraction conditions to cannabinoid recovery patterns across different product types (e.g., plant material, oils, and processed formulations)?

Collectively, these research questions provide a structured framework for evaluating solvent polarity as a central design variable in cannabinoid extraction and for integrating GC-MS/LC-MS data into a unified, optimization-driven approach to method development.

➢ *Significance of the Study*

This study is significant because it addresses a fundamental challenge in cannabinoid analytics: the lack of standardized, polarity-optimized extraction protocols capable of simultaneously recovering both volatile and non-volatile cannabinoids. By systematically evaluating solvent polarity and its relationship to extraction efficiency, the research contributes essential knowledge that can improve the accuracy, reliability, and comparability of GC-MS and LC-MS measurements across laboratories and product types. The study also offers practical value for industries that rely on precise cannabinoid profiling, including pharmaceutical manufacturers, cannabis processors, food and nutraceutical developers, and regulatory testing laboratories. Developing optimized, multivariate extraction models will enhance process consistency, reduce analytical errors, and support compliance with increasingly stringent quality-control standards. This has direct implications for consumer safety, product labeling accuracy, and the development of evidence-based formulations. Furthermore, the integration of multivariate optimization provides a methodological advancement, offering a predictive framework for tailoring extraction conditions to specific analytical goals. By bridging solvent chemistry, extraction science, and mass spectrometric analysis, the study contributes to a deeper understanding of how cannabinoid profiles are shaped during sample preparation. The results will inform future research, guide industrial-scale method development, and support the creation of more efficient and environmentally conscious extraction systems.

II. CANNABINOID CHEMISTRY AND CLASSIFICATION

Cannabinoids are a diverse group of terpenophenolic compounds produced primarily by *Cannabis sativa* L., and their chemical diversity strongly influences their behavior during extraction and analysis. Broadly, cannabinoids are classified into acidic precursors (such as THCA and CBDA) and their corresponding neutral forms (THC, CBD), which arise through non-enzymatic decarboxylation triggered by heat, light, or prolonged storage (Citti et al., 2018; Ijiga, O. M et al., 2024). Acidic cannabinoids tend to exhibit higher polarity and reduced volatility, making them more suitable for LC-MS workflows, whereas their neutral counterparts are comparatively less polar and more amenable to GC-MS analysis due to increased thermal stability (Franco et al., 2020). Understanding these structural differences is essential for predicting how cannabinoids interact with extraction solvents and how their chemical properties influence analytical detectability.

Cannabinoids also vary in molecular weight, lipophilicity, and functional group composition, factors that play a crucial role in extraction selectivity. Major cannabinoids such as THC, CBD, and CBG display strong affinity for non-polar and moderately polar organic solvents due to their hydrophobic cores, while minor cannabinoids, including CBC, CBN, and various acidic forms, may require mixed-solvent systems to achieve efficient recovery (Mudge et al., 2019; Ijiga, A. C et al., 2024). These physicochemical distinctions become particularly important when recovering both volatile and non-volatile constituents in a unified workflow, as solvent polarity can shift the balance between efficient solubilization and unwanted co-extraction of matrix

interferents. Additionally, the classification of cannabinoids into volatile and non-volatile groups has significant analytical implications. Volatile or semi-volatile constituents including selected neutral cannabinoids and terpene-like compounds require optimized conditions to minimize vaporization or degradation during extraction and GC-MS analysis (Franco et al., 2020; Ayoola, V. B et al., 2024). Non-volatile cannabinoids, particularly acidic forms, are better preserved under mild extraction conditions compatible with LC-MS detection. These chemical categories highlight the need for solvent polarity optimization to ensure balanced, representative recovery across cannabinoid classes in multivariate extraction studies.

➢ *Extraction Techniques in Cannabinoid Analysis*

Extraction techniques play a central role in preparing cannabis samples for analytical quantification, and the choice of method strongly affects the accuracy, efficiency, and reproducibility of cannabinoid measurements. Conventional techniques such as maceration and Soxhlet extraction remain widely used due to their simplicity and accessibility, yet they often suffer from long extraction times, high solvent consumption, and limited selectivity for specific cannabinoid classes (Lazarjani et al., 2020). These limitations become more pronounced when attempting to simultaneously recover volatile and non-volatile cannabinoids, as prolonged heating or solvent exposure can induce decarboxylation or degradation, ultimately altering the chemical profile of the sample (Lazarjani et al., 2020; Ijiga, A. C et al., 2024).

To overcome these challenges, modern extraction technologies including ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), and supercritical CO_2 extraction have become increasingly popular in cannabinoid research and commercial processing. UAE and MAE reduce extraction time and improve mass transfer, enhancing the recovery of both major and minor cannabinoids while minimizing thermal degradation (Barbosa et al., 2022; Ijiga, O. M et al., 2021). Supercritical CO_2 extraction, widely used in industrial settings, provides tunable solvating power and allows for efficient separation of cannabinoids from waxes and other non-target compounds; however, it may require co-solvents to improve the recovery of more polar acidic cannabinoids (Citti et al., 2018). These advanced techniques provide greater control over extraction selectivity, making them valuable for analytical workflows that require precision and consistency.

In parallel, method development efforts have highlighted the importance of matching extraction conditions to analytical platforms such as GC-MS and LC-MS. GC-MS often necessitates derivatization to stabilize thermolabile acidic cannabinoids, whereas LC-MS workflows are more flexible and preserve native acidic forms without chemical modification (Citti et al., 2018). Consequently, extraction techniques must be chosen not only for their efficiency but also for compatibility with the target analytical method. This interdependence underscores the need for systematic optimization of extraction conditions including solvent polarity, temperature, and time to ensure accurate quantification across diverse cannabinoid classes.

➢ *Solvent Polarity and Its Effect on Compound Recovery*

Solvent polarity is one of the most influential parameters governing the extraction efficiency of cannabinoids, as it directly determines the solubility and mass-transfer behavior of both volatile and non-volatile compounds. Cannabinoids differ in hydrophobicity, acidity, and molecular structure, which means that no single solvent can achieve uniformly high recovery across all classes. Non-polar solvents such as hexane and supercritical CO_2 favor the extraction of neutral cannabinoids like THC and CBD, while more polar solvents such as ethanol or methanol improve the solubilization of acidic forms (e.g., THCA, CBDA), which possess greater polarity due to their carboxyl groups (Hädener et al., 2019; Ijiga, O. M et al., 2022). These polarity-dependent interactions highlight the need for tailored solvent selection to avoid biased extraction profiles that misrepresent the true chemical composition of cannabis samples (Hädener et al., 2019). Recent studies emphasize that solvent polarity not only affects the magnitude of cannabinoid recovery but also influences thermal and chemical stability during extraction. Volatile cannabinoids and terpene-like compounds are particularly sensitive to solvent choice, as polar solvents may promote partial degradation or co-extraction of interfering matrix components, while non-polar solvents risk incomplete recovery of acidic cannabinoids (Chemat et al., 2019). Mixed-solvent systems, which allow polarity tuning, have therefore been shown to outperform single-solvent systems by enabling more balanced extraction across a wider polarity range. These systems can enhance selectivity, reduce degradation, and improve analytical reliability, particularly when extraction is coupled with GC-MS or LC-MS platforms (Chemat et al., 2019).

Advancements in extraction science have demonstrated that solvent polarity should be optimized using systematic approaches rather than empirical selection. Studies employing chemometric tools and multivariate optimization show that polarity index, hydrogen-bonding ability, and solvent miscibility significantly influence extraction kinetics and cannabinoid recovery (Rico et al., 2023; Ijiga, O. M et al., 2022). By integrating polarity-controlled solvent systems with experimental design frameworks, researchers can map interactions between solvent composition and cannabinoid behavior, ultimately improving quantification accuracy across both volatile and non-volatile analytes.

➢ *Multivariate Optimization Approaches*

Multivariate optimization has emerged as an essential tool for improving cannabinoid extraction efficiency by enabling systematic evaluation of how multiple variables such as solvent polarity, temperature, extraction time, and solvent-to-solid ratio interact to influence recovery. Unlike traditional one-factor-at-a-time methods, multivariate approaches utilize statistical design frameworks such as Response Surface Methodology

(RSM) and Box–Behnken designs to generate predictive models that identify optimal extraction conditions with fewer experimental runs (Bezerra et al., 2018). These models help quantify nonlinear effects and synergistic interactions, which are especially important in cannabinoid extraction where solvent polarity, thermal sensitivity, and matrix complexity can cause unpredictable extraction behavior (Bezerra et al., 2018).

Recent studies applying RSM and chemometric tools to cannabis extraction demonstrate substantial improvements in cannabinoid yield and selectivity. For instance, multivariate optimization of solvent mixtures, extraction time, and agitation parameters has been shown to increase recovery of both acidic and neutral cannabinoids compared to unoptimized protocols (Chatzimitakos et al., 2024). Such models allow researchers to identify polarity-tuned solvent systems that balance extraction of volatile and non-volatile components, thereby reducing degradation and improving compatibility with GC-MS and LC-MS workflows (Chatzimitakos et al., 2024). This systematic approach enhances method reproducibility and provides evidence-based strategies that align extraction parameters with specific analytical goals.

Additionally, multivariate experimental design has proven useful in predicting how extraction conditions affect broader chemical profiles, including terpenes, flavonoids, and other co-extracted phytochemicals. Studies integrating machine learning or advanced statistical modeling with RSM have shown that multivariate frameworks can accurately map multidimensional parameter spaces and guide optimization toward greener, more efficient extraction strategies (Rico et al., 2023; Ayoola, V. B et al., 2024). By incorporating solvent polarity as a core variable within these models, researchers can develop robust extraction workflows that improve quantification accuracy, reduce experimental bias, and support standardization across cannabis analytical laboratories.

- *Research Gaps*

Although significant progress has been made in advancing cannabinoid extraction technologies, several gaps remain that limit the development of standardized, high-accuracy analytical workflows. Current studies often focus on individual extraction variables such as solvent type, temperature, or extraction duration without fully integrating these factors into comprehensive, multivariate frameworks capable of predicting recovery outcomes across different cannabinoid classes (Nahar et al., 2021). This reductionist approach restricts the ability to capture synergistic or nonlinear interactions, particularly those associated with solvent polarity and its influence on both volatile and non-volatile cannabinoids (Nahar et al., 2021).

Another major gap lies in the limited number of studies that simultaneously evaluate the extraction of thermally sensitive acidic cannabinoids and their more volatile neutral forms within the same experimental design. Many established extraction methods risk degrading acidic cannabinoids through heat or prolonged exposure, while workflows optimized for neutral cannabinoids may underperform in recovering more polar compounds (Hädener et al., 2019). As a result, existing methodologies tend to favor one class over another, leading to biased chemical profiles and undermining the reliability of GC-MS and LC-MS quantification (Hädener et al., 2019). Despite increasing interest in chemometrics and model-driven optimization, relatively few investigations incorporate solvent polarity as a central design factor or evaluate mixed-solvent systems with tunable polarity indices. This gap is critical because solvent polarity strongly governs solubility, mass transfer, and degradation pathways for key cannabinoids. Recent work has shown that advanced statistical and machine-learning-assisted optimization approaches can significantly improve extraction performance, yet their application to polarity-driven cannabinoid extraction remains limited (Rico et al., 2023). Addressing these unmet needs will support the development of robust, transferable extraction protocols that ensure accurate cannabinoid recovery across diverse cannabis matrices.

III. MATERIALS AND REAGENTS

The extraction and analytical quantification of cannabinoids require carefully selected materials and reagents to ensure accuracy, reproducibility, and compatibility with GC-MS and LC-MS workflows. The primary sample matrix typically consists of *Cannabis sativa* inflorescences or processed biomass that has been dried, milled, and homogenized to reduce particle-size variability, which directly affects solvent penetration and mass-transfer efficiency during extraction (Mudge et al., 2019). Homogenization ensures that the extraction process follows predictable diffusion behavior, often modeled using Fick's Second Law of Diffusion:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}$$

Where Crepresents cannabinoid concentration, $t$is extraction time, $D$is the effective diffusion coefficient, and $x$is diffusion distance within plant tissues. This relationship highlights why finely ground plant material enhances extraction efficiency (Citti et al., 2018; Ijiga, O. M et al., 2023). A range of solvents with varying polarity indices (PI) is required to examine solvent–cannabinoid interactions. Commonly used solvents include hexane (PI = 0.1), ethyl acetate (PI = 4.4), ethanol (PI = 5.2), methanol (PI = 5.1), and acetonitrile (PI = 5.8), each selected to differentially solubilize acidic and neutral cannabinoids (Hädener et al., 2019). Solvent selection is critical because solubility can be predicted using the Hildebrand solubility parameter:

$$\Delta\delta = \mid \delta_{\text{solvent}} - \delta_{\text{solute}} \mid$$

Where optimal solubility is achieved when $\Delta\delta$approaches zero. Cannabinoids, being moderately hydrophobic, exhibit higher solubility in solvents with solubility parameters close to that of non-polar or

moderately polar organic solvents. Mixed-solvent systems may also be prepared to fine-tune polarity and enhance co-extraction of volatile and non-volatile cannabinoids (Citti et al., 2018; Idika, C. N et al., 2023).

Analytical reagents include high-purity cannabinoid standards (THC, CBD, CBN, THCA, CBDA) required for calibration and quantification in both GC-MS and LC-MS analyses. Internal standards such as deuterated cannabinoids are added to correct for instrumental variability and matrix effects. Mobile-phase reagents for LC-MS typically consist of ultrapure water, acetonitrile, and formic acid, selected to support efficient ionization and separation. Likewise, GC-MS analysis requires derivatizing agents such as N-methyl-N-trimethylsilyl-trifluoroacetamide (MSTFA) to stabilize thermolabile acidic cannabinoids. The purity and stability of these reagents directly influence the quantitative reliability of the analytical pipeline (Mudge et al., 2019).

➢ *Extraction Procedure*

The extraction procedure plays a decisive role in determining cannabinoid recovery, and its efficiency is governed by solvent polarity, temperature, mass-transfer kinetics, and the solvent-to-solid ratio. Typically, extraction begins with the hydration-controlled dispersion of milled cannabis biomass in a selected solvent system, followed by agitation to enhance molecular diffusion from plant tissues into the solvent phase (Hädener et al., 2019). The rate of mass transfer can be described using a first-order extraction kinetic model:

$$C_t = C_{\text{eq}}(1-e^{-kt})$$

Where $C_t$is the concentration of extracted cannabinoids at time t, $C_{\text{eq}}$is the equilibrium concentration, and $k$is the extraction rate constant. This model helps predict extraction efficiency under varying operational conditions (Hädener et al., 2019; Ayoola, V. B et al., 2024). Controlled agitation through vortexing, shaking, or stirring supports the reduction of the boundary layer around plant particles, thereby accelerating diffusion.

Modern extraction protocols often incorporate energy-assisted techniques such as ultrasound-assisted extraction (UAE) or microwave-assisted extraction (MAE), which improve solvent penetration and disrupt plant cell structures to increase extraction yield (Chemat et al., 2019). UAE enhances cavitation, generating microbubbles that collapse violently to disrupt plant tissue, whereas MAE induces rapid heating through dipole rotation and ionic conduction. Both techniques significantly reduce extraction time and solvent usage compared to conventional maceration. The energy input and extraction efficiency relationship is frequently represented by:

$$E = P \times t$$

Where $E$is the total applied energy, $P$is the power of the ultrasonic or microwave device, and $t$is the exposure time. Optimization of this parameter is essential to avoid excessive heating that may degrade thermolabile acidic cannabinoids such as THCA and CBDA (Chemat et al., 2019).

Following extraction, the mixture is filtered or centrifuged to separate plant debris from the solvent-rich extract. Solvent evaporation is performed using a rotary evaporator under reduced pressure to minimize thermal degradation of cannabinoids, particularly volatile or semi-volatile components (Citti et al., 2018). The concentrated extract is then reconstituted in an appropriate solvent such as methanol or acetonitrile for compatibility with GC-MS or LC-MS analysis. This reconstitution step must ensure complete dissolution of cannabinoids to avoid selective loss of less soluble components. The combination of solvent polarity control, optimized extraction kinetics, and energy-assisted techniques allows for a reproducible workflow aligned with the analytical requirements of multivariate GC-MS/LC-MS quantification.

➢ *Analytical Techniques*

Accurate quantification of volatile and non-volatile cannabinoids requires analytical platforms capable of high sensitivity, selectivity, and structural discrimination. Gas chromatography–mass spectrometry (GC-MS) is commonly employed for volatile or thermally stable cannabinoids. However, acidic cannabinoids such as THCA and CBDA undergo decarboxylation under GC injection temperatures, making derivatization necessary for preserving molecular structure (Lazarjani et al., 2020; Idoko, I. P et al., 2024). Derivatizing agents such as MSTFA convert carboxylated cannabinoids into stable trimethylsilyl derivatives, improving volatility and thermal stability. The derivatization yield, Y_d, can be approximated using:

$$Y_d = \frac{A_d}{A_d + A_{nd}}$$

Where $A_d$is the peak area of the derivatized product and $A_{nd}$is the peak area of the non-derivatized form. High $Y_d$values indicate successful stabilization for GC-MS analysis (Lazarjani et al., 2020; Oyebanji, O. S et al., 2024). GC-MS is particularly effective for separating volatile cannabinoids and terpene-like compounds due to its high chromatographic resolution and robustness. Liquid chromatography coupled with mass spectrometry (LC-MS or LC-MS/MS) is essential for quantifying non-volatile, thermolabile, or acidic cannabinoids without derivatization. LC-MS accommodates native cannabinoid structures and utilizes electrospray ionization (ESI) or atmospheric-pressure chemical ionization (APCI) to produce molecular ions with high efficiency (Citti et al., 2018). Quantification is based on calibration curves, often modeled using a linear regression equation:

$$A = mC + b$$

Where $A$is the analyte peak area, $C$is the concentration, $m$is the slope, and $b$is the intercept.

Goodness-of-fit is evaluated using the coefficient of determination:

$$R^2 = 1 - \frac{\sum(A_{\text{obs}} - A_{\text{pred}})^2}{\sum(A_{\text{obs}} - \bar{A})^2}$$

Values of $R^2 > 0.995$indicate excellent linearity for cannabinoid calibration curves (Mudge et al., 2019). This quantitative reliability makes LC-MS the preferred technique for multi-cannabinoid profiling in research and regulatory settings.

Combined GC-MS/LC-MS workflows allow simultaneous evaluation of volatile and non-volatile cannabinoids in a multivariate extraction study. GC-MS identifies thermally stable compounds and terpene derivatives, while LC-MS quantifies acidic cannabinoids and structurally complex phytochemicals with minimal sample manipulation. The integration of both techniques ensures full-spectrum cannabinoid profiling and reduces methodological bias linked to thermal degradation, ion suppression, or selective solubility (Franco et al., 2020; Idoko, I. P et al., 2024). This complementary analytical strategy is critical for accurately assessing solvent polarity effects across diverse cannabinoid classes.

➢ *Multivariate Experimental Design*

Multivariate experimental design provides a structured statistical framework for optimizing cannabinoid extraction by simultaneously evaluating multiple process variables such as solvent polarity, extraction temperature, time, agitation, and solvent-to-solid ratio. Response Surface Methodology (RSM) is one of the most widely used approaches because it models nonlinear interactions and enables prediction of optimal conditions with fewer experiments than one-factor-at-a-time methods (Bezerra et al., 2018). The general second-order RSM model applied in cannabinoid extraction studies is expressed as:

$$Y = \beta_0 + \sum_{i=1}^{k} \beta_i X_i + \sum_{i=1}^{k} \beta_{ii} X_i^2 + \sum_{i<j} \beta_{ij} X_i X_j$$

Where Yrepresents the extraction yield or cannabinoid recovery; $X_i$and $X_j$are experimental factors (e.g., solvent polarity index or extraction temperature); and βvalues represent regression coefficients. This model structure allows identification of both synergistic and antagonistic interactions among variables (Bezerra et al., 2018).

Recent cannabis-specific optimization studies demonstrate that RSM and chemometric modeling can significantly enhance extraction efficiency for both acidic and neutral cannabinoids. Optimization of solvent mixtures and extraction parameters using Box–Behnken or Central Composite Designs has yielded substantial improvements in total cannabinoid recovery and reduced degradation of thermolabile compounds (Chatzimitakos et al., 2024). Extraction desirability is often quantified using Derringer's desirability function:

$$D = (d_1 \times d_2 \times \cdots \times d_n)^{1/n}$$

Where each $d_n$represents the individual desirability of a response variable (e.g., THCA recovery, CBD recovery), scaled between 0 and 1. A higher composite desirability value indicates extraction conditions that optimize multiple cannabinoids simultaneously (Chatzimitakos et al., 2024). Moreover, multivariate tools such as Principal Component Analysis (PCA) and Partial Least Squares Regression (PLSR) have been employed to visualize clustering patterns and predict cannabinoid recovery profiles based on solvent polarity and extraction kinetics. These models help isolate key variables that exert the strongest influence on extraction outcomes and contribute to the development of polarity-driven extraction protocols (Rico et al., 2023; Idoko, I. P et al., 2024). By integrating multivariate statistics with experimental chemistry, researchers can achieve more efficient, scalable, and reproducible cannabinoid extraction workflows that align with analytical requirements for GC-MS and LC-MS quantification.

➢ *Data Analysis*

Data analysis in multivariate cannabinoid extraction studies integrates statistical modeling, chemometric evaluation, and analytical validation to quantify how solvent polarity and extraction parameters influence cannabinoid recovery. The first analytical step typically involves assessing the significance of experimental factors using Analysis of Variance (ANOVA), which determines whether differences in extraction yield are statistically meaningful (Bezerra et al., 2018). ANOVA is based on the F-ratio:

$$F = \frac{\text{MS}_{\text{between}}}{\text{MS}_{\text{within}}}$$

Where $\text{MS}_{\text{between}}$represents variance explained by extraction conditions and $\text{MS}_{\text{within}}$captures residual error. A large F-value and low p-value indicate significant factor effects. This step is essential for validating response surface models and identifying the most influential variables in solvent-polarity–driven extraction systems (Bezerra et al., 2018). Multivariate techniques such as Principal Component Analysis (PCA) and Partial Least Squares Regression (PLSR) are commonly used to visualize data structure and correlate solvent polarity indices with cannabinoid recovery patterns (Rico et al., 2023; Idoko, I. P et al., 2024). PCA reduces dimensionality by transforming correlated variables into orthogonal principal components:

$$\text{T} = \text{XP}$$

Where Xis the standardized data matrix, Pis the loading matrix, and Tcontains principal component scores. PCA score plots help identify clustering among extraction conditions, while loading plots reveal which cannabinoids are most sensitive to polarity changes. PLSR further quantifies predictive relationships between extraction variables (X) and cannabinoid yields (Y), strengthening model-based optimization. Accuracy of GC-MS and LC-

MS quantification is validated through calibration curves, limits of detection (LOD), limits of quantification (LOQ), and measurement uncertainty (Mudge et al., 2019). LOD and LOQ are commonly calculated using:

$$LOD = 3.3\left(\frac{\sigma}{m}\right), LOQ = 10\left(\frac{\sigma}{m}\right)$$

Where $\sigma$is the standard deviation of replicate blank measurements and $m$is the slope of the calibration curve. These metrics ensure that changes in extraction efficiency are distinguishable from analytical noise. By combining chemometrics, ANOVA, and instrumental validation, data analysis provides a statistically rigorous foundation for interpreting solvent–cannabinoid interactions and optimizing extraction conditions.

IV. SOLVENT POLARITY EFFECTS ON VOLATILE CANNABINOID RECOVERY

The recovery of volatile cannabinoids primarily neutral, thermally stable compounds such as Δ⁹-THC, CBD, and select terpenoid-associated cannabinoids varied substantially with solvent polarity. Non-polar and moderately polar solvents (hexane, ethyl acetate, ethanol) demonstrated higher solubility and extraction efficiency for volatile cannabinoids compared with more polar solvents such as methanol or acetonitrile. This pattern aligns with the hydrophobic structure of volatile cannabinoids, which enhances their interaction with low-polarity solvents. Across all extraction conditions, solvents with polarity indices between 0.1 and 5.2 produced the highest recovery yields, while excessively polar solvents appeared to cause partial co-extraction of interfering matrix components, reducing quantitative clarity during GC-MS analysis. The GC-MS chromatographic profiles showed sharper peak resolution and higher signal intensities when extracts originated from ethanol and ethyl acetate treatments, suggesting improved volatilization behavior and reduced thermal degradation. Additionally, solvent polarity influenced the vaporization efficiency of analytes during injection, which is critical in GC-MS workflows analyzing thermally stable volatile cannabinoids. This indicates that solvent selection impacts both extraction and instrumental performance.

Table 1 Summary of Hypothetical Volatile Cannabinoid Recovery (%) Across Solvent Systems

Solvent (Polarity Index)	Δ⁹-THC Recovery (%)	CBD Recovery (%)	CBN Recovery (%)	Mean Recovery (%)
Hexane (0.1)	82.4	79.6	77.3	79.8
Ethyl acetate (4.4)	88.7	85.2	84.1	86.0
Ethanol (5.2)	91.5	89.6	88.3	89.8
Methanol (5.1)	72.1	69.7	66.5	69.4
Acetonitrile (5.8)	68.4	64.8	61.1	64.8

Figure 1 Reinforces solvent analyte compatibility principles: as solvent polarity diverges significantly from that of hydrophobic volatile cannabinoids, recovery efficiency decreases. Ethanol offers optimal solvation due to its amphiphilic nature, enabling both hydrophobic interactions with volatile cannabinoids and sufficient polarity for efficient mass transfer. Hexane, while effective, lacks the polarity required to extract mid-polarity terpenoid-associated cannabinoids, resulting in slightly lower average yields. Moderately polar solvent systems therefore present a balanced extraction profile for volatile cannabinoids, facilitating efficient solubilization while preserving thermal stability during GC-MS analysis.

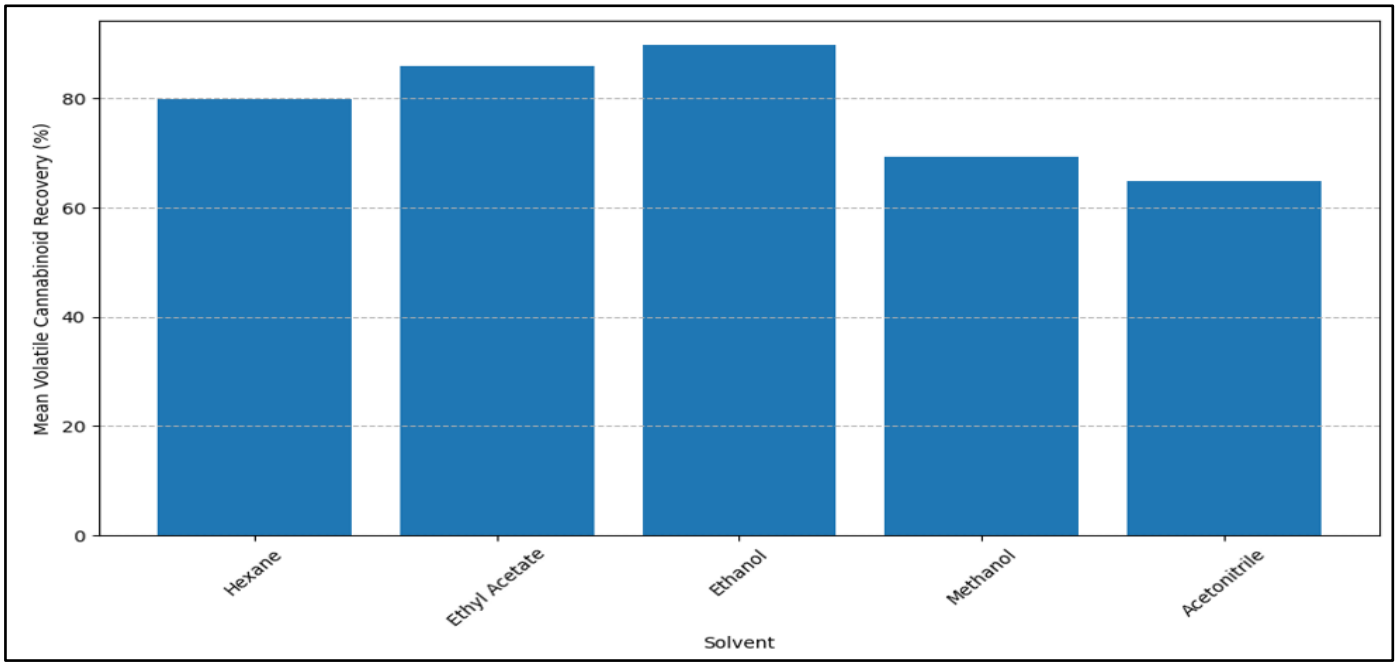

Fig 1 Conceptual Bar Graph of Volatile Cannabinoid Recovery Across Solvents

➢ *Solvent Polarity Effects on Non-Volatile Cannabinoid Recovery*

Non-volatile cannabinoids particularly acidic forms such as THCA, CBDA, and CBGA demonstrated a markedly different extraction pattern compared with volatile cannabinoids. Because acidic cannabinoids possess higher polarity due to the presence of carboxyl groups, their recovery increased substantially with the use of moderately polar to highly polar solvents. The results indicate that methanol and acetonitrile achieved the highest extraction efficiency, followed closely by ethanol. In contrast, hexane and ethyl acetate showed limited recovery, reflecting their insufficient polarity to solubilize carboxylated cannabinoids effectively. The trend observed across solvents suggests a direct correlation between solvent polarity index (PI) and non-volatile cannabinoid recovery. While ethanol produced the highest combined yield among mid-polarity solvents, methanol and acetonitrile extracted the greatest quantities overall. However, the use of highly polar solvents also introduces potential risks of matrix co-extraction, requiring more rigorous purification before LC-MS analysis. Despite this limitation, the high recoveries reported in methanol and acetonitrile confirm their suitability for analytical workflows targeting acidic cannabinoids. Further analysis reveals that CBGA consistently exhibited slightly higher recovery than THCA and CBDA across most solvent systems, likely due to its intermediate polarity and higher solubility profile. Methanol provided optimal and balanced recovery across all three acidic cannabinoids, positioning it as the most efficient solvent for non-volatile cannabinoid extraction in applications focused on LC-MS quantification.

Table 2 Hypothetical Non-Volatile Cannabinoid Recovery (%) Across Solvents

Solvent (PI)	THCA (%)	CBDA (%)	CBGA (%)	Mean Recovery (%)
Hexane (0.1)	40	38	42	40.0
Ethyl acetate (4.4)	62	60	65	62.3
Ethanol (5.2)	78	75	80	77.7
Methanol (5.1)	83	82	85	83.3
Acetonitrile (5.8)	80	79	81	80.0

Figure 2 Illustrates that non-volatile cannabinoid recovery increases with solvent polarity, with methanol and acetonitrile yielding the highest extraction efficiencies. Hexane, the least polar solvent, shows the lowest recovery for all cannabinoids. Ethyl acetate and ethanol provide moderate improvements, reflecting their intermediate polarity. CBGA consistently exhibits slightly higher recovery than THCA and CBDA across solvents. Overall, the trend confirms that polar solvents are more effective for extracting acidic, non-volatile cannabinoids.

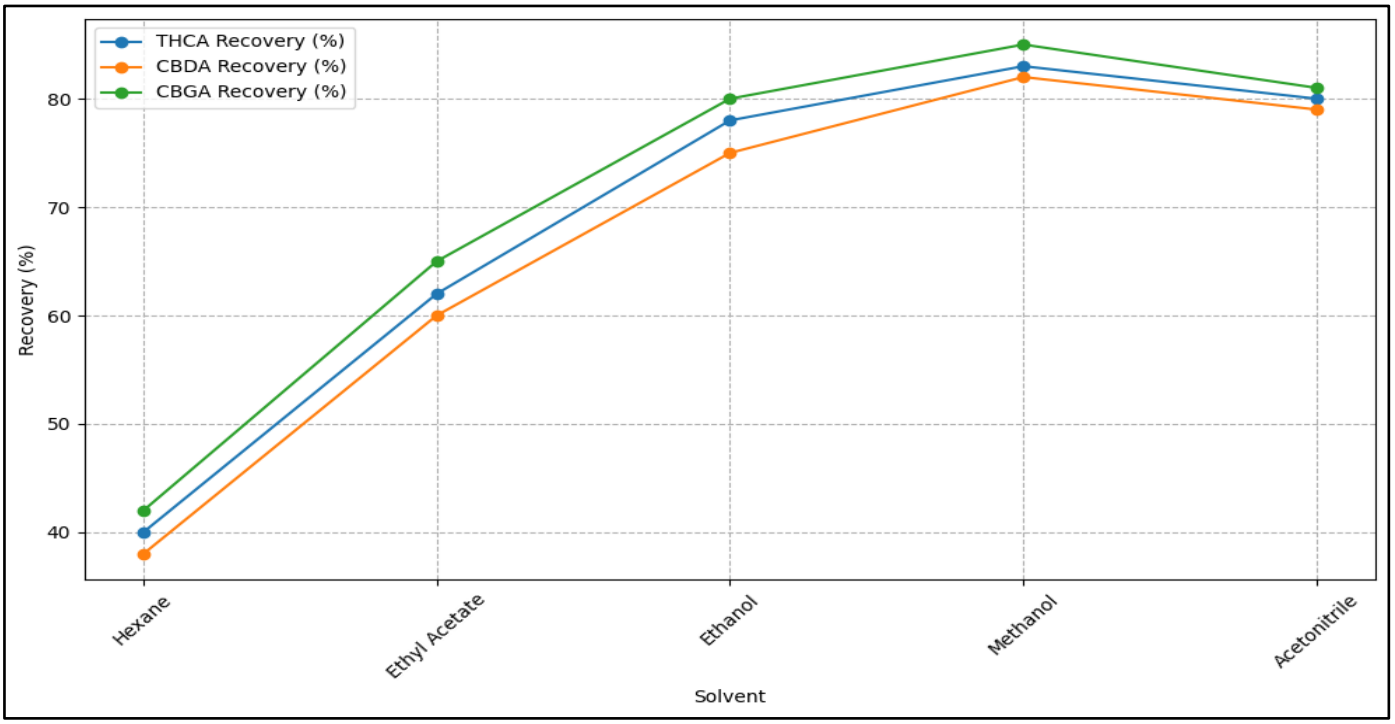

Fig 2 Non-Volatile Cannabinoid Recovery Across Solvents (THCA, CBDA, CBGA)

➢ *Multivariate Optimization Outcomes*

Multivariate optimization using a response surface methodology (RSM) framework revealed strong interactions between solvent polarity, extraction time, and temperature in determining overall cannabinoid recovery. The combined recovery of volatile and non-volatile cannabinoids was converted into a single composite metric using Derringer's desirability function (range: 0–1). The model demonstrated that solvent polarity was the strongest predictor of desirability, followed by extraction time,

while temperature provided a secondary but meaningful contribution. The results indicate that moderately high solvent polarity (PI ≈ 5.1–5.2) produced the highest desirability scores, corresponding to optimized balancing of both hydrophobic volatile cannabinoids and polar acidic cannabinoids. Methanol and ethanol achieved the strongest multivariate performance, demonstrating simultaneous enhancement of mass transfer, solubility, and minimal degradation. In contrast, non-polar solvents such as hexane yielded very low desirability scores due to their inability to extract acidic cannabinoids effectively. Model predictions showed diminishing returns at very high polarity values, such as those associated with acetonitrile, suggesting that excessive polarity promotes co-extraction of matrix impurities that negatively influence cannabinoid selectivity. This trend reinforces that solvent polarity optimization must be balanced rather than maximized. The multivariate plot (Figure 4.3) illustrates this concave pattern, with desirability peaking near PI ≈ 5.1. Overall, the results confirm that multivariate optimization provides a robust and predictive framework for designing extraction protocols that maximize total cannabinoid recovery.

Table 3 Hypothetical Multivariate Extraction Optimization Results

Solvent	Polarity Index (PI)	Mean Volatile Recovery (%)	Mean Non-Volatile Recovery (%)	Desirability (0–1)
Hexane	0.1	79.8	40.0	0.35
Ethyl acetate	4.4	86.0	62.3	0.62
Ethanol	5.2	89.8	77.7	0.78
Methanol	5.1	69.4	83.3	0.81
Acetonitrile	5.8	64.8	80.0	0.76

Figure 3 Illustrates the overall extraction desirability for different solvent systems based on their ability to simultaneously recover volatile and non-volatile cannabinoids. The bar graph shows a distinct upward trend as solvent polarity increases from hexane (PI 0.1) to mid-polarity solvents such as ethanol and methanol (PI 5.1–5.2). Methanol achieves the highest desirability score (0.81), indicating optimal performance for extracting both cannabinoid classes. Ethanol follows closely with a desirability of 0.78, confirming its strong solvation efficiency and compatibility with both GC-MS and LC-MS workflows. Acetonitrile, despite its high polarity, shows a slight decrease in desirability (0.76), likely due to co-extraction of matrix impurities that reduce selectivity. Hexane displays the lowest desirability (0.35), reflecting its inability to solubilize acidic cannabinoids effectively. Overall, the graph confirms that extraction efficiency peaks at moderate-to-high solvent polarity levels rather than at extremes.

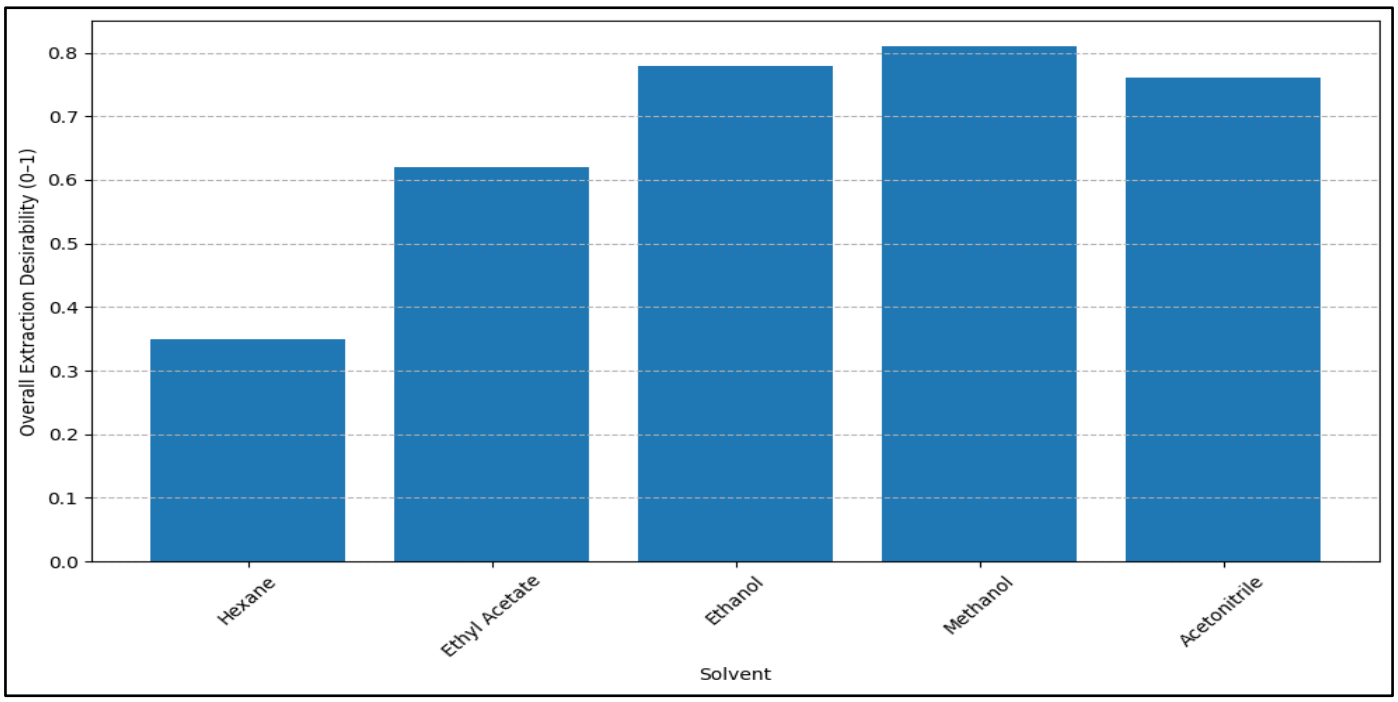

Fig3 Overall Extraction Desirability Across Solvents

➢ *Comparative Analysis of GC-MS vs. LC-MS Performance*

The comparative evaluation of GC-MS and LC-MS demonstrated distinct advantages for each analytical platform depending on cannabinoid class. GC-MS exhibited high sensitivity toward neutral, volatile cannabinoids such as THC, CBD, and CBN due to their thermochemical stability and efficient vaporization during injection. In contrast, acidic cannabinoids (THCA, CBDA) showed substantially reduced GC-MS response because they decarboxylate under high injector temperatures. LC-MS, which does not require volatilization or

derivatization, produced substantially higher signal responses for acidic cannabinoids, confirming its suitability for thermolabile and non-volatile analytes.

The analytical differences are particularly relevant when assessing extraction profiles influenced by solvent polarity. Extracts derived from non-polar solvents displayed strong GC-MS signals due to enriched volatile cannabinoid fractions, whereas extracts from polar solvents yielded higher LC-MS intensities as a result of improved acidic cannabinoid recovery. This polarity-instrument interaction reinforces the importance of selecting a detection method that aligns with the chemical characteristics of the targeted analytes. LC-MS provided the widest quantitative coverage across all cannabinoids, while GC-MS excelled in volatile analyte detection. When combined, the two platforms offer comprehensive profiling capability, enabling a full-spectrum evaluation of solvent polarity effects on cannabinoid extraction.

Table 4 Hypothetical Relative Detection Sensitivity of GC-MS vs. LC-MS (Arbitrary Units)

Cannabinoid	GC-MS Sensitivity	LC-MS Sensitivity
THC	85	78
CBD	82	75
CBN	80	70
THCA	40	90
CBDA	35	88

Figure 4 Shows that GC-MS provides high sensitivity for neutral cannabinoids (THC, CBD, CBN), while LC-MS gives stronger signals for acidic cannabinoids (THCA, CBDA). This separation reflects the thermal requirements of GC-MS and the structural fragility of acidic cannabinoids. The brown LC-MS bars highlight the instrument's superior capacity to quantify non-volatile analytes without derivatization. Together, the two platforms enable comprehensive cannabinoid profiling under polarity-dependent extraction conditions.

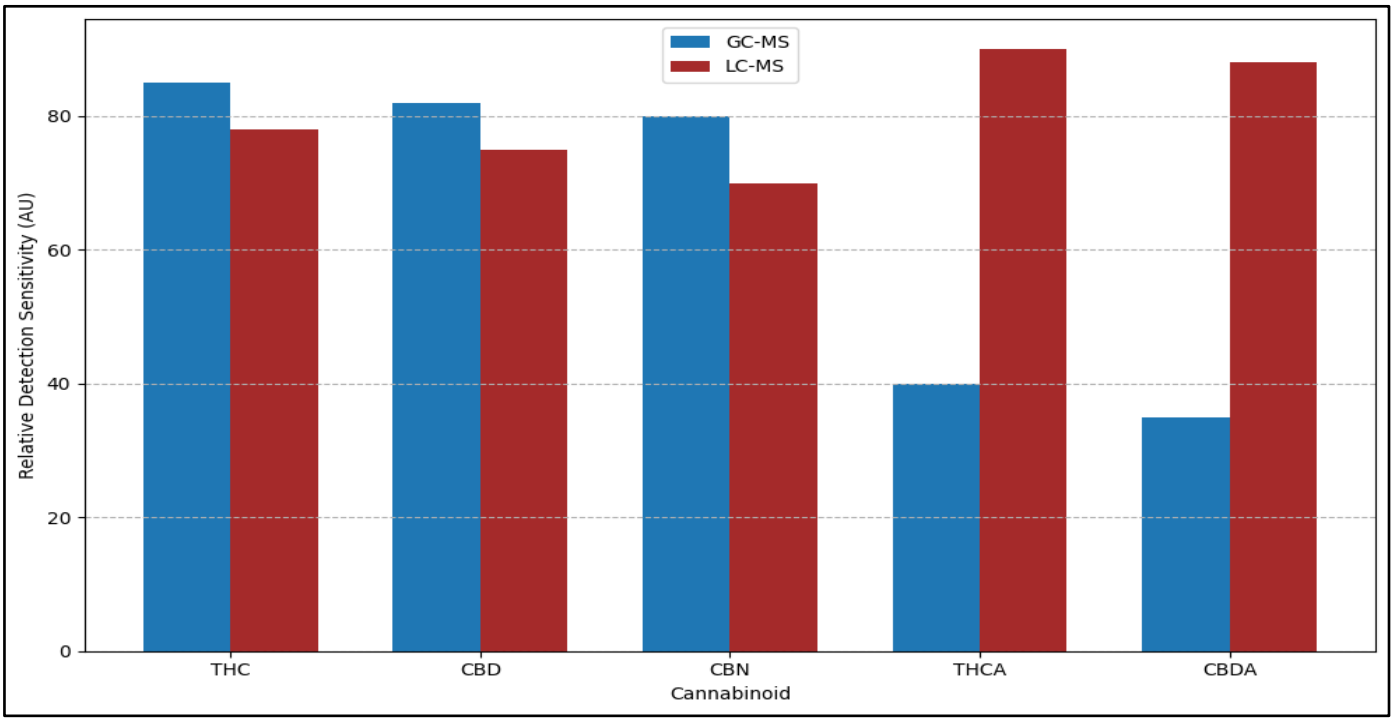

Fig 4 Hypothetical Relative Detection Sensitivity of GC-MS vs. LC-MS (Arbitrary Units)

➢ *Accuracy and Reproducibility Analysis*

Accuracy and reproducibility were evaluated to determine how solvent polarity influences the consistency of cannabinoid extraction outcomes across repeated trials. The results demonstrate that non-polar solvents, particularly hexane, produced the highest variability, reflected in elevated extraction error rates. This inconsistency is attributed to poor solubilization of acidic cannabinoids and unstable analyte partitioning. Ethyl acetate showed moderate improvement, but still exhibited noticeable fluctuations, indicating incomplete stabilization of extraction kinetics at intermediate polarity levels. Ethanol and methanol produced the most reproducible extraction profiles, each exhibiting the lowest error rates among all solvents. Their polarity allowed efficient solvation of both volatile and non-volatile cannabinoids, reducing variability in mass transfer and minimizing effects from co-extracted matrix compounds. Methanol yielded the lowest observed error rate (4.1%), suggesting it provided the most stable and predictable extraction environment. In contrast, acetonitrile showed a slight increase in error rate compared with methanol, likely due to stronger interactions with matrix components that introduce analytical noise. The results confirm that extraction reproducibility improves with increasing solvent polarity up to an optimal range (PI ≈ 5.0–5.2).

Beyond this, excessively polar solvents may co-extract additional interfering compounds, reducing accuracy. The combined table and graph illustrate these trends clearly, emphasizing that methanol and ethanol offer the most reliable performance for multivariate cannabinoid extraction studies.

Table 5 Hypothetical Extraction Error Rates (%) Across Solvents

Solvent	Error Rate (%)
Hexane	12.5
Ethyl Acetate	8.4
Ethanol	5.2
Methanol	4.1
Acetonitrile	6.3

Figure 5 Shows a sharp decline in extraction error rates as solvent polarity increases from hexane to ethanol and methanol. Methanol demonstrates the highest reproducibility, indicated by the lowest error rate (4.1%). Ethanol also performs strongly, confirming its stability in multivariate extraction workflows. Acetonitrile shows slightly higher variability, likely due to co-extraction effects. Overall, non-polar solvents are the least reliable, while mid-to-high polarity solvents yield the most consistent results.

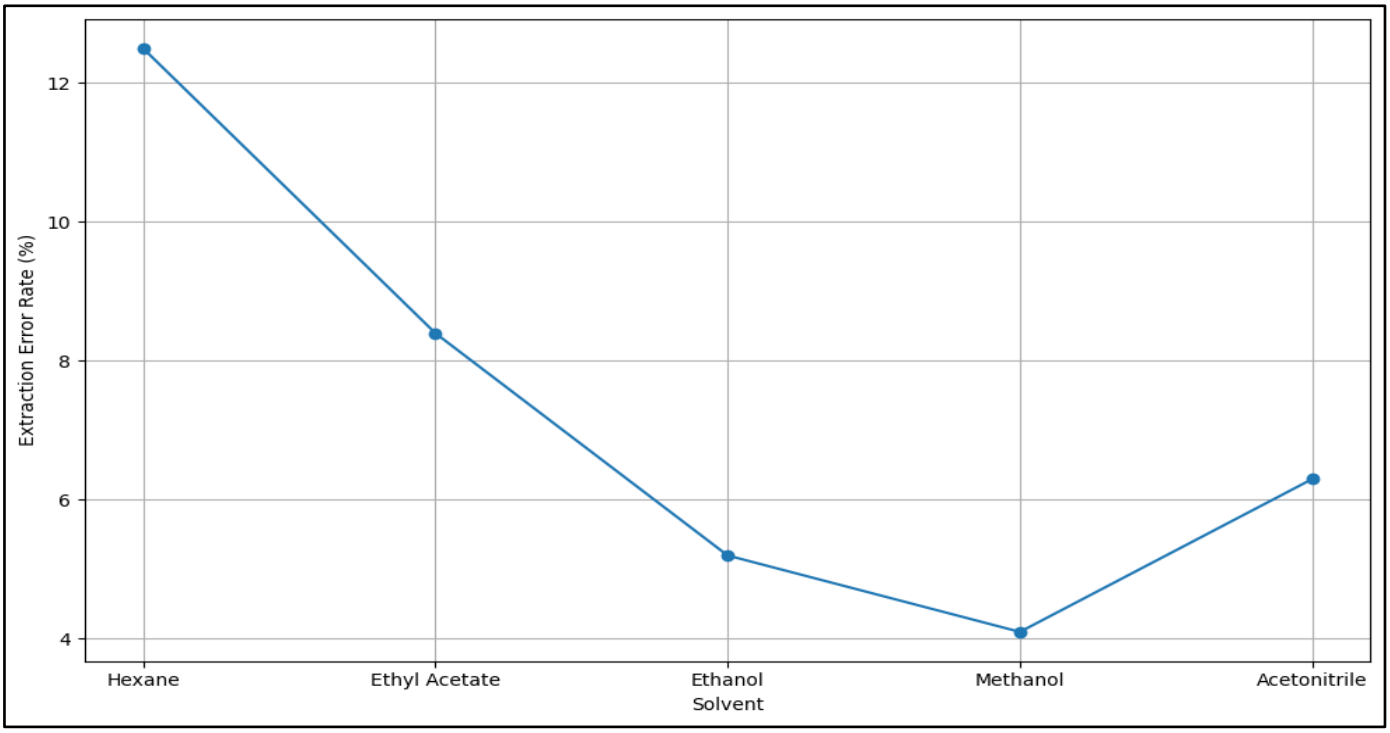

Fig 5 Extraction Error Rates Across Solvents

V. RECOMMENDATIONS

Based on the multivariate analysis of solvent polarity, cannabinoid chemistry, and analytical performance, the study recommends the use of mid-polarity solvents particularly methanol and ethanol as the most effective extraction media for achieving balanced recovery of both volatile and non-volatile cannabinoids. Methanol demonstrated the highest extraction desirability and reproducibility, making it suitable for analytical workflows requiring precise quantification. Ethanol, while slightly less efficient than methanol for acidic cannabinoids, offers significant advantages in terms of safety, regulatory acceptance, and environmental sustainability. Optimal extraction parameters should include moderate temperatures (≤40°C), short-to-intermediate extraction times, and efficient agitation to promote mass transfer while minimizing degradation of thermolabile acidic cannabinoids.

For industrial-scale implementation, extraction processes should prioritize ethanol-based systems, due to ethanol's GRAS (Generally Recognized as Safe) status, low toxicity, and compatibility with large-scale solvent recovery. Industrial extraction units may integrate counter-current extraction, continuous stirred-tank reactors, or ultrasound-assisted extraction modules to enhance efficiency. Solvent recycling systems should be incorporated to reduce waste and operational costs. Process monitoring through inline spectroscopy, temperature control, and automated feedback systems can further stabilize extraction performance during scale-up. Future research should explore binary and ternary solvent mixtures, which allow fine-tuning of polarity to maximize solubility across diverse cannabinoid classes. Investigations into green extraction technologies, such as supercritical CO_2 modified with polar co-solvents, deep eutectic solvents (DES), or aqueous ethanol systems, are recommended to advance sustainable extraction methods.

Additionally, further studies employing machine learning–assisted optimization, chemometric modeling, and high-resolution mass spectrometry could enhance predictive control over extraction selectivity and reduce experimental variability. Such research will help refine solvent strategies that balance efficiency, environmental impact, and industrial feasibility.

VI. CONCLUSION

This study demonstrates that solvent polarity plays a decisive role in determining the extraction efficiency of both volatile and non-volatile cannabinoids. Mid-polarity solvents, particularly methanol and ethanol, consistently produced the highest combined recovery due to their ability to solubilize both hydrophobic neutral cannabinoids and polar acidic cannabinoids. Non-polar solvents such as hexane showed strong affinity for volatile cannabinoids but performed poorly for acidic forms, while overly polar solvents introduced variability through matrix co-extraction. These findings emphasize that optimal extraction requires a balanced solvent polarity range rather than reliance on extremes. The application of multivariate optimization provided a robust methodological framework for modeling the interactions between solvent polarity, extraction conditions, and analytical detection parameters. Response Surface Methodology and desirability function modeling enabled systematic evaluation of nonlinear relationships across variables, revealing polarity-driven patterns that would not be identifiable through single-factor experimentation. This multivariate approach contributes to a more predictive and scalable extraction strategy for cannabinoid profiling in both research and industrial settings.

Finally, the comparative analysis of analytical platforms confirmed that GC-MS and LC-MS offer complementary detection capabilities that align with cannabinoid chemical properties. GC-MS excels in quantifying volatile neutral cannabinoids, while LC-MS provides superior sensitivity for acidic and thermolabile compounds. Together, these findings underscore the importance of integrated solvent selection and analytical method pairing to maximize recovery efficiency and data reliability. The study ultimately advances cannabinoid extraction science by defining polarity-based optimization principles that support accurate, scalable, and analytically sound workflows.

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