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A Green HPLC-PDA Approach for Screening and Quantification for Undeclared Pharmaceuticals alongside Curcumin in Herbal Diabetic Remedies to Assess Herbal Hazards

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Abstract
Herbal supplements are widely used for diabetes management due to their perceived safety and natural origin. However, concerns have arisen regarding the adulteration of these products with synthetic additives and pharmaceuticals. This study aimed to investigate the concentration of curcumin and the presence of undeclared synthetic antidiabetic drugs in commercial herbal supplements used for diabetes.HPLC-PDA method was developed and validated for the determination of pioglitazone, gliclazide, dapagliflozin, and curcumin. Chromatographic separation was performed on a BDS C8 column (150 × 4.6 mm, 5 µm) using a mobile phase composed of 0.03 M ammonium formate buffer (pH 3, adjusted with trifluoroacetic acid) and methanol in 48:52 (v/v) at a flow rate of 1.5 mL/min. The method greenness was tested before application. The detection wavelengths were set at 225 and 430 nm. The method was applied to ten herbal antidiabetic supplements that were randomly obtained from local markets.The method showed excellent linearity ($r^2 \geq 0.9996$) across the range of 0.5-50 µg/mL for all tested drugs, with LODs ranging from 0.16-0.24 µg/mL and LOQs from 0.31-0.47 µg/mL. Precision (intra- and inter-day RSD%) was <2%, and mean accuracy ranged from 99.37% to 100.76%. Among the ten samples tested, CUR was detected in three samples at a concentration of (3.61 – 4.74 µg/mL). Only one of these ten samples contained an undeclared synthetic antidiabetic drug. Finally, the greenness assessment of the method was assessed by NEMI, Complex GAPI, Eco-scale, and Agree tool, where the results indicated that the developed method was green. In conclusion, the validated HPLC-PDA method provides a trustworthy instrument for regular herbal antidiabetic treatments, highlighting the necessity of more stringent quality assurance and obtaining products from authorized producers.

Keywords: Herbal supplement, HPLC-PDA, Adulteration, Antidiabetic drug, Herbal adulteration, Antidiabetic herbs, Curcumin, Greenness assessment.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic condition marked by elevated blood glucose levels and reduced insulin sensitivity. Over time, it can lead to progressive β-cell dysfunction, increasing the risk of cardiovascular, renal, and other systemic complications [1, 2] . In 2019, the World Health Organization (WHO) reported that diabetes was one of the top ten causes of death globally, responsible for around 1.6 million deaths worldwide [3].

Nowadays, herbal medicines (HMs) are increasingly used in diabetes management, being perceived as safer alternatives to conventional drugs [4, 5]. This is especially true in the Arab world where the research reported that up to 80% of individuals in the Arab countries use HMs for managing or preventing common health conditions [6-9]. In the Middle East, the market alone surpassed USD 8 billion in 2022 and continues to grow [10]. A recent cross-sectional study at Tanta University Hospitals (Egypt) reported that 59.6% of patients used complementary and alternative medicine (CAM) in the past year, with herbal products being the most common form (78.4%) [11]. Despite their popularity, HMs face major challenges of standardization and purity.

Among the most utilized HMs is curcumin (CUR). It possesses anti-inflammatory, antioxidant, and hypoglycemic properties, making it a promising complementary therapy for T2DM [12]. A study in mouse models demonstrated that high oral doses of CUR were well tolerated and improved glycemic control and inflammation, supporting its potential as an adjunct therapy [13, 14]. Thus, current evidence highlights CUR as a promising drug candidate for adjunct therapy in diabetes treatment and supports its inclusion in HMs directed for T2DM. Despite these advances, limited research has focused on its standardization of CUR in HMs, which is essential for ensuring safe administration. CUR can significantly alter the pharmacokinetics of co-administered drugs by inhibiting key drug-metabolizing enzymes such as CYP3A4 and CYP2C9, as well as P-glycoprotein, thereby exerting pronounced pharmacological effects [15, 16]. Its hypoglycaemic effects may synergize with other antidiabetic agents, increasing the risk of hypoglycaemia [17]. These concerns highlight the need for standardizing CUR content in herbal supplements to ensure both safety and efficacy.

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Several analytical methods have been reported for CUR determination, with HPLC-DAD being the most widely applied due to its high sensitivity and selectivity. For instance, a validated method for the simultaneous estimation of silymarin and CUR has been reported [18]. Moreover, HPLC-PDA provides enhanced accuracy in CUR quantification by offering detailed spectral information for improved identification and quantification [19]. More recent studies have also confirmed the reliability of RP-HPLC for CUR quantification in complex formulations [20, 21]. Collectively, these reports support the selection of HPLC-PDA in the current study.

Adulteration of antidiabetic HMs is a major concern, as many products contain undeclared synthetic drugs despite being marketed as natural products [22]. Such contamination can result in unintended drug interactions, increased morbidity, and in severe cases, mortality. Numerous studies have demonstrated that many herbal antidiabetic products are tainted with artificial oral antidiabetic medications, which could have harmful clinical effects on unwary patients [23-27]. Examples include the detection of chlorpropamide using HPLC-UV [28] and the identification of undeclared glibenclamide[29]. Additionally, metformin, gliclazide, rosiglitazone, glimepiride, nateglinide, phenformin, and repaglinide are among the most commonly identified synthetic antidiabetic adulterants in HMs [22]. This practice, typically intended to enhance the perceived efficacy of herbal products, reflects growing consumer demand but carries significant clinical risks [30, 31].

To address these issues, this study focused on detecting three high-risk, widely used synthetic antidiabetic drugs; pioglitazone (PGZ; insulin sensitizer), gliclazide (GLZ; insulin secretagogue), and dapagliflozin (DAPA; SGLT2 inhibitor) in commercial HMs. This selection is based on their widespread clinical use, relatively low cost and distinct mechanisms of action, as well as potential interactions with CUR [32, 33]. For Instance, potential drug-drug interactions are of particular concern, as both CUR and PGZ improve insulin sensitivity but through distinct mechanisms. PGZ primarily acts via PPARγ activation, whereas CUR modulates inflammatory signalling and oxidative stress. Their concurrent administration may therefore produce synergistic glucose-lowering effects, necessitating close blood glucose monitoring to minimize the risk of hypoglycaemia and related adverse outcomes [34]. In the case of GLZ, GLZ is an oral antidiabetic sulphonyl urea that acts by inducing insulin secretion [35]. Its inadvertent inclusion of HM may result in life-threatening consequences. The case is potentiated in herbal products containing CUR. This is because CUR has been shown *in vitro* to inhibit CYP2C9 activity, which may reduce the metabolic clearance of drugs such as GLZ, thereby increasing their systemic exposure. Beyond this pharmacokinetic interaction, CUR also exhibits intrinsic hypoglycaemic properties by enhancing insulin sensitivity and suppressing hepatic glucose production, potentially leading to additive glucose-lowering effects when co-administered with antidiabetic agents [36].On the other hand, inhibition of P-glycoprotein (P-gp) by CUR could increase systemic levels of drugs like DAPA, causing potential risk [37]. This is especially important where a recent study has identified the nephropathic effect of combining CUR and sodium glucose transporter type 2 [38].

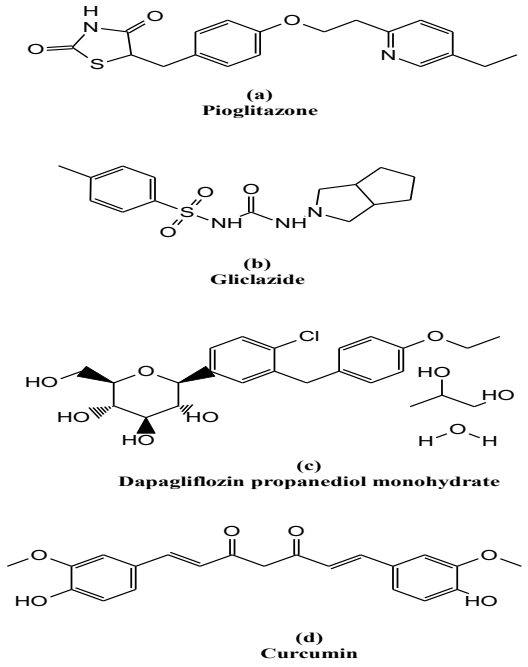


Fig. 1. Chemical structures of Pioglitazone (a), Gliclazide (b), Dapagliflozin propanediol monohydrate (c), and Curcumin (d).

Based on the potential interactions between CUR and PGZ, GLZ and DAPA, there is a need for the accurate determination of CUR concentration simultaneously with those possible pharmaceutical adulterants in herbal medicine to avoid inadvertent drug interactions. To the best of our knowledge, literature review revealed no green analytical technique available for the simultaneous determination of CUR and PGZ, GLZ and DAPA in herbal medications. Considering these concerns, the present study aimed to

develop and validate a high-performance liquid chromatography coupled with photodiode array detection (HPLC-PDA) method for the simultaneous quantification of CUR and detection of adulteration of some oral hypoglycaemics namely: PGZ (**Fig.1a**), GLZ (**Fig. 1 b**), DAPA (**Fig.1c**), and CUR (**Fig.1d**) in HMs. This study develops a novel HPLC-PDA method that, for the first time, enables the simultaneous quantification of CUR and detection of common antidiabetic adulterants in herbal medicines. The method greenness was also assessed, and the validated approach was successfully applied to analyze herbal medicines marketed across the Greater Cairo Area.

2. Materials and methods

2.1. Reagents and Chemicals

HPLC-grade methanol was obtained from Merck (Darmstadt, Germany). Trifluoroacetic acid (TFA), and ammonium formate were purchased from El-Gomhouria Pharmaceutical Company (Cairo, Egypt). Analytical standards of PGZ (>99% purity) were obtained from October Pharma (Cairo, Egypt); GLZ (>99% purity) from EPICO (Cairo, Egypt); and DAPA (>99% purity) from EVA Pharma (Cairo, Egypt). CUR was purchased from Lobal Chemie (Mumbai, India). Ultrapure water was produced using a Milli-Q water purification system (Millipore, MA, USA).

2.2. Instruments and Chromatography

Chromatographic analysis was performed using a Waters Alliance 2695 separation module coupled with a Waters 2996 photodiode array (PDA) detector (Waters Corporation, Milford, MA, USA). Separation was carried out on a BDS C8 column (150 mm × 4.6 mm, 5 µm). The supporting instruments included an Adwa AD1030 pH meter (Adwa Instruments Inc., Szeged, Hungary), a Scientech SA210D REV-B analytical balance (Scientech Inc., Boulder, CO, USA), a JSR digital hotplate stirrer (JS Research Inc., Gongju, South Korea), a Codyson CD-4860 ultrasonic cleaner (Codyson Electronics Co. Ltd., Shenzhen, China), and a single-stage vacuum pump from Acculab (Acculab Instruments, New York, USA).

The analysis was performed using a mixture of 48% buffer (0.03 M ammonium formate, pH 3 adjusted by TFA) and 52% methanol (HPLC grade) as a mobile phase. The flow rate was set at 1.5 mL/min, with an injection volume of 50 µL. Total run time was 10 minutes. Dual detection was monitored at PGZ, GLZ, DAPA at 225 nm, and CUR at 430 nm.

2.3. Sample Collection

Herbal antidiabetic supplement samples (n=10) were randomly acquired from a total of 10 unique retailers across Cairo and Giza governorates, Egypt. Samples were selected due to their location in areas with a diverse range of herbal products and high consumer traffic. These included 6 independent herbal shops and 4 health food stores. From each selected retailer, one distinct antidiabetic product was chosen from different brands with a 'Diabetes Management' claim on its label. All purchases were made anonymously.

2.4. Method Validation

The performance of the developed method was validated with reference to the International Council for Harmonization (ICH) guidelines for analytical techniques [39].

Analysis of antidiabetic drugs and curcumin

2.5.1. Linearity and Calibration Curve

Calibration curves were constructed by plotting peak areas versus concentrations for PGZ, GLZ, DAPA, and CUR, where six concentration levels were prepared for each drug, ranging from 0.5 to 50 µg/mL.All levels were measured for three replicates (n=3). The relation between analyte concentration and response from the detector was described using a linear regression model applied with least squares fitting. From calibration results, the LODs were calculated using the formula LOD = 3.3 σ/S, where σ represents the standard deviation of the y-intercept from the regression calibration curve, and S is the slope of the curve. The LOQs were determined using the visual evaluation method.

2.5.2. Accuracy and Precision

Both accuracy and precision were thoroughly evaluated to determine the reliability and appropriateness of the analytical method. For this purpose, samples with known concentrations of the analytes (PGZ, GLZ, DAPA, and CUR) were prepared at three distinct concentration levels. To determine all possible errors (systematic or random), the accuracy was measured through recovery studies performed on five replicate samples for each defined concentration level: 7.5, 25, and 45 µg/mL.

Analysis performed on the same day was used to assess intraday precision (repeatability), while average measurements obtained over a consecutive three days without changing conditions are referred to as interday precision (intermediate precision), where samples were run five times each at 10, 20, and 30 µg/mL concentration level. Precision in our results is estimated based on %RSD with an acceptable limit of ≤ 2% for each concentration level, across different days and occasions.

2.5.3. Specificity of the Method

The specificity of the method was evaluated through detecting the retention times (RT) of each standard while considering possible interfering with substances or even excipients. The specificity detection was augmented by simultaneous observation of the associated spectrum as recorded by the PDA system offering a two-dimensional detection via the retention time and the

fingerprint UV spectrum. This assessed whether the method could differentiate accurately between target analytes with any possible contaminations and additions.

2.5.4. System suitability

System suitability tests were completed to ascertain that the chromatographic system was suitable for the concurrent determination of PGZ, GLZ, DAPA, and CUR. The experiments included parameters such as retention time (RT), capacity factor (K′), theoretical plates, tailing factor, and resolution of the method, and when evaluating the results, the chromatographic system was ascertained to be selective, effective, and reproducible.

2.5.5. Robustness

The method's robustness was evaluated by changing critical factors like the temperature (±2 °C), pH (±0.2), and ratio of organic solvent (±2%). These changes were made with the assumption that they would influence chromatographic separation as well as quantitation of the analytes. To test the dependability of the methods under slight changes, each parameter was tested within defined ranges: 1) temperature: higher and lower temperature-controlled conditions were used to evaluate method stability and performance; 2) pH: separations and retention times were analyzed for different values of pH adjusted in the mobile phase. 3) Organic solvent: The ratio of organic solvent in the mobile phase was changed to study its impact on resolution and peak shape on a systematic basis.

Results variability was examined within precision defined as %RSD. For all levels of concentration tested using deviation calculations, results should be less than 2% RSD.

2.6. Application for Herbal Samples

Herbal Samples Treatment: Ten different herbal samples were analyzed in this study. For each sample, approximately 1.0 g of the dried, powdered herbal material was accurately weighed and extracted with 10 mL of methanol. The mixtures were left to stand at room temperature for 24 hours to allow sufficient extraction of the analytes. After maceration, the samples were filtered. A fixed volume of 5 ml of each filtrate was transferred into a water bath to evaporate the excess methanol under gentle heat (25 °C) for gentle evaporation to dryness. The resulting dry residues were then reconstituted in 2 mL of the mobile phase, vortexed for 30 seconds, and filtered through a 0.45 µm syringe filter prior to HPLC-PDA analysis.

The resulting chromatogram for each drug was monitored for the detection of the cited drugs via observation of retention times and fingerprint spectrum. Quantitation was performed using the calibration curve equation for each analyte.

2.7. Greenness assessment of the procedure

The greenness of the developed and validated HPLC-PDA method was assessed using four widely recognized tools: the Analytical Eco-Scale, NEMI, Complex GAPI, and AGREE. These tools offer a comprehensive evaluation of the method's environmental impact. The Eco-Scale provided a quantitative score, NEMI enabled visual identification of hazardous materials, and Complex GAPI assessed the overall procedure in detail. AGREE reflected the method's alignment with Green Analytical Chemistry principles [40-42].

3. Discussion & results

3.1. Method Development & Optimization

The development of a robust analytical method for the simultaneous quantification of PGZ, GLZ, DAPA and CUR required systematic optimization trials. The experiments focused on maximizing the separation efficiency and resolution, especially to overcome the structural similarities of the analytes that facilitate peak overlap during chromatography. In addition, enhancing detection sensitivity was essential to quantitatively identify any trace adulterants that may possibly be present in matrices of herbal complexity.

The method development process began with the evaluation of several chromatographic columns to identify the most suitable option for achieving efficient separation of PGZ, GLZ, DAPA, and CUR. Initially, a BDS C18 column (150 × 4.6 mm, 5 µm) was employed, as it is commonly used in similar analyses. While this column provided acceptable separation and produced sharp peaks, co-elution issues were observed, particularly with PGZ and GLZ, which hindered accurate quantification. To overcome this limitation, an XSelect C18 column, known for its enhanced resolving power, especially for structurally similar analytes, was subsequently evaluated. While the column provided satisfactory separation, it produced broader peak shapes and significantly longer retention times. As a result, the total run time increased, making the method less practical for routine quality control settings, where rapid analysis and high throughput are essential for efficiency and cost-effectiveness. Finally, the BDS C8 column (150 × 4.6 mm, 5 µm) was tested to see if its shorter alkyl chain could help separate the analytes differently, and it provided the best balance. It achieved sharp, well-resolved peaks with acceptable retention times for all four analytes, making it suitable for the final method. **Supplementary Fig. 1.** illustrates selected trials during the method development process.

Regarding the mobile phase, several trials were conducted to optimize retention, resolution, and peak shape for all four analytes. Initial experiments using 0.3% formic acid (pH 2.5) mixed with methanol resulted in moderate retention; however, peak broadening and overlap, especially between GLZ and DAPA, limiting the method's specificity. To improve chromatographic performance, formic acid was replaced with 0.2% TFA, which significantly enhanced peak sharpness and sensitivity, especially for GLZ and DAPA Nevertheless, this adjustment also prolonged retention times, increasing the overall runtime and reducing method efficiency. Subsequently, 0.02 M ammonium formate (pH 2.5) was tested. This buffer improved the resolution between

PGZ and GLZ, but adversely affected CUR's peak profile, leading to broader and less defined elution. This suggested that curcumin's retention and stability were particularly sensitive to mobile phase composition and pH, likely due to its polyphenolic structure and limited solubility at low pH. To address this, both buffer concentration and pH were further optimized. The final optimized mobile phase consisted of 0.03 M ammonium formate, adjusted to pH 3 with TFA, and mixed with methanol in a 48:52 (*v/v*) ratio. This combination yielded sharp, symmetrical, and well-resolved peaks for all analytes, eliminated overlaps, and maintained a reasonable total runtime. This composition was thus selected for the validated HPLC-PDA method. The flow rate and injection volume were also critical parameters. A flow rate of 1.5 mL/min provided the optimal balance between separation efficiency and analysis speed. Although lower flow rates, such as 1.2 mL/min, were tested, the 1.5 mL/min setting consistently yielded superior chromatographic performance. The injection volume was 50 µL. Under these conditions, PGZ, GLZ, DAPA, and CUR separated atretention times: 2.383 min, 5.606 min, 7.955 min, and 9.730 min, respectively **Fig. 2**.

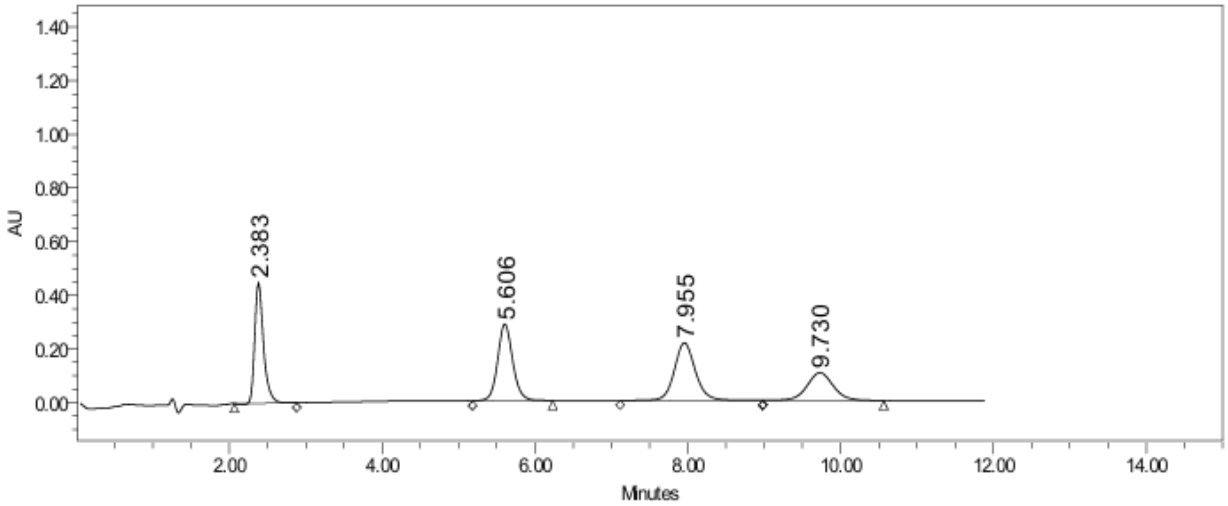


Fig. 2. Optimized Chromatogram of PGZ, GLZ, DAPA, and CUR using a BDS C8 column (150 × 4.6 mm, 5 µm) and a mobile phase composed of 0.03 M ammonium formate buffer (pH 3, adjusted with trifluoroacetic acid) and methanol (48:52, v/v).

Selecting an appropriate detection wavelength was essential to ensure both sensitivity and selectivity for all analytes. Multiple wavelengths were evaluated to determine the optimal conditions. A wavelength of 225 nm was selected as the primary detection point, as it provided the strongest and most consistent signals for PGZ, GLZ, and DAPA **Fig. 3**. CUR, due to its distinct polyphenolic chromophore, exhibited maximal absorbance at 430 nm, which was therefore used for its detection **Fig. 3**. Additionally, wavelengths of 241.7 nm and 220 nm were tested to assess their ability to enhance sensitivity for minor components, but they did not offer significant improvements over 225 nm. The final method employed a PDA detector simultaneously set at 225 and 430 nm, enabling clear, selective, and sensitive detection of all four analytes within a single analytical run detection. Wavelength of 225 nm was found to be the most suitable for the simultaneous monitoring of PGZ, GLZ, and DAPA, as this setting consistently yielded sharp and stable peaks for the three drugs. This choice aligns with previous findings reporting efficient UV absorbance for PGZ [43, 44], GLZ [45, 46], and DAPA [46] in the same region. On the other hand, CUR, owing to its extended conjugated aromatic structure, showed a distinct absorption maximum around 430 nm, which is in line with earlier spectrophotometric studies that confirmed its strong absorbance in the visible range [47, 48]. **Fig. 3** displays the associated spectrum of each drug at its corresponding peak.

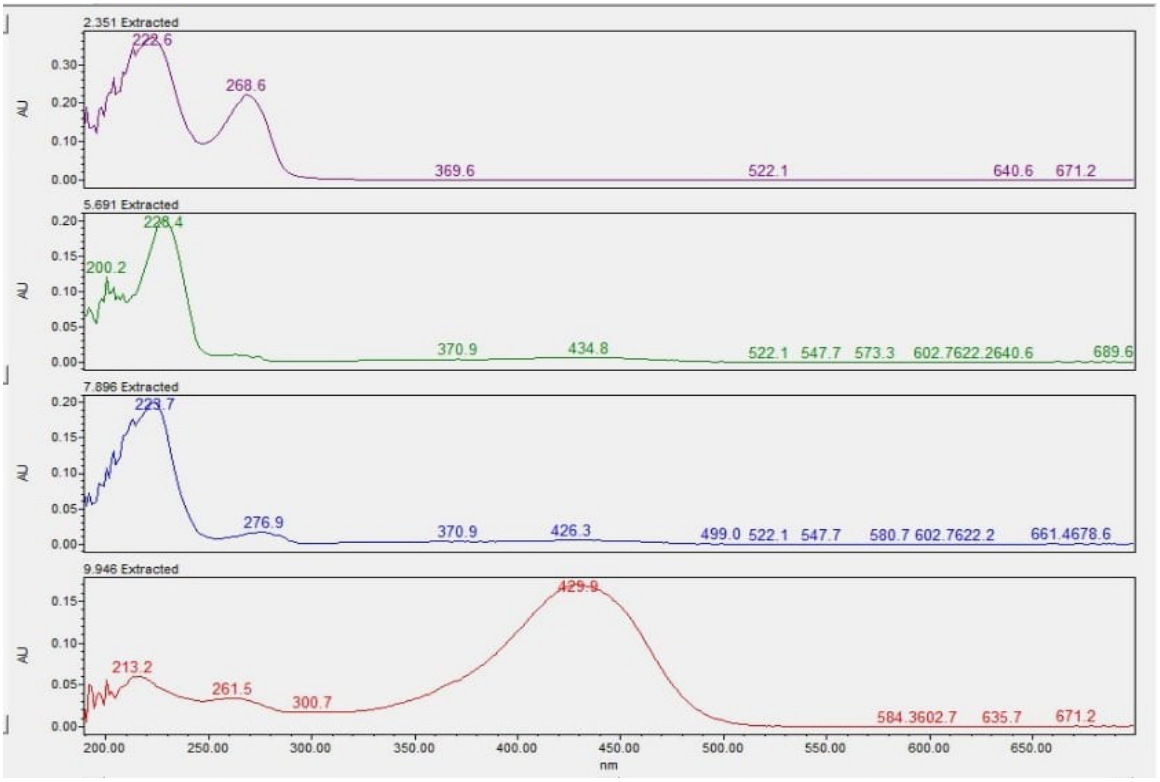


Fig. 3. Photodiode-array (PDA) spectra of the four analytes obtained at their respective retention times: (A) 2.383 min (PGZ), (B) 5.606 min (GLZ), (C) 7.955 min (DAPA), and (D) 9.730 min (CUR). PGZ, GLZ, and DAPA exhibit λmax near 225 nm, whereas curcumin displays a maximum absorption around λ430 nm.

In summary, the BDS C8 column combined with the selected mobile phase provided excellent separation. The dual wavelengths of 225 and 430 nm allowed sharp, distinct peaks. The flow rate of 1.5 mL/min with a 50 µL injection volume allowed efficient, rapid analysis. The retention times (RT) for the analytes were 2.383 min for PGZ, 5.606 min for GLZ, 7.955 min for DAPA, and 9.730 min for CUR, demonstrating effective separation throughout the chromatographic analysis and simultaneous identification via distinct spectrum for each drug (**Fig. 4**).

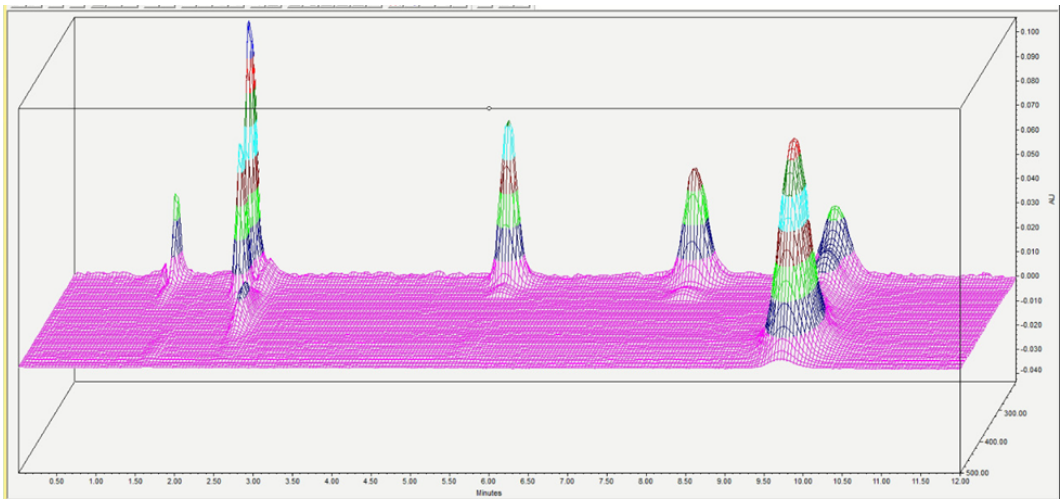


Fig. 4. Three-dimensional HPLC-UV chromatogram illustrates the specificity of the developed method. Each target analyte is well separated with distinct retention times, demonstrating the method's ability to discriminate between analytes without interference from potential impurities.

A brief comparison of the current green HPLC-PDA method with other reported analytical techniques is provided in **Table 1**. The current study demonstrates high specificity using UV spectral fingerprinting across the full range, offering a cost-effective solution suitable for quality control labs. This method is favorable in terms of greenness (Ecoscale 84%) and has moderate energy demand, making it a more sustainable option compared to other method.

Table 1. Comparison of the current HPLC-PDA method with other reported analytical approaches for detection of antidiabetic adulterants in herbal medicines.

Analytes	Detector / Capability	Specificity	Cost / Accessibility	Greenness	Energy / Sustainability	References
PGZ, GLZ, DAPA, CUR	UV spectral fingerprinting (PDA) across full range	High (retention time + spectral fingerprinting)	Moderate, feasible in QC labs	Favourable (Ecoscale 84%)	Moderate energy demand, lower than MS; aligns with greenness goals	Current study
GBM	UV absorbance at fixed λ only	Limited (retention time only)	Low cost, highly accessible	Not assessed	Low energy demand	[49]
MF, GCZ, GBM, GMR.	Mass-based detection (MRM, ESI+)	Excellent (MRM transitions)	High cost, requires LC-MS/MS	Not assessed	High energy demand for MS operations	[24]
MF, GBM	Surface-Enhanced Raman Spectroscopy (SERS)	Moderate specificity with SERS-based detection	moderate cost for SERS systems	Moderate, eco-friendly (SERS)	Low energy demand for SERS	[50]
MF, PHF, BF, GBM, GCZ.	Mass spectrometry (ESI+ for MS/MS)	High specificity with mass transitions	High cost, requires LC-MS/MS	Not assessed	High energy demand for MS operation	[51]
GBM (as an adulterant)	Thin-layer chromatography (TLC)	Moderate specificity	Low cost	not assessed	Low energy demand	[52]
Biguanide, sulfonylurea, thiazolidinedione	Mass spectrometry (MS) coupled with HPTLC	High specificity with mass transitions	Moderate cost, requires HPTLC-MS	not assessed	Moderate energy demand	[53]
Sulfonylureas	Immunochromatography (qualitative detection)	Broad-specific detection of multiple sulfonylureas	Low cost, suitable for field tests (test strips)	not assessed	Low energy demand	[54]
MF, BF, PHF, RGZ, PGZ, CPM, GPZ, TBM, GCZ, GBM, GMR, RGN, GQD, NGN.	HPLC for separation, LC-Q-TOF-MS/MS for mass spectrometry-based confirmation	High specificity with mass transitions (LC-Q-TOF-MS/MS)	High cost, requires HPLC and LC-Q-TOF-MS/MS	not assessed	High energy demand (LC-Q-TOF-MS/MS)	[26]

Abbreviations: PGZ, Pioglitazone; GLZ, Gliclazide; DAPA, Dapagliflozin; CUR, Curcumin; MF, Metformin; BF, Buformin; PHF, Phenformin; RGZ, Rosiglitazone; CPM, Chlorpropamide; GPZ, Glipizide; TBM, Tolbutamide; GBM, Glibenclamide; GMR, Glimepiride; RGN, Repaglinide; GQD, Gliquidone; NGN, Nateglinide.

3.2. Analytical method validation

3.2.1 Linearity and Calibration Curve

All four analytes showed high linearity over the tested concentration range of 0.5 to 50 µg/mL, with correlation coefficients (r^2) consistently above 0.999, indicating a strong agreement between concentration and response. These results confirm that the method exhibits excellent linearity across this range for all analytes, fulfilling validation criteria for quantitative analysis in both pharmaceutical and herbal formulations. The calibration curves for PGZ, GLZ, DAPA, and CUR are presented in **SupplementaryFig.2**, demonstrating the strong linear relationship between concentration and peak area across the studied range. **Table 2** provides a summary of these findings.

The LOQ values for PGZ, GLZ, DAPA, and CUR were found to be 0.47, 0.43, 0.47, and 0.31 µg/mL, respectively. The LOD values were 0.24 µg/mL for PGZ, 0.19 µg/mL for GLZ, 0.23 µg/mL for DAPA, and 0.16 µg/mL for CUR.

Table2. Summary of Method Validation parameters

Method Validation Parameters	Pioglitazone	Gliclazide	Dapagliflozin	Curcumin
Linearity Range (μg/mL)	0.5 to 50 μg/mL			
R^2	0.9996	0.9999	0.9999	0.9997
slope	74291	78440	81615	204873
Intercept	-10939	-12819	-14494	-138077
LOQ (μg/ mL)	0.47	0.43	0.47	0.31
LOD (μg/ mL)	0.24	0.19	0.23	0.16
Concentrations	**Accuracy %**			
7.50μg/ mL	100.24±1.38	98.72± 0.25	98.88± 1.15	100.69±0.08
25.00μg/ mL	99.36± 0.28	99.66± 0.56	101.55± 0.69	99.33± 0.17
45.00μg/ mL	98.51± 0.28	99.74±0.27	100.97± 0.03	98.29 ± 0.16
	Precision (RSD%)			
	Intraday Precision			
10.00μg/ mL	0.97 %	0.46%	0.21%	0.08%
20.00μg/ mL	0.47 %	0.13%	0.05 %	0.17%
30.00μg/ mL	0.15%	0.18%	0.11%	0.16%
	Interday Precision			
10.00 μg/ mL	1.85%	1.60%	0.54%	1.49%
20.00μg/ mL	0.19%	1.81%	0.38%	0.21%
30.00 **μg/ mL**	1.04 %	1.37%	0.23%	0.39%

3.2.2 Accuracy andPrecision

The method was found accurate for the determination of PGZ at the three tested levels 7.5, 25,and 45 μg/mL and it ranged from (98.51 ± 0.28%) to (100.24 ±1.38%), while for GLZ at the same three levels it ranged from (98.72± 0.25%) to (99.74±0.27%) ,while for DAPA at this three levels it ranged from (98.88 ± 1.15%) to (101.55±0.69%) ,and the accuracy for CUR at the same three levels respectively was ranged from (98.29±0.16%) to (100.69 ± 0.08%). The results indicated that all the tested drugs met the acceptable accuracy limits at all concentrations, as shown in **Table 2**. The recovery values for each analyte fell within the ICH-recommended range of 98±2 %.

Precision was evaluated by repeatability (intraday) and intermediate precision (interday), as represented in **Table 2**. In all the drugs, RSD values were ≤2%, confirming that the method precision across different concentration levels as the repeatability precision (%RSD) for PGZ, GLZ, DAPA, and CUR ranged from 0.15–0.97%, 0.13–0.46%, 0.05–0.21%, and 0.08–0.17 %, respectively, while the intermediate precision (%RSD) ranged from 0.19–1.85% for PGZ, 1.60–1.81% for GLZ, 0.23–0.38% for DAPA, and 0.21–1.49% for CUR.

3.2.3. Specificity

Each drug showed a well-resolved peak at its specific retention time, with no overlapping or interfering peaks observed in the chromatograms. The absence of any co-eluting peaks confirms that the method is specifically detecting each compound in the presence of the others. Meanwhile, the PDA detection allowed for simultaneous monitoring of the characteristic spectrum of the eluted compounds at its specific retention time (**Fig 3).**

3.2.4. System Suitability

The system suitability tests showed that the chromatographic system was well-suited for analyzing PGZ, GLZ, DAPA, and CUR simultaneously. System suitability parameters were evaluated for all analytes to ensure proper chromatographic performance. The retention times (RT) for PGZ, GLZ, DAPA, and CUR were found to be 2.383, 5.606, 7.955, and 9.730 minutes, respectively. The corresponding peak areas were consistent and well-resolved, contributing to area percentages of 25.38%, 27.67%, 29.22%, and 17.72% in the same order.

Peak heights ranged from 104173 (CUR) to 449442 (PGZ), reflecting appropriate detector response. The resolution between each successive peak was satisfactory, with values of 11.8, 5.7, and 3.3, indicating adequate separation across the chromatogram.

The capacity factor (K') values were within acceptable limits, ranging from 1.4 (PGZ) to 8.7 (CUR), confirming sufficient retention. The USP plate counts demonstrated good column efficiency, with values of 2135.1, 4019.2, 4237.7, and 3988.7, respectively. Tailing factors for all analytes remained within acceptable limits (≤1.4), confirming symmetrical peak shapes and proper column performance. For full details, refer to **Table 3**.

Table 3. System Suitability & Robustness

System suitability	Pioglitazone	Gliclazide	Dapagliflozin	Curcumin
RT	2.383	5.606	7.955	9.730
Area	3632241	3960038	4181618	2535709
Area %	25.38%	27.67%	29.22%	17.72%
Height	449442	287354	215751	104173
Resolution	1st peak	11.8	5.7	3.3
K Prime	1.4	4.6	7.0	8.7
USP Plate Count	2135.1	4019.2	4237.7	3988.7
USP Tailing	1.4	1.1	1.1	1.0
Robustness				
Temp (Peak area ±SD)	3441874.00±19996.70	3985884.67±3207.84	4180890.33±3170.66	9948288.33±161109.03
Temp RSD %	0.581 %	0.080 %	0.076 %	1.619 %
PH (Peak area ± SD)	3444624.00± 3641.61	3999872.00±14966.16	4180649.00±9094.14	9902252.67±71160.81
PH RSD %	0.106 %	0.374 %	0.218 %	0.719 %
Organic solvent (Peak area ± SD)	3523227.67±70056.53	3982509.33±766.76	4217269.33±38318.75	9962358.67±198584.94
Organic solvent RSD%	1.989 %	0.019%	0.909%	1.993%

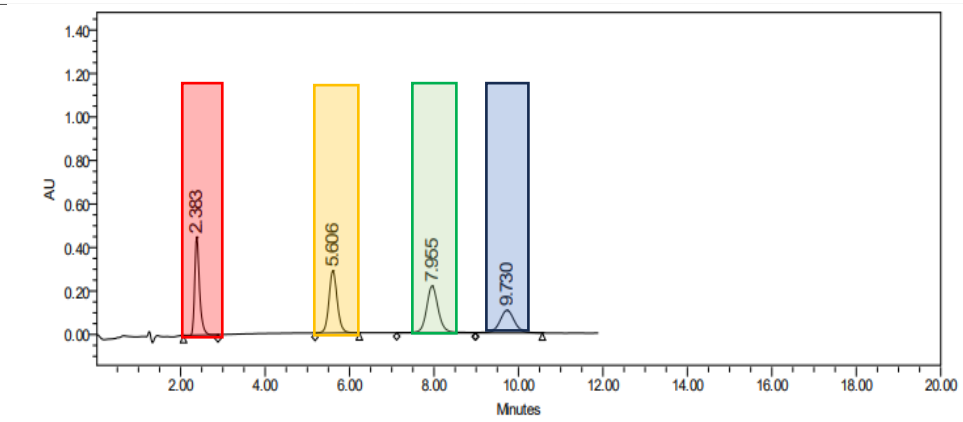
3.2.5. Robustness

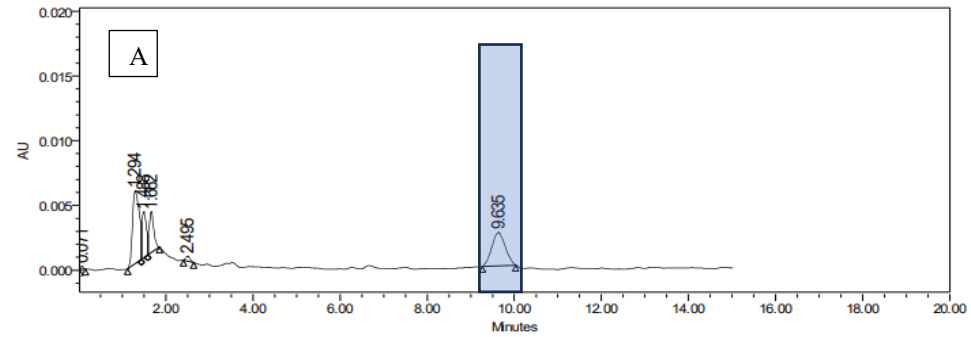
The robustness of the developed HPLC-PDA method was evaluated by introducing small, deliberate variations to key chromatographic parameters, including the mobile phase pH (±0.2), column temperature (±2 °C), and organic solvent ratio (±2%).

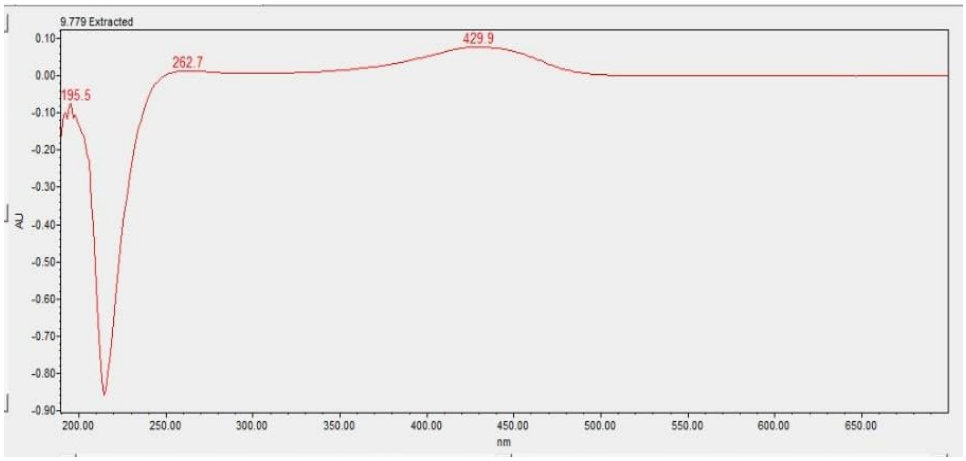
The results demonstrated no marked changes in the retention times and peak areas of the analytes. For instance, the %RSD for temperature variations was 0.581% for PGZ, 0.080% for GLZ, 0.076 % for DAPA, and 1.619 % for CUR. Similarly, pH changes resulted in %RSD values of 0.106 % for PGZ, 0.374 % for GLZ, 0.218 % for DAPA, and 0.719% for CUR, and the variation in organic solvents' ratio resulted in RSD% values of 1.989 % for PGZ, 0.019% for GLZ, 0.909% for DAPA, and 1.993% for CUR. Accordingly, the effect of varying in temperature, pH, and in the organic solvents' ratio showed %RSD values below 2% in all cases, proved that the method is robust. A detailed summary of the robust study is shown in **Table 3**.

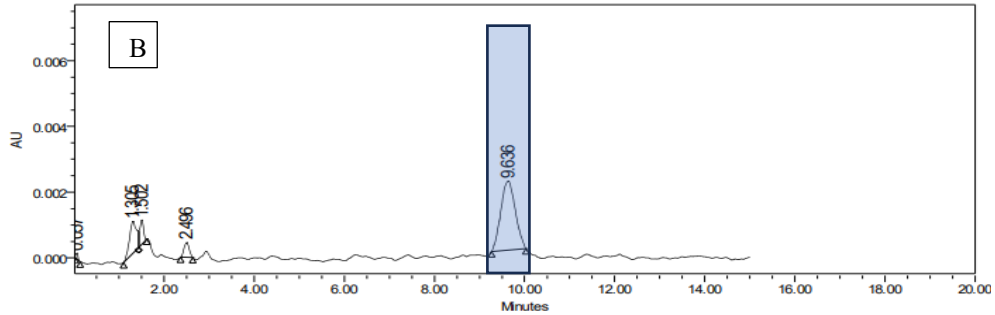
3.3. Applications for diabetic herbal products

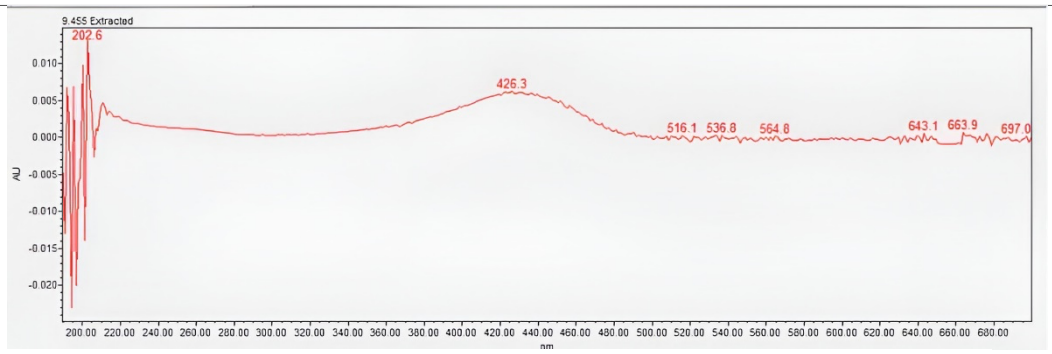
CUR was only found in products A, B, and C at a concentration of around 4.74, 4.54 and 3.61µg/mL, respectively **(Fig. 5 A - C**). The presence of CUR in some of the tested samples should not necessarily be considered a sign of adulteration, as CUR is a well-known natural compound traditionally used in various herbal formulations, especially those targeting diabetes management. But its inclusion could be regarded as adulteration if not clearly declared on the product label, along with its concentration, as it may interact with certain antidiabetic medications and potentially lead to an excessive reduction in blood glucose levels. Therefore, its detection in the sample is more likely to reflect its intended use as a functional ingredient rather than an undeclared synthetic addition. Out of the tested herbal products, one herbal product (D) was confirmed to be adulterated with GLZ at a concentration of around 2.32 µg/mL. Thus, it was evident from the GLZ specific peak (5.58 min **Fig. 5D**), which was confirmed by the PDA chromatogram which showed identical chromatogram of GLZ (**Fig. 2**). It is worth mentioning that GLZ is one of the sulphonylureas. Inadvertent inclusion in HMs may induce uncontrolled induction of insulin secretion leading to hypoglycemia[55]. The remaining herbal products (E – J) were analyzed using the HPLC-PDA method, and no traces of the studied synthetic drugs (**Fig. 5)**.

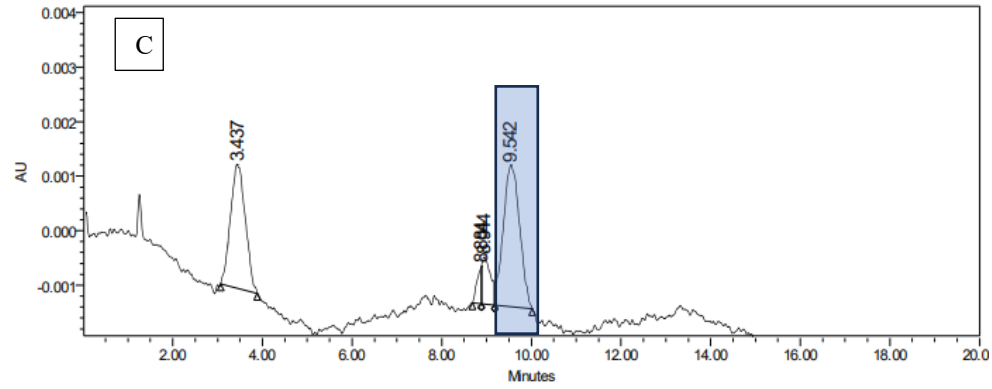

AU
Minutes
2.383
5.606
7.955
9.730

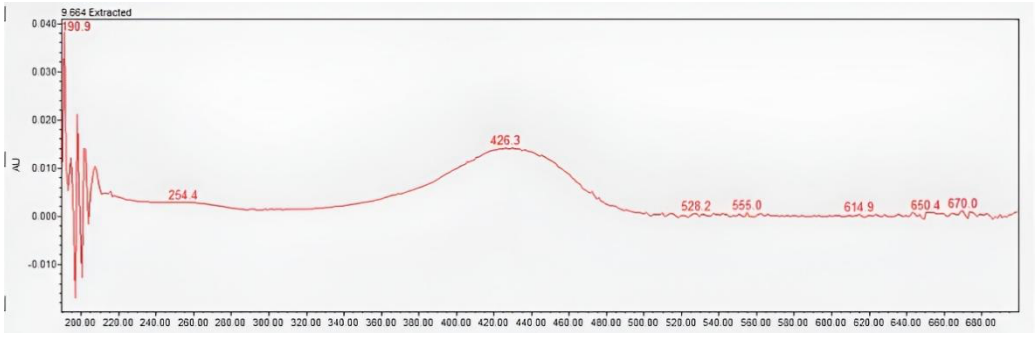

A
AU
Minutes
9.635
2.495

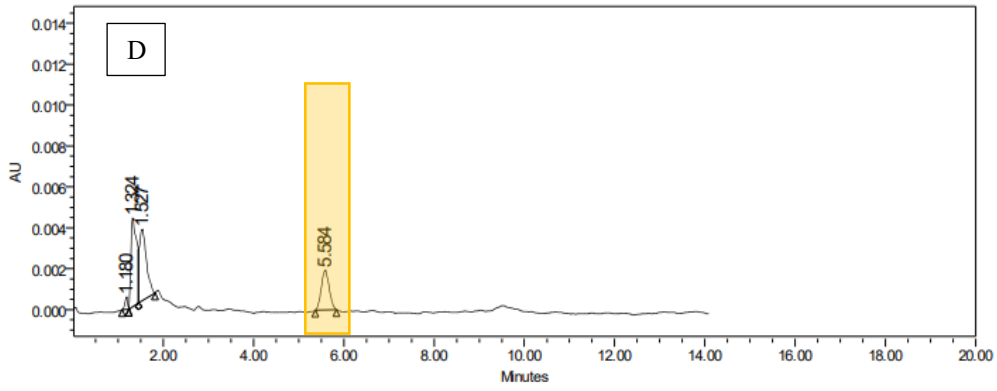

9.779 Extracted
429.9
262.7
195.5
AU
nm


B
AU
Minutes
9.636
2.496


9.455 Extracted
202.6
426.3
516.1
536.8
564.8
643.1
663.9
697.0
AU
nm


C
3.437
9.542
AU
Minutes


9.864 Extracted
190.9
426.3
254.4
528.2
555.0
614.9
650.4
670.0
AU


D
1.180
1.324
1.527
5.584
AU
Minutes

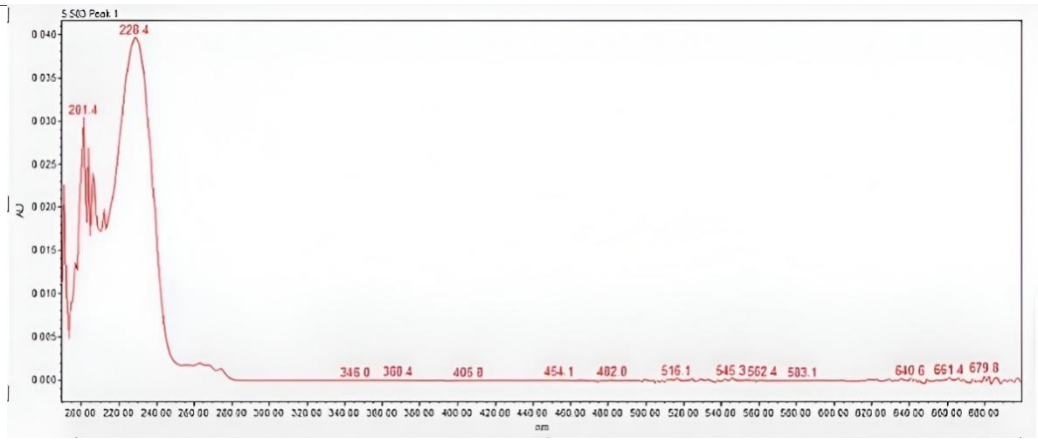
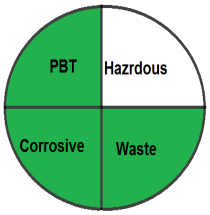


Fig. 5. The chromatograms of the marketed samples (A–D). Samples A, B, and C refer to CUR, while sample D refers to GLZ. The chromatograms for CUR are highlighted in blue, and for GLZ, it is highlighted in yellow. These chromatograms represent the spectrum of the detected peaks, further confirming the identity of CUR in samples A-C and GLZ in sample D.

3.4. Greenness assessment

The environmental impact of the mobile phase, instruments and methods used in this study were evaluated using various green chemistry metrics. The components of the mobile phase included methanol and an ammonium formate buffer (pH 3), adjusted with a small amount of trifluoroacetic acid (TFA). The TFA was used in minimal quantities to adjust the pH, ensuring that its effect on the overall environmental impact was kept to a minimum. The results of the green assessment are summarized in **Table 4**.

Table 4. Greenness Assessment

Mobile phase	Complex GAPI	NEMI	Eco-scale	Agree assessment
Methanol ammonium formate buffer (pH 3, adjusted with trifluoroacetic acid			**Reagent Penalty points methanol 6 ammonium formate 0 TFA 4 Amount of solvent (1.5ml/min in 10 min) 4 Instruments HPLC - PDA 0 Waste 2 Total penalty points 16 Analytical eco-scale 84**	

3.4.1. Complex GAPI Score

The Complex GAPI value was calculated to be 82, indicating a moderate environmental impact based on the reagents used [40]. This value reflects the careful selection of solvents and reagents, particularly the use of volatile methanol (which is biodegradable and recyclable) and the use of TFA only in trace amounts to adjust pH, thus minimizing its environmental impact.

The method also avoids excessive energy consumption and does not involve derivatization steps or toxic sample treatment, which further enhances the GAPI profile. As shown in **Table 4**.

3.4.2. NEMI (National Environmental Management Indicators)

The mobile phase components were classified into various environmental categories such as PBT (Persistent, Bioaccumulative, and Toxic), Hazardous, Corrosive, and Waste [41]. The evaluation showed a low environmental impact, as illustrated in the NEMI diagram in **Table 4**.

3.4.3. Eco-Scale Assessment

The eco-scale score for the mobile phase components was calculated based on the penalty points assigned to each reagent [40].

The total penalty points amounted to 16, leading to an eco-scale score of 84 as shown in **Table 4**. This indicates excellent environmental compatibility, as scores above 75 are generally considered to represent green methods. The main penalties were related to the use of methanol and TFA, yet these were kept within safe and justifiable limits.

3.4.4. AGREE Assessment

The AGREE assessment score, which integrates the 12 principles of Green Analytical Chemistry into a single visual output and numerical score, showed a final value of 0.7, as shown in Table 4. This score signifies that the method strongly aligns with green analytical practices, particularly in terms of minimal reagent use, operator safety, reduced waste generation, and method efficiency measures the overall sustainability of the method, was 0.7, indicating a good agreement with sustainable practices [42].

4. Conclusions

The proposed HPLC-PDA assay proved to be a reliable and practical tool for the accurate determination of CUR down to a concentration of 0.5µg/mL of herbal extract and the sensitive detection of PGZ, GLZ and DAPA additives down to 0.25 µg/mL. These low concentrations enable the accurate and sensitive assessment of the HM safety against possible adulteration and inadvertent drug-drug interactions. On the other hand, the method demonstrated an acceptable greenness profile, with a Complex GAPI score of 82 and an AGREE assessment of 0.7, confirming its environmental compatibility. When applied to marketed samples, it successfully enabled quantification of CUR and revealed undeclared adulteration with GLZ in one product, underscoring its real-world applicability. Importantly, these findings emphasize the need for stricter regulatory oversight, implementation of standardized quality control protocols, and raising public awareness to safeguard patients from the hidden risks of adulterated herbal products, particularly those marketed for chronic diseases such as diabetes.

Conflicts of interest

There are no conflicts of interest to disclose.

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