RESEARCH ARTICLE
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Development of a UV–Vis Spectroscopy Method Allied with Chemometrics for Simultaneous Analysis of Dexketoprofen Trometamol and Thiocolchicoside in Commercial Tablets

ABSTRACT

Background: Herein, a simple UV–Vis spectrophotometric method coupled with chemometrics including principal component analysis (PCA) and partial least squares (PLS) regression/prediction analysis was utilized for the simultaneous determination of dexketoprofen trometamol (DEX) and thiocolchicoside (TCC) in their binary pharmaceutical dosages.

Methods: Different binary dosages of DEX and TCC at known concentrations were prepared via the central composite experimental design methodology. The UV–Vis spectra of pharmaceutical sets were recorded in the spectral region of 200-800 nm, and with the help of these data, the chemometrics models were created with Unscambler X10.4 software. Full cross-validation strategy and NIPALS algorithms were applied to evaluate the performance of models in terms of accuracy and predictive abilities.

Results: The PCA models showed statistically successful findings with high eigenvalues. The values of R^2, RMSEC and RMSECV were found to be 0.9939, 0.0028 and 0.0033 mg for TCC, respectively, by PLS regression. The R^2, RMSEC, and RMSECV were obtained for DEX as 0.9939, 0.0036, and 0.0048 mg, respectively. The R^2, RMSEC, and RMSECV were obtained for the binary mixtures of DEX and TCC as 0.9901, 0.0042, and 0.0051 mg, respectively. Lastly, the commercial pharmaceutical tablets including DEX and TCC ingredients were tested with high prediction abilities.

Conclusion: The developed UV–Vis method allied with chemometrics enables more sensitive and cost-effective measurement for the simultaneous determination of DEX and TCC. The method could be applied for quality control analysis of many pharmaceutical preparations.

Keywords: Chemometrics, dexketoprofen trometamol, pharmaceutic, thiocolchicoside, UV–Vis spectroscopy

What is already known on this topic?

- UV–Vis spectroscopy method is extremely valuable in sustainable green chemistry, owing to the necessity of no sample preparation procedures, the use of no or very little organic chemicals and the production of any dangerous chemical waste.
- The application of the UV–Vis spectroscopy method based on a chemometrics approach for drug analysis has received great attention in the area of green analytical chemistry.

INTRODUCTION

Dexketoprofen trometamol (DEX) is classified as a non-steroidal anti-inflammatory drug that exhibits analgesic, antipyretic, and anti-inflammatory properties. Its mechanism of action involves potent inhibition of prostaglandin synthesis through the cyclooxygenase pathway. This compound is orally administered as tablets for the management of mild to moderate pain, including dental, muscular, and skeletal discomfort.[1-3]The drug demonstrates a rapid onset of action, exhibiting its effects within 30 minutes, and is well tolerated during short-term therapy.[4] With a molecular weight of approximately 375.421 g/mol, thiocolchicoside (TCC) functions as a muscle relaxant, also exhibiting anti-inflammatory and analgesic properties.[5,6] While its precise mechanism remains elusive, this substance is thought to exert its effects through antagonism of nicotinic acetylcholine receptors. Nevertheless, it also demonstrates competitive antagonism at GABAA and glycine receptors, resulting in potent convulsant activity. Consequently, its usage is contraindicated in individuals predisposed to seizures.[1,7]The TCC exhibits a color range from light to dark yellow, possesses a water solubility of 10 mg/mL,

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What this study adds on this topic?

- A rapid, environmentally friendly, inexpensive, and non-destructive UV–Vis spectroscopy method with chemometrics can be used with high prediction abilities for the simultaneous determination of dexketoprofen trometamol and thiocolchicoside in pharmaceutical dosages.
- The use of toxic and expensive chemicals is avoided, and the pharmaceutical ingredients could be effortlessly qualified and quantified without any laborious procedures.

and a LogP value of 0.34. It demonstrates approximately 25% oral bioavailability, with intramuscular administration leading to a peak plasma concentration within 30 minutes in individuals.

According to the literature, a combination of dexmedetomidine and total intravenous anesthesia has demonstrated greater efficacy in pain management at 24 hours compared to dexmedetomidine administered alone.[8] The DEX and TCC are found together in several commercially available pharmaceutical tablets. However, limited research has simultaneously quantified both compounds using high-performance liquid chromatography (HPLC).[9] Due to the simplicity of spectrophotometric techniques, they have emerged as a reliable alternative technique to HPLC for pharmaceutical analysis. However, a significant challenge in the simultaneous analysis of multiple drugs is the presence of spectral overlapping. Chemometrics techniques stand as a robust analytical method capable of resolving such spectral overlaps. Chemometrics involves the application of mathematical and statistical approaches to optimize experimental procedures and extract maximum information from spectral data. This has led to a growing interest in employing chemometrics for the spectral analysis of multicomponent pharmaceutical mixtures in recent years.[10]

MATERIALS AND METHODS

General

Dexketoprofen trometamol and TCC were purchased from Sigma Aldrich Corporation (St. Louis, MO, USA) (Fig. 1), and the commercial tablets [(Leodex Plus; containing 25 mg/8 mg), (Aseket-Tiyo; containing 25 mg/8 mg)] were acquired from a local pharmacy in Türkiye. All chemicals were of spectroscopy grade and were bought from Sigma Aldrich Corp. and VWR BDH Corp (Radnor, PA, USA). All spectrophotometric measurements were performed on a UV–Vis spectrophotometer (VWRUV-1600PC, VWR International GmbH, Wien, Austria). A Millipore water machine was utilized to obtain ultra-pure water (Merck KGaA Inc., DA, Germany).

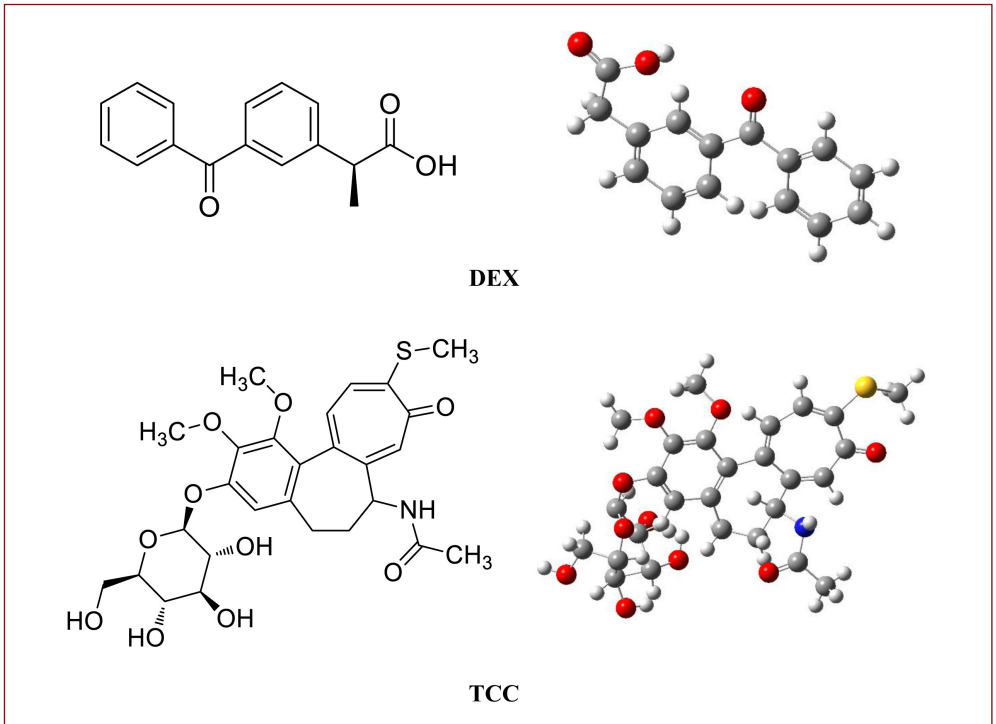


Figure 1. Chemical structures of dexketoprofen trometamol and thiocolchicoside.

Preparation of Pharmaceutical Combinations by Composite Experimental Design

For the stock solution of TCC, 0.0079 g of TCC standard in 1.4017 mL of MeOH was used. For the stock solution of DEX, 0.0320 g of DEX standard in 1.2585 mL of MeOH was used. The central composite experimental design (CCD) methodology was employed to construct binary combinations of DEX and TCC. A 5-level, 2-factor CCD was constructed using the Design–Expert 12 program (Stat–Ease Inc., MN, USA) for each of the 2 ingredients. In the CCD matrix, the independent variables namely pharmaceutical ingredients [DEX (X_1) and TCC (X_2)] were coded at 5 different levels (−1.44, −1, 0, +1, +1.44), which comprised a total of 13 points (mixtures) (Tables 1 and 2). The solutions of DEX and TCC were analyzed in the range of 0.15-0.27 mg and 0.02-0.11 mg per 20-fold diluted mixtures from the stock solutions of DEX and TCC, respectively.

For each commercial drug, 10 tablets are ground into powder, an amount equivalent to 1/20 of an average tablet weight was weighed, and the weighed powder was then dissolved in MeOH and mixed [Leodex Plus – One tablet weighed 0.2555 g. A total of 10 tablets were crushed, and 0.0127 g of powdered drug (equivalent to 1/20 of a single tablet) was weighed. Crushing and weighing 10 tablets aimed to minimize potential errors caused by concentration variations between tablets during manufacturing. The weighed powder was dissolved in 5 mL of MeOH. Aseket–Tiyo – One tablet was weighed at 0.2843 g. A total of 10 tablets were crushed, and 0.0142 g of powdered drug (equivalent to 1/20 of a single tablet) was weighed and dissolved in 5 mL of MeOH]. To remove impurities, all solutions were filtered using a 0.45 μm filter, and the samples were diluted 20 times for the UV–Vis spectroscopy analyses.

Table 1. Composite Experimental Design for the Preparation of Pharmaceutical Combinations of Dexketoprofen trometamol and Thiocolchicoside Using Coded Values (5 Levels/2 Factors) and Diluted Concentrations (mg)

5 Levels / 2 Factors	−1.414	−1	0	+1	+1.414
DEX (X_1)	17.93	20	25	30	32.07
TCC (X_2)	2.344	4	8	12	13.656
DEX (X_1)	0.15	0.17	0.21	0.25	0.27
TCC (X_2)	0.02	0.03	0.07	0.10	0.11

DEX, dexketoprofen trometamol; TCC, thiocolchicoside.

Table 2. Sample Data for Dexketoprofen trometamol (X_1) and Thiocolchicoside (X_2) Concentrations (mg)

Sample Code	DEX (*X1*) (mg)	TCC (*X2*) (mg)	Total Concentration (mg)	Diluted Total Concentration (1/20 ratio) (mg)
1	20	4	24	0.20
2	30	4	34	0.28
3	20	12	32	0.27
4	30	12	42	0.35
5	25	8	33	0.28
6	25	8	33	0.28
7	25	8	33	0.28
8	25	8	33	0.28
9	25	8	33	0.28
10	17.93	8	25.93	0.22
11	32.07	8	40.07	0.33
12	25	2.34	27.34	0.23
13	25	13.66	38.66	0.32

UV–Vis Spectroscopy Measurements

All spectrophotometric data were collected in the wavelength region of 200-800 nm. Before the measurements by UV–Vis spectrophotometer, a blank measurement was taken using MeOH to condition the device and prevent the appearance of a solvent peak. Subsequently, the repeated measurements were taken for the pure active ingredients, the 13 binary standard solutions, and the pure drug standards of DEX and TCC.

Chemometrics

The chemometrics analyses constructed over spectral data were performed by using UnscramblerX10.4 (CAMO Software Inc., Oslo, Norway) as an Excel file for the chemometrics analyses. Before the chemometrics analyses, first derivative Savitzky–Golay smoothing and standard normal variate pre-treatments were carried out. For the simultaneous analysis of DEX and TCC, the binary mixtures were measured by the UV–Vis spectrophotometer, and then the principal component analysis (PCA) score and partial least squares (PLS) regression/prediction plots[11,12] were built by the UnscramblerX10.4 chemometrics software.

RESULTS

In this study, UV–Vis spectrophotometric analyses allied with chemometrics were carried out for the simultaneous determination of DEX and TCC in their binary pharmaceutical dosages. The chemometric analyses including PCA and PLS regression/prediction were applied to evaluate the spectra and contribute to the reliability of spectral results. The "cross-validation" method was used to calculate the reliability estimation of the PLS regression models and to validate them.[11-16] There is an optimum rank value for each of the calibrations created for chemometric quantitative models. The criterion for determining this optimum rank is to compute the RMSEC, RMSECV, slope, offset, and R^2 values obtained from the test set or cross-validation analysis. The estimation values obtained from the developed PLS regression models were evaluated to assess model statistical performance. The similarity of the applied methods in terms of predictive power was examined. The reliability and robustness of the models were also analyzed, and the differences between them, including their accuracy levels, were compared. The predictive ability of these developed regression models is further validated through model verification procedures. Moreover, the influence of

the chosen statistical methods and the characteristics of the sample on the predictive performance of the models was estimated.

According to the results that were evaluated with chemometrics for each drug ingredient in a single standard formulation, the PLS regression model for TCC standard showed the limit of detection (LOD) value as 0.0028 mg and the R^2 value was 0.9939 in a single formulation of TCC (Fig. 2a). The PCA model for the classification of TCC standard in single formulation shows that Factor 1 explains most of the data in the analysis. Distinctions along this axis may be strongly associated with changes in concentration (Fig. 2b). The PLS regression model for DEX standard showed the LOD value as 0.0036 mg; $R^2 = 0.9939$ in the single formulation (Fig. 3a). The PCA model for the classification of DEX standard in single formulation (Fig. 3b). The PLS regression model for the simultaneous determination of DEX and TCC in the mixture formulation shows R^2 value as 0.9900 (Fig. 4a). The PCA model for DEX and TCC standard in the mixture formulation shows a higher dependence on Factor 1 than Factor 2 (Fig. 4b).

Finally, simultaneous determinations of the active ingredients of DEX and TCC in real pharmaceutical tablets were performed by using the developed/validated UV–Vis spectroscopy method. In the analyses at this stage, 2 different commercial tablets purchased from pharmacy stores were used. The "unknown sample" coded samples created from 2 different commercial tablets were tested with the calibration models. It was observed that quite successful results were obtained for the simultaneous determination of binary active ingredients in real samples with the obtained prediction models. For the real tablet samples, each film-coated tablet contains 8 mg TCC and 36.9 mg DEX; the predicted and reference values are given in Fig. 5 and also the deviation is given.

DISCUSSION

This approach offers more sensitive and cost-efficient results for the simultaneous quantification of DEX and TCC by UV–Vis spectrophotometric method. Statistically successful R^2 and RMSEC values for DEX were obtained as 0.9939 and 0.0036 mg, respectively, by the PLS regression

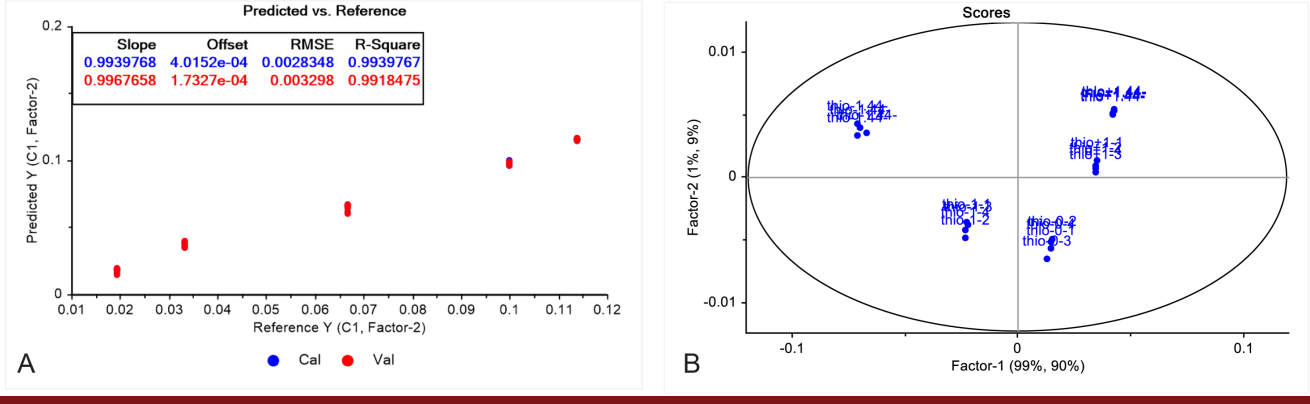


Figure 2. (a) Partial least squares regression model for the quantification of thiocolchicoside standard (Cal, calibration data; Val, validation data) and (b) Principal component analysis model for the qualification of thiocolchicoside standard.

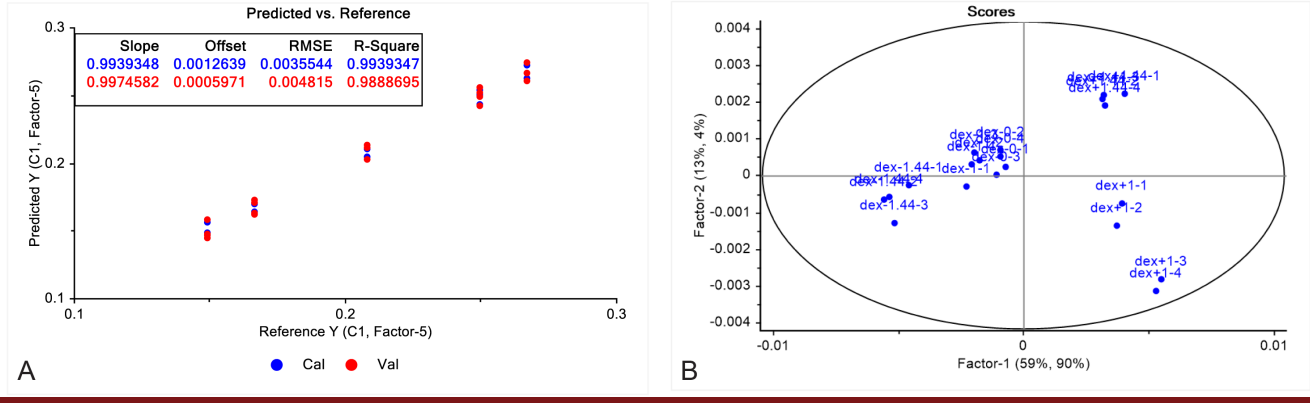


Figure 3. (a) Partial least squares regression model for the quantification of dexketoprofen trometamol standard (Cal: calibration data; Val: validation data) and (b) Principal component analysis model for the qualification of dexketoprofen trometamol standard.

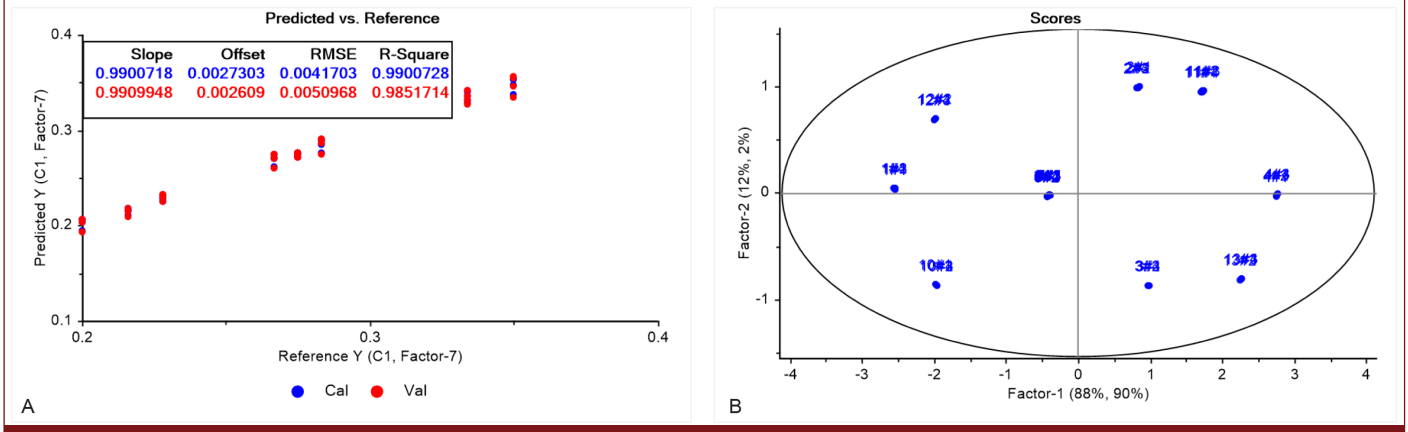
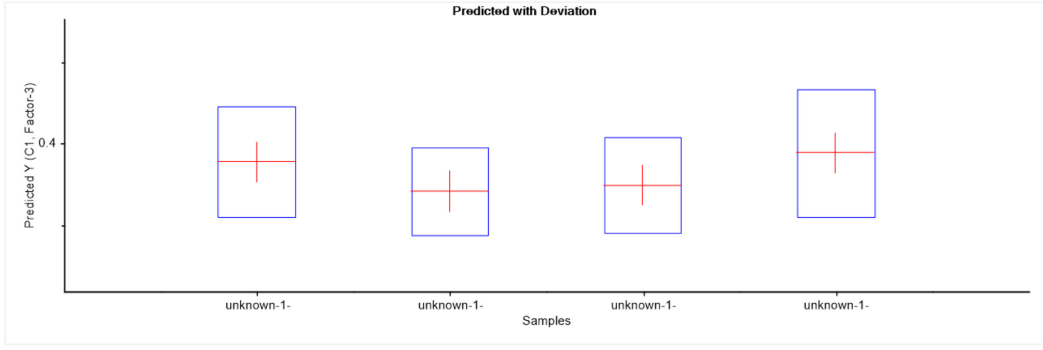
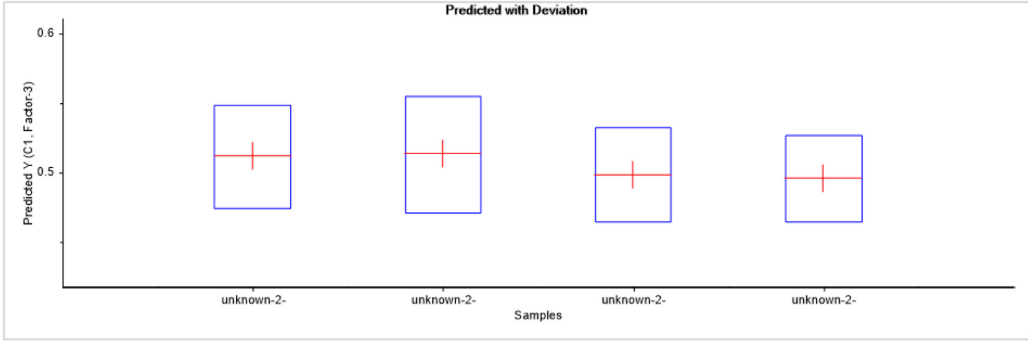


Figure 4. (a) Partial least squares regression and (b) Partial least squares regression model for the simultaneous quantification and qualification of thiocolchicoside and dexketoprofen trometamol standards in binary formulations (Cal: calibration data; Val: validation data).



Predicted Y (C1, Factor-3)	Predicted	Deviation	Reference
unknown-1-1	0.3885	0.0338	0.3742
unknown-1-2	0.3705	0.0268	0.3742
unknown-1-3	0.3743	0.0291	0.3742
unknown-1-4	0.3940	0.0392	0.3742



Predicted Y (C1, Factor-3)	Predicted	Deviation	Reference
unknown-2-1	0.5114	0.0371	0.5100
unknown-2-2	0.5128	0.0419	0.5100
unknown-2-3	0.4980	0.0341	0.5100
unknown-2-4	0.4951	0.0310	0.5100

Figure 5. Partial least squares prediction models for the simultaneous quantification of thiocolchicoside and dexketoprofen trometamol standards in real pharmaceutical tablet samples.

models. Similarly, statistically significant R^2 and RMSEC values for TCC were obtained as 0.9939 and 0.0028 mg, respectively, by the PLS regression models. The PLS regression model for the simultaneous determination of DEX and TCC in the mixture formulation shows R^2 value as 0.9900. The implementation of these chemometrics models underscores their critical role as robust analytical tools for in-process monitoring and quality assurance, thereby ensuring the precision and uniformity of pharmaceutical dosages.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: This study did not involve human participants and was conducted using a publicly accessible website; therefore, ethical approval was not required..

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.Ö., S.N.D., S.D.Ç., F.N.A.; Design – N.Ö., S.N.D., S.D.Ç., F.N.A.; Supervision – N.Ö., S.N.D., S.D.Ç., F.N.A.; Resources – N.Ö., S.N.D., S.D.Ç., F.N.A.; Materials – N.Ö., S.N.D., S.D.Ç., F.N.A.; Data Collection and/or Processing – N.Ö., S.N.D., S.D.Ç., F.N.A.; Analysis and/or Interpretation – N.Ö., S.N.D., S.D.Ç., F.N.A.; Literature Search – N.Ö., S.N.D., S.D.Ç., F.N.A.; Writing – N.Ö., S.N.D., S.D.Ç., F.N.A.; Critical Review – N.Ö., S.N.D., S.D.Ç., F.N.A.

Declaration of Interests: The authors have no conflicts of interest to declare.

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