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Quantitative Relationships Analysis of Structure and Activity of Asam-5-Aryledene-*N,N'*-dimethylbarbituric Derivatives as an Uric Acid Drug

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Abstract:

Objective: This study aims to obtain the best equation model for QSAR which can be used as a gout drug. Quantitative analysis of the structure-activity relationship of 5-aryledene-*N,N'*-dimethylbarbituric acid derivatives has been carried out as a drug for gout.

Methods: QSAR analysis was performed using the PM3 method using atomic net charge, log P, E_{HOMO}, E_{LUMO}, dipole moment (μ), and polarisabilities (α) as descriptors, followed by analysis using the multilinear regression method.

Results: The results of the QSAR analysis of 5-aryledene-*N,N'*-dimethylbarbituric acid derivatives which were calculated by the multilinear regression method resulted in 4 models of QSAR equations.

Conclusions: Based on the best QSAR equation model (model 3), there is a selected quantitative

relantionship with the most suitable parameters to describe the structural relationship of 5-aryledene-*N,N'*-dimethylbarbituric acid derivatives on xanthine oxidase inhibitor activity, namely atoms (C_2), (N_3), (C_5), and (C_6).

Keywords: Gout, QSAR, 5-Aryledene-*N,N'*-dimethylbarbituric acid derivatives

1. Introduction

Gout is a disease that is widely known at the time of Hippocrates, the father of modern medicine who lived between 460 BC to 377 BC. Gout is often referred to as the disease of kings and kings of disease, because it often appears in groups of people with high socioeconomic abilities[1]. Uric acid is an acid that is formed due to purine metabolism in the body. Purine comes from foods that contain protein. Examples of foods that contain lots of purines are offal, meat, shellfish, crab, shrimp, chips, beans, spinach, kale, cabbage, durian. , pineapple, tape, alcohol, and coffee[2]. Under current conditions, gout is one of the most common particular diseases found in society, with increasing incidence and prevalence in the last decade[3,4]. Gout sufferers in their therapy often use the drug allopurinol as a drug that lowers uric acid levels[5].

Allopurinol works by inhibiting the action of the xanthine oxidase enzyme in forming uric acid because it has a xanthine-like structure. Xanthine is a substrate of xanthine oxidase. Xanthine oxidase (XO) is involved in the metabolic pathway leading to the formation of uric acid. Allopurinol has side effects such as nausea, diarrhea, and skin redness accompanied by itching, headache, and liver and kidney damage[6]. Therefore, there is a need for a safe alternative treatment as a natural xanthine oxidase inhibitor.

Of the several drug compounds in medical therapy, there are new compounds that need to be known for their biological activity in computational chemistry so that it can be known whether these drug compounds are good or not to be used as gout drugs, these compounds are derivatives of acid-5-aryledene-*N*,*N*'-dimethylbarbiturate compounds, which has been studied experimentally and has known IC_{50} data to calculate the activity of the drug compound. Derivatives of acid-5-aryledene-*N*,*N*'-dimethylbarbiturate are compounds derived from barbituric acid, the content contained in barbituric acid can provide a calming effect, relax muscles, and can induce or start the anesthetic process so that it can relieve pain and aches which immediately attacks the sufferer of gout. This derivative of the acid-5-aryledene-*N*,*N*'-dimethylbarbiturate compound also contains a heterocyclic compound on the nitrogen atom. Where, nitrogen atoms are produced from the

process of catabolism of purine substances.

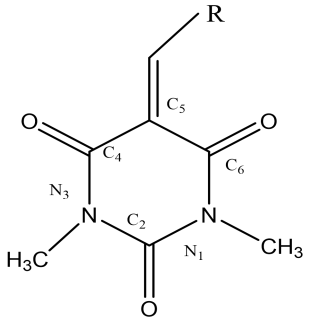
Advances in information technology at this time can be used as an alternative to the search for new drugs. Computational chemistry has high potential in medicinal chemistry, not only accelerating the drug discovery process but also changing the way drug discovery and design are carried out. Rational Drug Design (RDD) facilitates and speeds up the drug design process, which involves various methods for identifying new compounds. One of the most frequently used computational chemistry applications in the design of drug compounds is the study of Quantitative Structure-Activity Relationships (QSAR). The QSAR study aims to find an empirically consistent relationship between the molecular properties and biological activity of a compound[7].

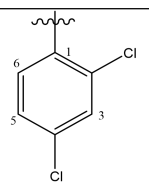
2. Material and methods

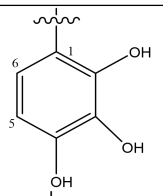
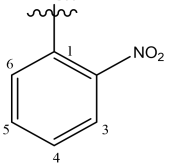
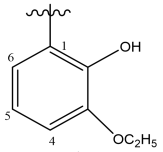
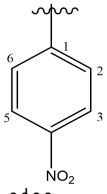
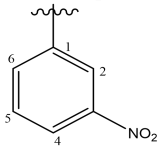
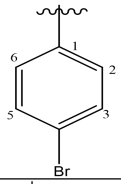
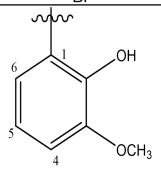
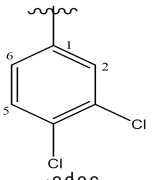
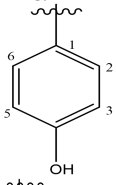
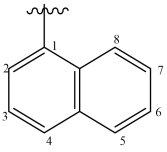
Subjects

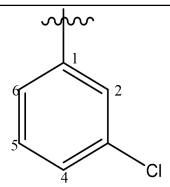
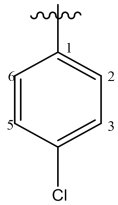
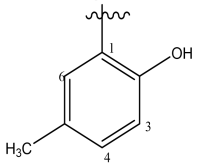
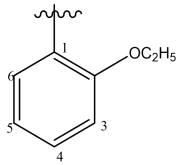
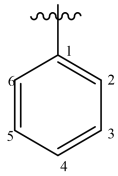
The materials used in this study were 5-aryledene-*N*,*N*'-dimethylbarbituric acid and its derivatives along with IC_{50} data obtained from Khan *et al*.,[8] which can be seen in Table 1. This study uses computer methods in the application of computational chemistry with one of the most frequently used computational chemistry applications in the design of drug compounds is the study of Quantitative Structure-Activity Relationships (QSAR) which aims to find empirically consistent relationships between molecular properties and biological activity of compound.

Table 1. Structure of 5-aryledene-*N*,*N*'- dimethyl barbituric acid derivatives



No. Compound	R	IC_{50} (µM)
1		20.97

No. Compound	R	IC_{50} (μM)
2		24.25
3		26.94
4		41.00
5		70.19
6		71.49
7		75.03
8		93.70
9		98.90
10		118.22
11		120.5

No. Compound	R	IC_{50} (µM)
12		125.5
13		196.34
14		233.8
15		278.8
16		327.0

Source: Khan et al., (2013)

Methods

Calculation of Predictions using the PM3 Semiempiric Method

The first step is to draw each 5-aryledene-*N,N*'-dimethylbarbituric acid compound and its derivatives in two-dimensional (2D) form as presented in Table 1. The drawing was done using the HyperChem Professional 8.0 for Windows program. Furthermore, the structure of the compound in 2D form is converted into 3D by adding H atoms on the [Build]-[Add H & Model Build] menu. The 3D structure is optimized for geometry using the PM3 method with the Polak-Ribiere algorithm or the gradient method, with a value of RMS = 0.001 kcal/(Å.mol). Before the geometry optimization is run, it is necessary to make settings in the HyperChem program by selecting the [Setup] [Semi-empirical] [PM3] [Option] [Convergence limit] 0.001 kcal/Å.mol [Iteration limit] menu to adjust. Geometry optimization is run by selecting the [Compute] [Geometry optimization] [Pattern-Ribiere] [RMS Gradient of] 0.001 kcal/Å.mol or maximum cycles adjusted [Screen refresh period] 1 cycles. Optimization was stopped after reaching the convergence limit that had been set, namely 0.001 kcal/Å.mol. After the most stable structure is

obtained, the descriptor data is recorded via the single point menu.

Calculation of Physical-Chemical Properties

Single point calculations are used to obtain data on the net atomic charge values (N1, C2, N3, C4, C5, C6), dipole moment (μ), polarizability, E_{LUMO} and E_{HOMO}. This calculation is started by selecting the [File] [Start log] menu, then single point calculations are performed by selecting the [Compute] [Single point] menu, then selecting the [File] [Stop log] menu to stop data recording. The data that has been recorded is stored in the form of [log file]. To obtain EHOMO and ELUMO value data, orbitals calculations are carried out after a single point calculation is carried out. Calculation of orbitals is done by selecting the [Compute] [Single point] [Orbitals] menu. Data on the value of molecular polarizability (α) by calculating QSAR properties, namely by selecting the [Compute] [QSAR properties] menu, then selecting the desired variable [Compute]. Then the optimized structure is saved as file.hin.

Correlation Analysis Between Variables

The independent variables used are: net atomic charge (N1, C2, N3, C4, C5, C6), dipole moment, LUMO energy, HOMO energy, polarizability, log P and 1/log IC_{50}. All variables were analyzed using the SPSS program on the [analyze] [correlate] [bivariate] menu to obtain correlation values for the variables.

QSAR Equation Analysis using Multilinear Regression Method

The Multilinear Regression method is analyzed to obtain the QSAR equation model by selecting the [analyze]-[regression]-[linear] menu using the backward method which was processed with SPSS Statistics 25 for Windows. The results obtained were in the form of the QSAR equation along with statistical parameter values such as r, r^2, SE, F, and PRESS values. In addition to these statistical parameters, the calculation results also obtain the constant values and coefficient values for each independent variable involved in the resulting equation.

Determination of the Best QSAR Equation Model

The best equation model is selected by analyzing mathematical equation models based on statistical criteria. The best QSAR equation model is the one that represents the three Hansch parameters which must have a statistical parameter value of $r>0.8$, high r^2 value, low SE, F_{count}/F_{Table} value of more than 1, and the smallest PRESS value.

3. Results

Structure Optimization Results of 5-aryledene-N,N'-dimethylbarbituric Acid Derivatives

The structural framework used in determining the net atomic charge and other descriptors in this study is the basic structural framework of 5-aryledene-*N,N*'-dimethylbarbiturate acid compounds. Derivatives of 5-aryledene-*N,N*'-dimethylbarbituric acid compounds that have been formed and structured optimized using the HyperChem Professional 8.0 application for Windows with the PM3 method can be seen in Figure 1.

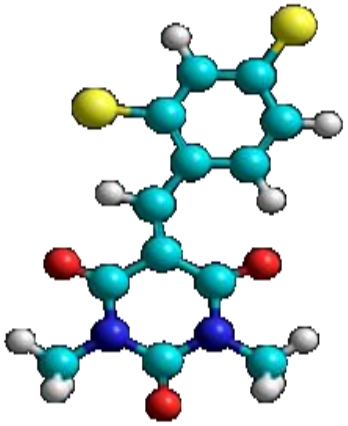


Figure 1. Structural model of the of 5-aryledene-*N,N*'-dimethylbarbituric acid

Automatically the calculation results file is recorded in the form of a notepad file, so to view the recording results also use a notepad file. Through the notepad file, complete data can be obtained, including the total energy, heat of formation, binding energy and atomic charge of all atoms making up the optimized structure of the compound. After that, the data obtained was processed using the Microsoft Excel 2010 application.

Descriptor Calculation Results

Descriptors are parameters or properties of molecular structure that are used as independent variables in the calculation of theoretical IC_{50} values. The descriptors used in this study are net atomic charge, dipole moment, log P, HOMO-LUMO energy, and polarizability, which are fully presented in Table 2 and Table 3.

Table 2. Calculation results of the electronic structure of internal fitting compounds

No. Compounds	qN1	qC2	qN3	qC4	qC5	qC6	M	Elumo	Ehomo	α (A^3)	Log P	1/Log IC_{50}
2	-0.042273	0.252992	-0.035665	0.313624	-0.288749	0.346294	4.523	-1.405429	-9.261108	27.18	-2.66	0.72
5	-0.036312	0.251766	-0.029789	0.304265	-0.236936	0.334460	3.896	-2.215477	-10.403	26.99	-0.39	0.54
6	-0.034704	0.251703	-0.030554	0.307312	-0.248953	0.330903	4.902	-1.962996	-10.27192	26.99	-0.39	0.54
7	-0.040201	0.252590	-0.032155	0.310047	-0.265234	0.340410	1.285	-1.671354	-9.780804	27.9	0.47	0.53
8	-0.052946	0.265214	0.265214	0.319037	-0.280402	0.337929	3.672	-1.223603	-9.414862	28.38	-1.6	0.51
9	-0.039797	0.252509	-0.031931	0.309604	-0.263787	0.340232	1.074	-1.725808	-9.438203	29.13	-0.03	0.50
10	-0.041807	0.252857	-0.033456	0.314365	-0.287314	0.345322	2.701	-1.468003	-9.290762	25.91	-0.61	0.48
11	0.234981	0.181343	-0.036363	0.292136	-0.233151	-0.228963	1.823	-1.591072	-8.375594	31.45	0.49	0.48
13	-0.040664	0.252657	-0.032493	0.311017	-0.269894	0.341291	1.673	-1.63608	-9.475353	27.2	0.2	0.44
14	-0.042520	0.252997	-0.035241	0.312603	-0.284343	0.344831	4.092	-1.391834	-9.195309	27.74	-0.45	0.42
15	-0.053843	0.265242	-0.055219	0.319994	-0.284615	0.338677	3.638	-1.153378	-9.344003	29.58	-0.23	0.41
16	-0.041967	0.252921	-0.033157	0.311958	-0.274212	0.342059	2.544	-1.504712	-9.707597	25.27	0.42	0.40

Table 3. The results of the calculation of the electronic structure of the external test compound

No. Compounds	qN1	qC2	qN3	qC4	qC5	qC6	M	Elumo	Ehomo	α (A^3)	Log P	1/Log IC_{50}
1	-0.039818	0.252333	-0.031912	0.307359	-0.256218	0.339702	1.674	-1.736219	-9.494611	29.13	-0.03	0.76
3	-0.059497	0.265086	-0.072754	0.305947	-0.057204	0.360515	2.435	-1.234689	-10.00526	26.99	-0.39	0.70
4	-0.053004	0.265278	-0.054918	0.319285	-0.281048	0.338199	3.903	-1.206746	-9.3845.88	30.22	-1.26	0.62
12	-0.040718	0.252702	-0.032406	0.310154	-0.266321	0.340655	1.695	-1.622303	-9.603744	27.2	0.20	0.48

The calculation method for obtaining the descriptors used in this study is in accordance with the descriptor calculation method used by Motta *et al*.[9], Hadanu[10-12] in the analysis of the relationship of quantitative-structure and activity of medicinal compounds.

Results of Correlation Analysis Between Variables

This correlation analysis between variables aims to see from the start how the relationship between variables really is. This is done mainly by looking at the effect of each substituent at a certain position on the activity of xanthine oxidase inhibition. In this analysis the independent variables and dependent variables were all included in one data group, then analyzed with SPSS for Windows version 25 software to determine the correlation value between variables. Correlation values can be calculated by first plotting all the variables tested for correlation, then analyzing them using the bivariate correlation method which automatically calculates the correlation values between related variables. This method is in accordance with the QSAR analysis research conducted by Hadanu[10-12], Putri *et al*.[13], and Nurainy[14].

Results of Multilinear Regression Analysis

The results of multilinear statistical analysis using the backward method, the data used were 16 compounds, 4 compounds were used as test data which were selected because they had similarities with other compounds and the remaining 12 compounds were used as fitting data. Before selecting good internal fitting data and external test data, it is necessary to conduct an experiment and compare the values. The results of the analysis of the fitting compounds can be seen in Table 4.

Table 4. Multilinear statistics calculation results

QSAR Models	R	r^2	Fcal/Ftab(0,05)	SE	PRESS
1	0.999[a]	0.998	0.240	0.01196	0.42988
2	0.999[b]	0.998	0.799	0.00846	0.37026
3	0.999[c]	0.998	10.995	0.00715	0.15941
4	0.999[d]	0.997	20.051	0.00765	0.67514

4. Discussion

Correlation between variables in this study including net atomic charge, dipole moment, HOMO-LUMO energy, polarizability and log P showed a very strong correlation. This is indicated by the absolute value of the correlation which is close to 1 or -1. Evidence of a close correlation can be

seen, among others, in several relationships between net atomic charge and IC^{50} as well as between descriptors that have a fairly high correlation, for example: correlation between variables qN1-qC2(-0.987), qN1-qC4(-0.883) , qC2-qC4(0.888), qN1-qC5(0.607), qC2-qC5(-0.631), qC4-qC5(-0.871), qN1-qC6(-0.998), qC2-qC6(0.973), qC4-qC6(0.801), qC4-ELumo(0.592), qC5-ELumo(-0.774), qN1-EHomo(0.640), qC2-EHomo(-0.599), qC6-EHomo(-0.656), ELumo-EHomo(0.626), qN1-polarizability(0.660), qC6-polarisability (-0.690), EHomo-polarisability(0.601), dipole moment-log P(-0.642), and log P-log $1/IC_{50}$ (-0.712). The negative value of the correlation does not indicate the strength of the effect of the substituents on the activity of xanthine oxidase inhibition, but only indicates the direction of the effect. Negative correlation values indicate a negative relationship, meaning that the effect of one variable is inversely proportional to the other variable. If it is related to the log $1/IC_{50}$ value, it is clear that the independent variable that has a relatively large correlation to the activity of xanthine oxidase inhibition is the log P variable. The correlation value is -0.712. Determining the bivariates relationship between variables, using the bivariate analysis method using SPSS for Windows software version 25 according to the methods carried out by previous researchers including QSAR analysis research by Suardiani and Kesuma[15], Yeni *et al*.[16], and Widiyanti *et al*.[17].

Determination of the Best QSAR Equation Model

Based on the calculation results of multilinear regression statistics using SPSS for Windows version 25 software, 4 QSAR equation models were obtained. Of the four QSAR equation models obtained, the best 1 equation model was selected, namely QSAR equation 3 model. QSAR Equation 3 model was chosen as the best QSAR equation among the four alternative equation models based on statistical validity criteria. The QSAR eequation 3 model have statistical validity criteria including the value of r and r^2 close to 1 which is equal to 0.999 and the value of r^2 is 0.998, this shows very optimal data linearity. From the values of r and r2 obtained, the model equations 1, 2, 3, and 4 are relatively the same in size up to 2 decimal places. The lowest SE value, namely the model QSAR equation 3, has the smallest SE value (0.00715). The equation 2 model have a F_{count} value that exceeds the F_{Table} value or a F_{cal}/F_{tab} ratio of more than 1. The QSAR equation 3 model is chosen because it has a large F_{cal}/F_{tab} value of 10.995, and has the smallest PRESS value of 0.1. The PRESS values are relatively smaller than models 1, 2, and 4. The values of r = 0.999 and r^2 = 0.998 indicate that the correlation between the independent variables and the activity of xanthine oxidase inhibition is very close. This means that the change in the IC_{50} value of a series of 5-aryledene-N,N'-dimethylbarbiturate acid derivatives of 99.80% was caused by changes in electronic structure, dipole moment, LUMO energy, HOMO energy, polarizability, and log P, all of which is the independent variable. The resulting F value indicates that the equation 3

model meets the significance requirements. At the 95% confidence level as indicated by the F_{cal}/F_{tab} ratio which has a value of more than 1, which is 10.995. The determination of the best equation model uses the same method as research related to QSAR analysis conducted by Hadanu *et al.*[18], Catalani *et al.*[19], and Kim *et al.*[20]. Model equation 3 can be written as the following equation.

1/Log IC_{50} Prediksi= -3.718 - 12,228 (qC2) - 0.056 (qN3) - 7.564 (qC5) + 0.405 (qC6) - 0.042 (μ) - 0.415 (E_{Homo}) + 0.045 (α) - 0.127 (log P); n=12; r=0.999; r^2=0.998; SE=0.00715; F_{cal}/F_{tab}= 10.995; PRESS=0.159.

To see the accuracy of the QSAR model obtained, it is necessary to calculate the IC_{50} value of the external test compound. Where, the external test compound is a derivative of the 5-aryledene-N,N'-dimethylbarbiturate acid compound whose experimental IC_{50} value is known, but is not included in the calculation process to determine the QSAR equation model. This is intended so that the validation of the QSAR model obtained is more accurate, because apart from being validated with fitting compounds, it is also validated with external test compounds.

From the results of the correlation graph between the predicted IC_{50} of the external test compound and the experimental IC_{50} value of the 4 compounds that have been separated as test compounds, it can be seen that the R^2 value has a very low value, therefore it is necessary to remove one external compound so that the R^2 value gets a good value. From the calculation results, compound 1 is omitted because the predicted value obtains a value that is inversely proportional to the experimental results and the resulting R^2 value is very low, if compound 1 is included in the calculation of the external test compound. Therefore, only 3 compounds were included in the external test compounds, namely compounds 3, 4, and 12. From the results of calculating the correlation graph between the predicted IC_{50} and the experimental IC_{50} obtained, it can be seen that the R^2 value in the test of the three compounds was very good, when compared to the test the 4 compounds previously, but it is necessary to test each model of the equation again, to get the accuracy of the best QSAR equation model.

From the results of the correlation graph between IC_{50} predictions of external test compounds and experimental IC_{50} values, the equation 3 model has a good R^2 value of 0.9123. This shows that the model equation 3 is a good equation to determine the theoretical IC_{50} value of the modeled compound. The high R^2 value from the correlation graph between the predicted IC_{50} of the external test compound and the experimental IC_{50} value strengthens the QSAR equation 3 model as the best QSAR equation.

Influenced Descriptors and Active Sites of 5-Aryledene-N,N'-Dimethylbarbituric Acid Derivatives

The descriptors that influence the best QSAR equation model (equation 3 model) are qC2, qN3, qC5, qC6, dipole moment, HOMO energy, polarizability and log P. Then determine the active side of the best QSAR equation model (QSAR equation model 3). Determination of the active site aims to design or find a 5-aryledene-*N*,*N*'-dimethylbarbituric acid derivative that can increase activity higher. In the structure of this 5-aryledene-*N*,*N*'-dimethylbarbiturate acid derivative, it can be understood that the active functional groups of the main compounds are in the ketone group (C=O) and the amine group (N-CH_3) which can be seen in Figure 2.

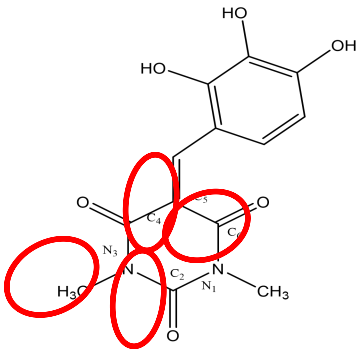


Fig. 2. Functional groups and active sites in the structure of the 5-aryledene-*N*,*N*'-dimethylbarbituric acid

Substitution of this group will result in a significant change in modeling the synthesis of this compound through retrosynthetic methods and functional group interconversion. The position of the substituents on the active side of the compound is the main consideration for producing a new xanthine oxidation inhibitor compound, a 5-aryledene-*N,N*'-dimethylbarbiturate acid derivative with higher biological activity. Based on the results of the equation 3 model, the best QSAR equation is found in atoms (C2), (N3), (C5), and (C6) as active sites (Figure 2) which can be carried out Functional Group Interconversion (FGI) using the retrosynthetic method so that they can produce compounds with higher theoretical activity. Determination of the active side of the 5-aryledene-N,N'-dimethylbarbituric acid derivative based on the best QSAR equation model[21,22].

Conclusions

The best QSAR equation model that expresses the quantitative relationship between structure and activity of 16 homologous compounds of gout drugs derived from 5-aryledene-*N,N*'-dimethylbarbituric acid, namely:

1/Log IC_{50} Prediction = -3.718 - 12.228(qC2) - 0.056(qN3) - 7.564(qC5) + 0.405(qC6) - 0.042(μ) - 0.415(E_{Homo}) + 0.045(α) - 0.127(Log P); n=12; r=0.999; r^2=0.998; SE=0.00715;

F_{Count}/F_{Table}=10.995; PRESS=0.159.

The most suitable parameters to describe the structural relationship of 5-aryledene-*N,N'*-dimethylbarbituric acid derivatives on xanthine oxidase inhibition activity are C2, N3, C5, and C6 atoms. In these atoms Functional Group Interconversion (FGI) can be carried out using the retro synthetic method so as to produce compounds that have higher theoretical activity.

Authors Contribution

Ruslin Hadanu, Samsia Abd Samad, processed the research data, performed the analysis,drafted the manuscript and designed the figures, performed the calculations, worked on the manuscript. Muhammad Fath Azzajad, assisted in interpreting the results. All authors discussed the results and commented on the manuscript.

Statement of Human Rights

The study was carried out following the ethical standards of the responsible committee for human experimentation (institutional and national).

Statement of Informed Consent

Informed consent was obtained from the participants on the Internet at the end of the e-questionnaire to publish their anonymized information in this article.

Declaration of Conflict of Interests

The authors declared that they had no potential conflicts of interest in the research, authorship, and/or publication of this article.

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