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HEALTH SCIENCES

The Dosage Effect of Manganese Superoxide Dismutase (MnSOD Val16Ala) Polymorphism in Acne Vulgaris and *In Silico* Identification Analysis of Biological Features of Variation

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Abstract: The exact cause of acne vulgaris remains unclear. However, evidence suggests polymorphism in the manganese superoxide dismutase (*MnSOD*) gene increases acne vulgaris risk by altering the protein's secondary structure. This study aimed to perform *in silico* and *in vitro* analyses of the *MnSOD* Val16Ala substitution, involving 119 acne vulgaris patients and 96 controls. Bioinformatic tools, including SIFT, PolyPhen, SNPs&GO, Panther, PhD-SNP, SNAP2, I-mutant, and I-TASSER, were utilized for *insilico* analyses. Genotypes and allele frequencies were determined by real-time PCR. Odds ratios (OR) and 95% confidence intervals assessed association strength. *In silico* results indicated the conversion of *MnSOD* Val16Ala is tolerated; nevertheless, the I-mutant score suggested decreased protein stability. A significant statistical correlation was found in the allele positivity [OR:2.216, 95%CI:1.269-3.87, chi2:7.95, p:0.0048]. In the homozygous model, a significant difference was observed [OR:2.724, 95% CI:1.145-6.48, chi2:5.33 p: 0.021]. The results demonstrated that the rs4880 "C" allele significantly affected acne development [OR:1.701, chi2:7.62, p: 0.005]. Due to alterations in structure, the inclusion of every variant allele of *MnSOD* has a more significant impact on redox balance. The findings unequivocally demonstrated that the *MnSOD* Val16Ala gene polymorphism has a considerable impact on the allele dosage of acne vulgaris.

Key words: Acne vulgaris, *in silico* SNP analyses, *MnSOD,* SIFT, rs4880, Val16Ala.

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of pilosebaceous follicles whose etiopathogenesis is not fully known. It is caused by four main factors: increased sebum production with changed lipid content; hyperkeratinization of the infundibular pilosebaceous duct; *Cutibacterium acnes* (*C. acnes*) colonization; and inflammation (Hazarika 2021, Kiratikanon et al. 2024, Zhu et al. 2020). These factors are interrelated, with oxidative stress underpinning all these pathogenetic mechanisms.

Neutrophils are attracted to the pilosebaceous follicles by the chemotactic effect of *C. acnes*. Once there, they generate reactive oxygen species (ROS) to eliminate the bacteria. Within a healthy cell, surplus ROS are neutralized through antioxidant mechanisms, including enzymes like catalase (CAT) and superoxide dismutase (SOD), as well as molecular scavengers such as glutathione and thioredoxin. Oxidative stress arises when ROS concentrations reach toxic levels, damaging biomolecules like DNA, proteins, and lipids. Oxidative stress in acne leads

to inflammation by damaging the pilosebaceous unit and surrounding tissue (Dos Santos et al. 2019, Lim et al. 2021).

Despite the prevalence of acne vulgaris, there is a lack of research on the role of antioxidative systems and genetic factors in its development. Disruption of the balance between oxidants and antioxidants leads to the release of inflammatory molecules and proteases. Mitochondrial superoxide dismutase 2 (SOD2) encoding by manganese superoxide dismutase (MnSOD), is a crucial enzyme that scavenges radicals, maintaining the balance between oxidants and antioxidants to protect cells from damage. The substitution of thymine (T) with cytosine (C) at position 47 (C47T) on the *MnSOD* gene changes valine (GTT) to alanine (GCT), altering enzyme activity due to structural changes (Shimoda-Matsubayashi et al. 1996). The aim of this study is to investigate the relation between acne vulgaris and *MnSOD* Val16Ala gen polymorphism both *in silico* and *in vitro* analyses. This study is the first *in silico* investigation characterizing the *MnSOD* Val16Ala substitution utilizing computational approaches and linked clinical data.

MATERIALS AND METHODS

Study design

This case–control study was conducted at Çanakkale Onsekiz Mart University and received approval from the Clinical Research Ethics Committee on 27/04/2016 (decision number 08-03). All procedures adhered to ethical standards set by institutional and national ethics committees overseeing human subjects research, and the 1975 Helsinki Declaration, revised in 2000, and included participants who sought treatment at our clinic from May 2016 to June 2019. Adult participants and parents of underage participants provided informed consent.

Study population, inclusion and exclusion criteria

The study comprised 119 patients diagnosed with acne vulgaris and 96 healthy adults as controls. The patient group consisted of 59 males and 60 females, with a mean age of 23.50 ± 7.15 years. The control group included 48 males and 48 females, with a mean age of 28.78 ± 11.79 years. They had not used any systemic or topical acne medication for the last six months. They were free of systemic ailments, did not use systemic medication, and had no history of smoking or alcohol intake. The control group was selected from individuals who visited the clinic for minor dermatological issues, such as ingrown toenails or basic skincare concerns. To ensure the accuracy of acne status, all participants underwent a thorough clinical evaluation conducted by dermatology specialists. During the dermatological examination, the presence of acne-related lesions (comedones, papules, pustules, nodules, and cysts) was carefully assessed. Additionally, individuals with a history of acne or current signs of acne were excluded from the study. Only those who had not undergone any systemic or topical treatments that could affect skin health (such as retinoids, antibiotics, or hormonal therapies) within the past six months, and those who had not used any anti-acne cosmetic products, were included. This ensured that the control group was confirmed to be unaffected by acne and free from potential external influences on skin health. They also did not engage in regular exercise beyond daily activities. All participants provided written informed consent.

Genetic structure analysis

The venous blood samples were collected to the 2 ml in EDTA-coated tubes for genomic DNA extraction, using the GeneJET Whole Blood Genomic DNA Purification Kit (Thermo Fisher Scientific, Waltham, MA, USA). Primers used were forward 5'-AGCCTGCGTAGACGGTCC-3'and reverse 5'-TCGGGGAGGCTGTGCTTC-3'. The allele-specific probes were designed as FAM-labeled (T allele) probe: 5'-6-FAM-AGCCCAGATACCCCAAAACCGGAGCC-TAMRA-3' and HEX-labeled (C allele) probe: 5'-HEX-AGCCCAGATACCCCAAAGCCGGAGCC-TAMRA-3'. 'Real-time PCR allele-specific probes-based method detected the MnSOD genepolymorphism, with PCR reactions conducted in 50 µl volumes using 96-well plates and an optical adhesive film. The thermal profile included initial denaturation at 95°C for 10 minutes, followed by 35 cycles of 95°C for 20 seconds, 60°C for 30 seconds, and 72°C for 20 seconds.

In silico analysis

SNP information was retrieved from the NCBI databases (NCBI/dbSNP), including SNP ID, accession number, protein, position, and residue change. The *MnSOD* gene-encoded protein's primary sequence was acquired from the NCBI/dbSNP database (Gene ID 6648, SNP ID rs4880). Amino acid substitution (AAS) prediction methods employed bioinformatics prediction tools for sequence and structural information. We utilized various bioinformatics tools to predict the functional consequences of SNPs from the dbSNP database.

The tools utilized in this study were SIFT (Sorting Intolerant From Tolerant, https://sift.bii.a-star.edu.sg/www/SIFT_seq_submit2.html, Access Date: 25.12.2024), PolyPhen-1 (Polymorphism Phenotyping v1), PolyPhen-2 (Polymorphism Phenotyping v2, http://genetics.bwh.harvard.edu/pph2/index.shtml, Access Date: 25.12.2024) SNPs & GO (Single Nucleotide Polymorphism and Gene Ontology, https://snps-and-go.biocomp.unibo.it/snps-and-go/index.html, Access Date: 26.12.2024) Predict-SNP (Predictor of Human Deleterious Single Nucleotide Polymorphisms, https://loschmidt.chemi.muni.cz/predictsnp1/, Access Date: 26.12.2024), PANTHER (Protein ANalysis THrough Evolutionary Relationships, https://www.pantherdb.org/tools/csnpScoreForm.jsp, Access Date: 27.12.2024), PhD-SNP (Predictor of human Deleterious Single Nucleotide Polymorphisms, https://snps.biofold.org/phd-snp/phd-snp.html, Access Date: 27.12.2024), SNAP2 (Screening for Non-Acceptable Polymorphisms, https://service.rostlab.org/snap2web/, Access Date: 29.12.2024) and Mut-Pred v1.2 (Mutation Prediction, https://mutpred.mutdb.org/, Access Date: 29.12.2024). These tools were employed to determine if a genetic variant was tolerated or deleterious. If any of the predictions indicated a high-risk variation, further investigation was conducted to assess the impact of the variation. The deep fold analysis of MnSOD original amino acid sequence and the changed val16ala amino acid sequence were carried out by using I-TASSER (Iterative Threading ASSEmbly Refinement, https://aideepmed.com/DeepFold/, Access Date: 25.12.2024) online tool with default parameters.

Genetic diversity analysis

Genotypes and allele frequencies were calculated using the allele counting method. The Fisher exact test identified disparities in allele frequencies. Hardy- Weinberg equilibrium (HWE) was calculated for both controls and cases using the De Finetti program. Chi-square tests evaluated genotype frequencies, considering five genetic models (co- dominant, dominant, recessive, over-dominant, and log-additive) and calculating odds ratios (ORs) with 95%

confidence intervals (CIs). A P-value less than 0.05 was considered statistically significant.

RESULTS

In silico analysis and SNP characterization.

The results of *in silico* analyses are presented in Table I. According to SIFT results Val16Ala changes tolerated with a score of 0.295 (Reliability Index (R.I.:0.94) PredictSNP, PANTHER, PhD-SNP, and SNAP2 scores all corroborated SIFT's findings, and the Val16Ala alteration was determined to be tolerated with a similar confidence ratio. In contrast, PolyPhen-1 and PolyPhen-2 results tolerated with similar score and confidence rate; but PolyPhen-2 classified Val16Ala as deleterious of these changes. We are interested in predicting stability changes using I-mutant because the results of PolyPhen 2 suggest that Val16Ala alterations could be deleterious. According to I-mutant results, Val16Ala mutation decreases stability; but overall protein still tolerate valine>alanine substitution that located at position 16 of the precursor protein while at position -9 of the processed mature (active) protein. The deep-fold analysis performed with the I-TASSERI-TASSER online tool revealed an elongation in the first α-helix structure due to the Val16Ala alteration, together with the ligand (Mn^{+2}) binding affinity was found to decrease from 0.64 to 0.60 depending on the variation (Figure 1).

Genetic structure analysis

The *MnSOD* 118C/T substitution leads to three genotypes: TT, CT, and CC. In 119 acne cases, genotype frequencies were TT: 38.29%, CT: 58.42%, CC: 22.29%. In controls, frequencies were TT: 46.76%, CT: 40.48%, CC: 8.76%. There was

Table I. Results of *in silico* analyses of *MnSOD* rs4880 polymorphism.

SNP ID: Rs4880	Score	% Expected Accuracy	Confidence	Pathogenicity	Reliability Index	Effect on MnSOD Protein Function and Structure
Nucleotide change	C47T	-	-	-	-	
Amino Acid Change	V16A	-	-	-	-	
SIFT	0.295	0.8691	87%	Neutral	0.94	Tolerated (Benign)
POLYPHEN-1	0.002	0.6688	67%	Neutral	-	Tolerated (Benign)
POLYPHEN-2	0.002	0.6752	68%	Deleterious	sensitivity: 0.99; specificity: 0.18	Tolerated (Benign)
SNPs & GO	0.05	NA	NA	NA	9	Benign
PredictSNP	NA	0.75291	75%	Neutral	-	
PANTHER	NA	0.7138	87%	Neutral	-	
PhD-SNP	NA	0.7828	78%	Neutral	7	Neutral
Inform meaning for caption		0.7682	77%	Neutral	-	
I-Mutant score				Stability Decrease	8	Stability Decrease

RI – Reliability Index; ΔΔG – Free energy change (kcal/mol); SIFT – Sorting Intolerant From Tolerant; PolyPhen-2 – Polymorphism Phenotyping v2; SNPs&GO – Single Nucleotide Polymorphism & Gene Ontology; PANTHER – Protein ANalysis THrough Evolutionary Relationships; PhD-SNP – Predictor of Human Deleterious Single Nucleotide Polymorphisms; SNAP2 - Screening for Non-Acceptable Polymorphisms 2.

a significant difference in *MnSOD* genotypes between individuals with acne and controls (TT: 38.29% vs 46.76%; CT: 58.42% vs 40.48%; CC: 22.29% vs 8.76%). The frequency of the *MnSOD* 118C allele was higher in the acne group compared to controls (OR: 1.763, 95% CI: 1.181-2.632, p=0.005). The *MnSOD* 118T>C polymorphism (rs4880) was significantly associated with a higher risk of acne. The odds ratio for the CT genotype was 2.083 (95% CI: 1.155-3.756, p=0.0143) and for the CC genotype was 2.724 (95% CI: 1.145-6.48, p=0.021) compared to the TT genotype. Additionally, there were notable correlations between TT genotypes and acne compared to (CT + TT) genotypes in both groups (OR: 2.216, 95% CI: 1.269-3.87, p=0.004). The dominant model indicated a 2.2 times increased risk of developing acne in individuals with heterozygous or double mutant genotypes (OR: 2.22, 95% CI: 1.27-3.87, p=0.0048) (Table II).

When we compare the *MnSOD* 118C/T substitution in a different model (Table III), the dominant model shows the acne development risk increases 2.2 times more in heterozygotes and double mutant individuals [OR:2.22; %95 CI: 1.27-3.87, p: 0.0048].

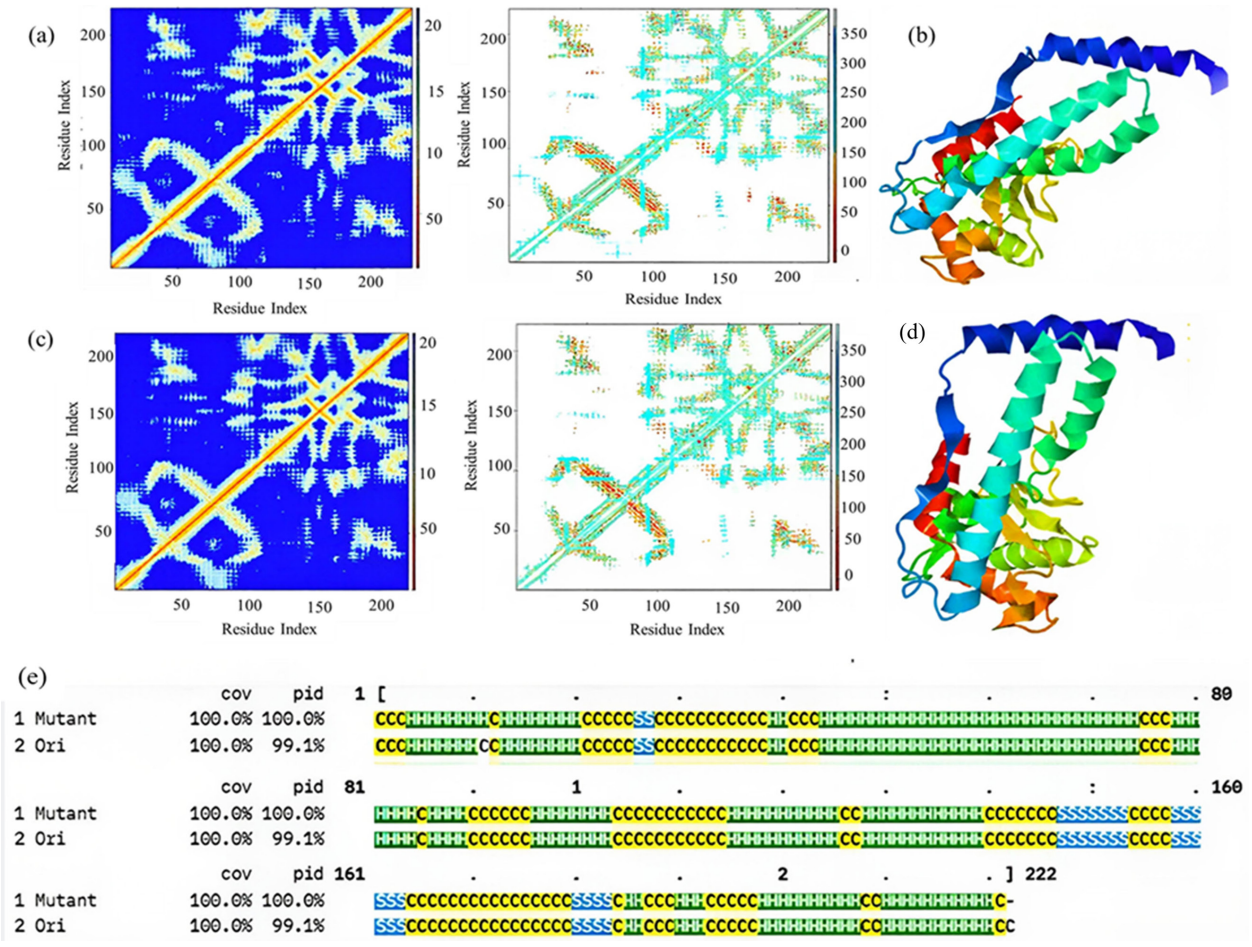

Figure 1. **DeepFold analysis of original amino acid sequence (Ori) and the changed Val16Ala amino acid sequence (Mutant) a) The DeepFold simulations for Ori sequence are guided by the consensus distance map (left) and orientation map (right), b) The top model of DeepFold analysis for Ori sequence, c) The DeepFold simulations for Mutant sequence are guided by the consensus distance map (left) and orientation map (right), d) The top model of DeepFold analysis for Mutant sequence, e) Comparing of Ori and Mutant structure results (C: Coil structure, H: Helix Structure, and S: Strand structure).**

Table II. Genotypes and allele frequencies of the MnSOD rs4880 polymorphism in patients with acne and healthy controls.

Tests for association (95% CI)												
Tests for deviation from HWE			allele freq. difference		heterozygous		homozygous		allele positivity		Armitage's trend test	
			[T] vs [C]		[T.C.] vs [CC]		[TT+] vs [CC]		[TT] vs [TC+CC]		Common OR	
Healthy	Acne Vulgaris		OR=1.763		OR= 2.083		OR=2.724		OR=2.216		OR=1.701	
nTT=48 (46.76)	nTT=37 (38.29)											
nCT=38	nCT=61		CI	[1.181-	C.I.=	[1.155-	C.I.= [1.145-6.480]		C.I.= [1.269-3.870]			
(40.48)	(58.42)		2.632]		3.756]							
nCC=10 (8.76)	nCC=21 (22.29)		χ^2: 7.75		χ^2: 6.01		χ^2: 5.33		χ^2: 7.95		χ^2: 7.62	
f_T=0.70± 0.034	f_T= ±0.031	0.57										
			p=0.005 (P)		p=0.014		p=0.021		p=0.0048*		p=0.0058*	
F=-0.061	F=-0.044											
p=0.549 (Pearson)	p=0.631 (Pearson)		OR=1.763		OR= 2.083		OR=2.724		OR=2.216		OR=1.701	

OR – Odds ratio; CI – Confidence interval; HWE – Hardy–Weinberg equilibrium; SD – Standard deviation; *p < 0.05 was considered statistically significant" for consistency.

Table III. Comparison of MnSOD rs4880 polymorphism in different models among acne patient and control subjects.

Variation	Acne vulgaris (n:119)	Healthy controls (n:86)	Power of variation
Dominant Model CT+TT vs CC	21: 98	10:86	OR:2.216 %95 CI [1.269-3.87] z-statistics:7.95 p: 0.0048 inform meaning for caption
Recessive Model CC vs CC+TT	82:37	48:48	OR:1.412 %95 CI [0.61-3.23] z-statistics:0.817 p: 0.414
Over-dominant Model CC+TT: CT	58:61	58:38	OR:1.375 %95 CI [0.706-2.675] z-statistics:0.937 p: 0.349

OR – Odds ratio; CI – Confidence interval; p – Probability value; *p < 0.05 was considered statistically significant" for consistency.

DISCUSSION

Oxidative stress, an imbalance between free oxygen radicals and antioxidant defense mechanisms, leads to abnormalities in acne vulgaris. Acne involves type 4 hypersensitivity against *P. acnes*, neutrophil recruitment, tissue damage from neutrophil-released enzymes, and excessive ROS production, causing inflammation. Altered sebum composition in acne vulgaris results in decreased linoleic fatty acid, insufficient to inhibit ROS formation. Elevated ROS levels in comedonal content led to inflammation. Therefore, *P. acnes*, the effect of neutrophils, increased and altered sebum content, inflammation and oxidative stress, oxidative stress, and acne vulgaris development are closely interrelated (Dos Santos et al. 2019, Hazarika 2021, Kiratikanon et al. 2024, Lim et al. 2021, Shimoda-Matsubayashi et al. 1996, Zhu et al. 2020). At the same time, acne patients are systemically under oxidative stress, which is not a limited condition for acne lesions. It has been reported that the inhibition of systemic ROS production has therapeutic benefits (Bakry et al. 2021, Gholais et al. 2022, Yu et al. 2020).

MnSOD is an essential antioxidant enzyme counteracting superoxide radical. The *MnSOD* Val116Ala polymorphism impairs mitochondrial enzyme activity, decreasing redox balance due to structural alteration (Flekac et al. 2008). Previous studies link *MnSOD* Val116Ala polymorphism to several diseases, including diabetes, cardiomyopathy, male infertility, and depression (Doğan et al. 2019, García Rodríguez et al. 2019, Wigner et al. 2018).

Our study observed a significant correlation between *MnSOD* Val116Ala polymorphism and acne vulgaris. Reduced SOD enzyme activity in acne patients suggests oxidative stress contributes to acne development (Al-Shobaili 2014, Wigner et al. 2018). Al-Shobaili has suggested that monitoring catalase and SOD levels may be essential in evaluating disease activity and progression (Al-Shobaili 2014). The oxygen-derived free radicals remove by SOD/CAT system as, catalyzing the dismutation of the superoxide into hydrogen peroxide and then converted into water by catalase; thus, the lower SOD and CAT activity in acne patients means an alternate mechanism (Su et al. 2024). Perihan and colleagues showed a higher SOD and CAT level when comparing acne patients with healthy control; in contrast, lower SOD/CAT activity was obtained in scraping samples of severe acne vulgaris patients among all acne patients (Perihan et al. 2012). Kurutas et al. (2005), explained the impact of low SOD activity on acne pathogenesis as triggering Propionibacterium-induced acne development by causing the accumulation of superoxide anions in the epidermis (Kurutas et al. 2005). Studies indicate that suppressed ROS generation has therapeutic benefits. Certain phytochemicals (such as alpha-mangostin, apple polyphenols, berberine, ellagic acid, and gallic acid) that act by accelerating SOD activity may be useful in treating acne (Soleymani et al. 2020). Basak et al. (2001) highlights the critical role of superoxide dismutase (SOD) in managing oxidative stress during acne inflammation. Their findings suggest that SOD mitigates oxidative damage by neutralizing reactive oxygen species (ROS) and compensating for the partial inhibition of other antioxidant enzymes, such as glutathione peroxidase (*GSH-Px*). This supports the therapeutic potential of targeting ROS generation in acne treatment (Basak et al. 2001).

In that study, we evaluated the *MnSOD* Val16Ala gene polymorphism, highly investigated polymorphisms regarding ageing and oxidative stress. This polymorphism causes structural changes in the secondary structure of the protein and results in converting protein from β-sheet to α-helix (Liu et al. 2009). Our study is

the first to examine the relationship between the *MnSOD* Val16Ala gene polymorphism and the development of acne vulgaris. Our research found that acne risk increased by 1.76 times in allele frequency differences, 2 times in heterozygous (Ala/Val) genotype, and 2.72 times in double mutant genotype (Val/Val) individuals. Thus, we have found the dosage effects of the *MnSOD* Val116Ala polymorphism in acne development. This finding can be explained as the structural changes in MnSOD causing changes in redox balance and showing a more powerful effect in adding each allele.

This inaugural investigation on *MnSOD* Val16Ala polymorphism and acne vulgaris revealed a dosage-dependent association. Individuals with heterozygous (Ala/Val) or double mutant (Val/Val) genotypes have a higher likelihood of developing acne. Our findings suggest compromised antioxidant defense in acne patients, indicating antioxidant medications as a viable treatment option. Topical or oral antioxidant supplementation can enhance acne medication efficacy and reduce adverse effects. The *MnSOD* Val16Ala gene polymorphism may significantly influence acne development, and individuals with this polymorphism could benefit from antioxidant medications to restore redox balance.

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Author contributions

MMÇ and SK designed and directed the project; SK and SM enrolled the individuals and evaluated the clinical parameters of the subjects; MMÇ and MG performed the experiments; MG made in silico analysis; MMÇ and SK developed the theoretical framework; MMÇ, SK and MG wrote the article.

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Data availability

All data generated and analyzed during this study are included within the article.