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ORIGINAL ARTICLE

MIR146A rs2910164 (G/C) Polymorphism is Associated with Incidence of Preeclampsia in Gestational Diabetes Patients

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Abstract

Preeclampsia and gestational diabetes are common pregnancy disorders that may be interrelated. MIR146A rs2910164 (G/C) is a functional polymorphism that was associated with several diseases. This study aimed to investigate the frequency of rs2910164 polymorphism and its possible correlation with the incidence of preeclampsia in gestational diabetes patients. The study involved 250 pregnant women divided into 80 healthy control subjects, 85 gestational diabetes patients only, and 85 patients of gestational diabetes combined with preeclampsia. Systolic and diastolic blood pressures, urinary proteins, kidney and liver functions, glucose homeostasis parameters, and lipid profile were determined. Genotyping of the polymorphism was conducted by PCR-RFLP. The frequency of the minor C allele of rs2910164 polymorphism was significantly higher among patients of gestational diabetes combined with preeclampsia compared to the control group ($p=0.012$) and the gestational diabetes group ($p=0.014$). Patients of gestational diabetes and preeclampsia carrying CC genotype showed higher systolic and diastolic blood pressure, and increased urea, creatinine, urine protein, and dyslipidemia compared to the carriers of GG and GC genotypes. In conclusion, the results of the current study suggest that the rare CC genotype of MIR146A rs2910164 (G/C) polymorphism may be related to increased incidence of preeclampsia in gestational diabetes patients.

Keywords Pregnancy · Preeclampsia · Gestational diabetes · MIR146A · rs2910164

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Introduction

Preeclampsia is a common pregnancy disorder that originates in the placenta and causes fetal and maternal problems. It may threaten the life of both mother and fetus (Redman and Sargent 2005). Preeclampsia affects approximately 5–7% of pregnancies. It is defined as the new onset of hypertension and proteinuria after 20 weeks of gestation (Wagner 2004). Occurrence of preeclampsia in the first pregnancy is considered a major risk factor for recurrence in subsequent pregnancies (Li et al. 2014). Preeclampsia has several risk factors, such as family history, egg donation, obesity, and diabetes (English et al. 2015). This disorder is related to high risks of placental abruption, cardiovascular and cerebrovascular complications, acute renal failure, and maternal death (Mackay et al. 2001). Pathophysiological events of preeclampsia include placental ischemia and maternal endothelial dysfunction, leading to the clinical symptoms of hypertension, proteinuria, and edema (Maynard et al. 2003).

Gestational diabetes mellitus is defined as diabetes that is first diagnosed in the second or third trimester of pregnancy and is not clearly preexisting type 1 or type 2 diabetes (American Diabetes Association 2017). Women with obesity, family history of diabetes mellitus, or previous personal history of gestational diabetes are more susceptible to this disorder (Koivusalo et al. 2016). Gestational diabetes is widely considered an independent risk factor for preeclampsia (Bryson 2003; Ostlund et al. 2004). Other studies suggested that a history of preeclampsia may increase the risk of developing gestational diabetes in subsequent pregnancies (Lee et al. 2017).

MicroRNAs (miRNAs) represent a class of small noncoding RNAs that play a role in regulation of gene expression (Rong et al. 2013). MiRNA-146a is a 22 nucleotide long RNA with a proinflammtory role. Its expression is driven by nuclear factor kappa B (NF-κB) and it targets the 3′-UTR of mRNAs encoding signaling proteins that are involved in regulation of inflammation induced via innate immune response (Williams et al. 2008; Devier et al. 2015). The MIR146A rs2910164 (G/C) polymorphism alters the expression of mature miRNA-146a and was found to be related to several types of cancers (Gomez-Lira et al. 2015; Xia et al. 2016; Xiang et al. 2017). This polymorphism also showed association with other diseases such as metabolic syndrome (Mehanna et al. 2015), type 1 diabetes mellitus (Assman et al. 2015), atherosclerotic cerebral infarction (Zhong et al. 2016), and ischemic stroke (Qu et al. 2016). Figure 1 illustrates the hairpin structure of pre-miR-146a, the location of MIR146A gene at chromosome 5, and the location of rs2910164 (C/G) polymorphism (Zhang et al. 2014; Paterson and Kriegel 2017).

The current study aimed to investigate the relation of MIR146A rs2910164 (G/C) single nucleotide polymorphism (SNP) with the incidence of preeclampsia in gestational diabetes patients in an Egyptian population.

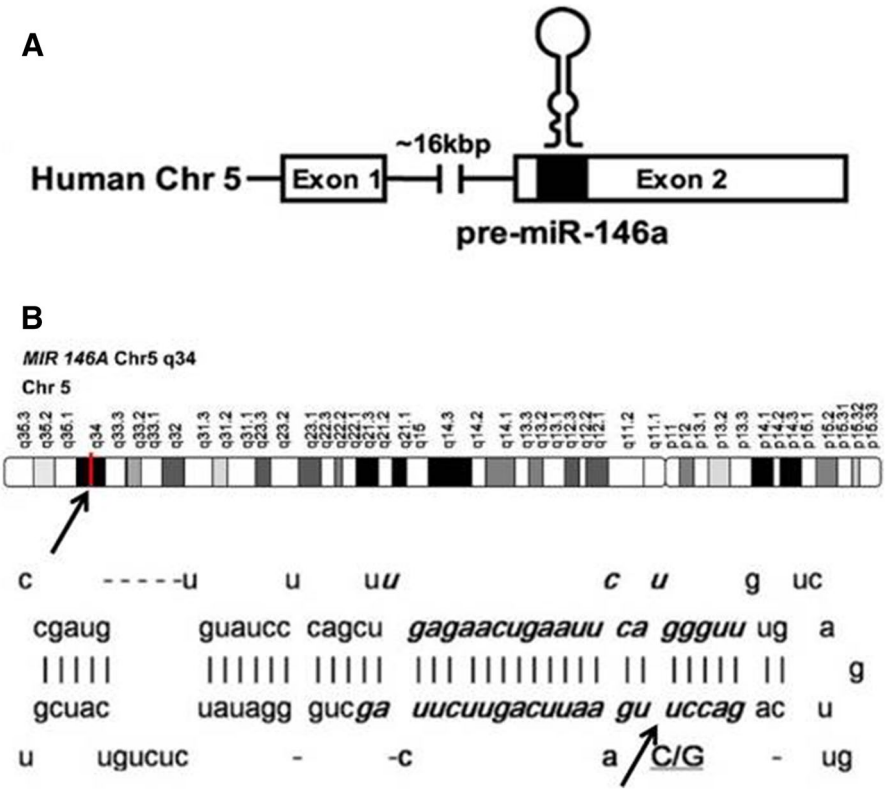

Fig. 1 Structure and location of MIR146A gene. **a** Basic exon structure of MIR146A gene, showing the hairpin structure of pre-miR-146a (Paterson and Kriegel 2017). **b** Location of MIR146A gene at chromosome 5 q 34, and location of rs2910164 (C/G) polymorphism (Zhang et al. 2014)

Subjects and Methods

Study Population

The study included 250 Egyptian age matched (26 ± 4.5 years old) pregnant women after 20 weeks of gestation, divided into 3 groups; 80 apparently healthy subjects with no history of general or chronic diseases (group 1), 85 gestational diabetes but not preeclampsia patients (group 2), and 85 gestational diabetes and preeclampsia patients (group 3). Patients were selected from the Obstetrics and Gynecology Department in the Ismailia General Hospital and the Suez Canal University Hospital. Patients with chronic diabetes, hypertension, liver, kidney, or inflammatory diseases were excluded. The study took place over a period of 6 months; from January till June 2017.

All participants were screened for gestational diabetes via the oral glucose tolerance test (OGTT). Blood pressure and proteinuria were also assessed for all subjects. Gestational diabetes was diagnosed using one-step 75 g OGTT according

to the American Diabetes Association criteria (American Diabetes Association 2017). Preeclampsia was diagnosed by the presence of gestational hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) and proteinuria (300 mg or greater in a 24-h urine specimen) (Wagner 2004).

All participants provided written informed consent following a protocol approved by the Research Ethics Committee of Faculty of Pharmacy, Suez Canal University (Code: 201709RH1). The study followed the principles of the Declaration of Helsinki.

Laboratory Measurements

Peripheral blood (5 ml) was drawn from participants, of which 3 ml was collected on EDTA for DNA extraction and plasma separation. The remaining 2 ml was collected in plain tubes where serum was separated after centrifugation and stored at − 20 °C. The following parameters were determined in serum: lipid profile: total cholesterol (TC), triglycerides (TG), and high-density lipoprotein-cholesterol (HDL-C) were determined by enzymatic colorimetric methods (Biodiagnostic, Egypt). Low-density lipoprotein-cholesterol (LDL-C) was calculated (Friedewald et al. 1972).

Kidney function markers; creatinine and urea, and liver enzymes; alanine aminotransferase (ALT); and aspartate aminotransferase (AST) were measured by enzymatic colorimetric methods (Biodiagnostic, Egypt).

Fasting plasma glucose was determined spectrophotometrically (Biodiagnostic, Egypt), and fasting plasma insulin was measured by ELISA (Monobind Inc, Lake Forest, USA). The homeostasis model assessment-insulin resistance (HOMA-IR) index was calculated (Matthews et al. 1985).

DNA Extraction and Genotyping

Genomic DNA was isolated from EDTA anticoagulated blood using the Wizard genomic DNA purification kit (Promega, Madison, USA) according to the manufacturer's instructions. MIR146A rs2910164 (G/C) polymorphism was genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique (Zeng et al. 2010). We chose to use PCR-RFLP as it is an easy, rapid, and relatively low-cost technique. A 372 bp fragment was amplified using the forward primer; 5′-CATGGGTTGTGTCAGTGTTAGA-3′, and the reverse primer; 5′-CCA AGAGTCTCGTATAACAGCA-3′. The PCR reaction was performed in a total volume of 25 µl; 1 µl genomic DNA (~ 100 ng/µl), 1 µl of each primer (10 pmol/µl), 12.5 µl Go Taq® Green Master Mix (2×) (Promega), and 9.5 µl DNase-free water. The PCR cycle consisted of 8 min at 95 °C, followed by 35 cycles of 30 s at 95 °C, 30 s at 53 °C, and 30 s at 72 °C, with a final extension at 72 °C for 10 min. Thermal cycling was conducted in Eppendorf Mastercycler® machine (Eppendorf, Hamburg, Germany).

The 372 bp PCR product (10 µl) was digested using 5 units of the restriction enzyme *Hpy*188I (New England Biolabs, Inc., Beverly, MA). The reaction was

incubated at 37 °C for 90 min, followed by electrophoresis in 2.5% agarose gel along with a 50 bp marker, where the genotypes were displayed as follows:

a. Two bands at 211 and 161 bp (GG genotype).
b. Three bands at 211, 134, and 27 bp (CC genotype).
c. Four bands at 211, 161, 134, and 27 bp (GC genotype).

To confirm the results of genotyping, ten random PCR product samples were sequenced, where sequencing data of all selected samples were found to be identical to the PCR-RFLP results.

Statistical Analysis

One-way ANOVA and Tuckey's post hoc test for multiple comparisons were used to compare the characteristics and clinical parameters in the study groups and to analyze the association of genotypes with different clinical parameters. Genotype and allele frequencies were compared using Fisher's exact test. The compatibility of the genotype frequencies with Hardy–Weinberg equilibrium was assessed using Chi-square test. Data are presented as means ± standard deviations (SD). Values of $p < 0.05$ were considered significant. Data were analyzed using SPSS, version 21.0.

Results

All the study groups were matched regarding age and number of gestations. Gestational diabetes and preeclampsia patients (group 3) had significantly higher SBP, DBP, urea, creatinine, ALT, AST, and urine protein relative to the control group (group 1) and the gestational diabetes group (group 2). In comparison with the control group, the two other groups (2 & 3) had significantly higher TG, TC, LDL-C, and lower HDL-C. Both groups also had higher levels of glucose homeostasis and insulin-resistance parameters compared to the control group. The comparison between the three groups is summarized in Table 1.

Genotype distributions and allele frequencies of MIR146A rs2910164 polymorphism in the study groups are shown in Table 2. The frequency of CC genotype among patients of gestational diabetes and preeclampsia was significantly higher than the control group ($p = 0.032$) and the gestational diabetes group ($p = 0.043$). Moreover, the minor C allele was significantly more detected in the group of gestational diabetes and preeclampsia patients (group 3) compared to the control group ($p = 0.012$) and the gestational diabetes group ($p = 0.014$). Allele and genotypes distribution analysis showed no significant difference between the control group (group 1) and the group of gestational diabetes only (group 2). All genotype distributions were in accordance with Hardy–Weinberg equilibrium.

The relationship between MIR146A rs2910164 (G/C) polymorphism genotypes and different clinical parameters in preeclampsia patients (group 3) was also investigated (Table 3). Carriers of CC genotype had significantly higher values of SBP

Table 1 General and biochemical characteristics of the study population

Variables	Group (1): control ($n=80$)	Group (2): gestational diabetes patients ($n=85$)	Group (3): gestational diabetes + preeclampsia patients ($n=85$)	ANOVA p value
Age (years)	26.30 ± 4.43	25.89 ± 4.22	26.79 ± 4.81	0.803
Number of gestations	2.22 ± 0.29	2.15 ± 0.35	2.03 ± 0.98	0.889
SBP (mmHg)	117.00 ± 3.84	120.34 ± 4.89	170.56 ± 17.68	0.017[a]
DBP (mmHg)	77.10 ± 3.54	83 ± 4.56	99.60 ± 11.13	0.028[a]
Urea (mg/dl)	12.39 ± 7.21	15.76 ± 8.98	39.61 ± 14.24	0.009[a]
Creatinine (mg/dl)	0.51 ± 0.30	0.58 ± 0.34	0.90 ± 0.60	0.011[a]
Urine protein (mg/24 h)	230.40 ± 39.81	356.50 ± 43.87	1884.00 ± 692.27	0.008[a]
ALT (IU/l)	22.12 ± 6.34	24.76 ± 7.89	48.40 ± 12.37	0.019[a]
AST (IU/l)	21.81 ± 5.87	26.89 ± 5.87	49.98 ± 15.76	0.015[a]
Glucose homeostasis parameters				
Fasting plasma glucose (mg/dl)	90.56 ± 16.74	133.76 ± 32.17	135.22 ± 28.75	0.038[b]
Blood glucose (1 h after OGTT)	169.34 ± 14.27	200.65 ± 34.82	196.49 ± 35.39	0.029[b]
Blood glucose (2 h after OGTT)	133.98 ± 20.11	169.83 ± 29.87	174.19 ± 36.29	0.031[b]
Fasting plasma insulin (mIU/ml)	4.75 ± 1.31	9.76 ± 2.83	11.21 ± 3.01	0.020[b]
HOMA-IR	1.54 ± 0.10	3.69 ± 0.84	3.76 ± 1.04	0.019[b]
Lipid profile				
TG (mg/dl)	173.10 ± 34.36	223.45 ± 38.79	218.18 ± 48.58	0.015[b]
TC (mg/dl)	222.83 ± 41.30	270.65 ± 40.76	267.18 ± 35.64	0.013[b]
HDL-C (mg/dl)	54.25 ± 12.10	44.78 ± 7.88	46.40 ± 8.44	0.021[b]
LDL-C (mg/dl)	132.72 ± 47.55	187.87 ± 34.86	186.88 ± 35.50	0.024[b]

Data are presented as mean ± SD. Comparisons were performed by ANOVA followed by Tuckey's post-hoc test for multiple comparisons

[a]Group (3) is significantly different from groups (1) and (2) at $p<0.05$

[b]Groups (2) and (3) are significantly different from group (1) at $p<0.05$

Table 2 Allele frequencies and genotype distribution of MIR146A rs2910164 (G/C) polymorphism in the study groups

	Group (1): control ($n=80$)	Group (2): gestational diabetes ($n=85$)	Group (3): gestational diabetes + preeclampsia ($n=85$)	p value	OR (95% CI)
Genotypes					
GG	46	49	37		
GC	29	30	32		
CC	5	6	16[ab]	0.032[a]	
				0.043[b]	
Alleles					
G allele	121	128	106		
C allele	39	42	64[ab]	0.012[a]	1.873 (1.164–3.015)
				0.014[b]	1.840 (1.154–2.934)

Comparisons were performed using Fisher's exact test (2×2 for allele frequencies comparisons and 2×3 for genotypes distribution comparison)

CI confidence interval, *OR* odds ratio

[a]Significant difference of group (3) from group (1) at $p < 0.05$

[b]Significant difference of group (3) from group (2) at $p < 0.05$

($p=0.001$), DBP ($p=0.003$), urea ($p=0.001$), creatinine ($p=0.001$), urinary protein ($p=0.001$), TG ($p=0.005$), TC ($p=0.009$), LDL-C ($p=0.006$), and lower HDL-C ($p=0.010$) compared to the carriers of GG genotype. Carriers of CC genotype had also significantly higher SBP ($p=0.008$), DBP ($p=0.028$), urea ($p=0.002$), creatinine ($p=0.001$), and urinary protein ($p=0.001$) compared to the carriers of GC genotype. Carriers of the heterozygote genotype GC showed significantly increased TG ($p=0.011$), TC ($p=0.013$), LDL-C ($p=0.015$) and decreased HDL-C ($p=0.019$) relative to the carriers of GG genotype. There was no significant difference between the carriers of the three different genotypes regarding the liver enzymes and the glucose homeostasis traits.

Discussion

Gestational diabetes and gestational hypertension have been long linked with each other (Yogev et al. 2004) as they have several common risk factors including increased maternal age, multiple numbers of gestations, nulliparity, and pre-pregnancy obesity (Schneider et al. 2012). Both diseases share pathophysiological disorders such as endothelial dysfunction, angiogenesis imbalance, increased oxidative stress, and dyslipidemia (Weissgerber and Mudd 2015). Vascular dysfunction has been reported in women with a history of gestational diabetes (Jensen et al. 2016). Decreased levels of endothelial progenitor cells (EPCs) and increased natural killer (NK) cells in peripheral blood during the first trimester may be considered early markers for increased risk of developing preeclampsia (Laganà et al. 2017).

Table 3 The relationship between MIR146A rs2910164 polymorphism genotypes and different clinical parameters in preeclampsia patients (group 3)

Variables	Carriers of GG ($n=37$)	Carriers of GC ($n=32$)	Carriers of CC ($n=16$)	ANOVA p value
SBP (mmHg)	140.96 ± 11.33	149.00 ± 12.00	169.64 ± 11.93	0.019[a]
DBP (mmHg)	92.38 ± 11.50	95.17 ± 7.89	110.83 ± 13.50	0.038[a]
Urea (mg/dl)	25.97 ± 9.15	28.77 ± 7.658	44.51 ± 12.15	0.018[a]
Creatinine (mg/dl)	0.65 ± 0.30	0.69 ± 0.12	1.40 ± 0.27	0.021[a]
Urine protein (mg/24 h)	1490.96 ± 544.81	1530.68 ± 335.94	2078.96 ± 688.81	0.020[a]
ALT (IU/l)	42.74 ± 14.71	44.60 ± 13.68	43.47 ± 15.71	0.891
AST (IU/l)	37.17 ± 13.52	39.80 ± 11.32	40.15 ± 12.23	0.890
Glucose homeostasis parameters				
Fasting plasma glucose (mg/dl)	133.89 ± 19.87	136.87 ± 31.17	134.22 ± 30.77	0.705
Blood glucose (1 h after OGTT)	194.24 ± 37.12	203.11 ± 38.21	196.89 ± 37.11	0.476
Blood glucose (2 h after OGTT)	173.34 ± 38.80	176.78 ± 39.70	175.90 ± 35.13	0.754
Fasting plasma insulin (mIU/ml)	9.99 ± 3.00	12.07 ± 3.15	10.11 ± 2.88	0.709
HOMA-IR	3.08 ± 0.79	3.87 ± 0.98	3.54 ± 0.84	0.699
Lipid profile				
TG (mg/dl)	180.62 ± 33.66	213.41 ± 31.408	225.26 ± 41.86	0.011[b]
TC (mg/dl)	250.73 ± 15.10	277.16 ± 16.58	290.73 ± 35.10	0.010[b]
HDL-C (mg/dl)	50.34 ± 8.14	42.94 ± 6.71	40.41 ± 7.40	0.028[b]
LDL-C (mg/dl)	160.32 ± 22.94	187.31 ± 21.36	200.20 ± 26.49	0.020[b]

Data are presented as mean ± SD. Comparisons were performed by ANOVA followed by Tuckey's post hoc test for multiple comparisons

[a]Carriers of the CC genotype are significantly different from GG genotype and GC genotype carriers at $p < 0.05$

[b]Carriers of the GC and the CC genotypes are significantly different from GG genotype carriers at $p < 0.05$

In the current study, patients of gestational diabetes only or gestational diabetes combined with preeclampsia had high levels of TG, TC, LDL-C and low HDL-C. Abnormalities of lipid profile during pregnancy have been associated with gestational diabetes (Wiznitzer et al. 2009; Ryckman et al. 2015) and with preeclampsia as well (Gohil et al. 2011; Siddiqui 2014).

In the group of combined gestational diabetes and preeclampsia, creatinine, urea, ALT, and AST levels were significantly high. Proteinuria and decreased renal function are characteristic of preeclampsia (Moran et al. 2004). The role of angiogenic and renin-angiotensin aldosterone system in the pathophysiology of preeclampsia is well established (Cornelis et al. 2011; van der Graaf et al. 2012). Elevated levels of liver enzymes have been also recorded in cases of preeclampsia (Girling et al. 1997; Munazza et al. 2011).

The aim of this study was to assess the relation of MIR146A rs2910164 (G/C) genetic variants with the risk of developing preeclampsia in gestational diabetes patients. The rare CC genotype showed increased frequency among the group of patients with combined gestational diabetes and preeclampsia compared to the control group and the group of gestational diabetes patients. MiRNAs are thought to be involved in placental development and accordingly in placenta-related complications such as preeclampsia (Chiofalo et al. 2017). The possible correlation of increased or decreased expression of miRNAs in placenta or in maternal serum with the onset of preeclampsia was recently investigated (Laganà et al. 2018). A recent study observed a relation of MIR146A rs2910164 polymorphism with severe preeclampsia in Black South African women with HIV infection on highly active antiretroviral therapy (HAART) (Maharaj et al. 2017). This relation can be explained by the effect of this polymorphism in decreasing the expression of mature miR-146a (Qu et al. 2016). MiRNA-146a targets interleukin-1 receptor-associated kinase-1 (IRAK1) and TNF receptor associated factor-6 (TRAF6), leading to inhibition of NF-κB via the toll-like receptor pathway (Ramkaran et al. 2014). Therefore, the decreased expression of miRNA-146a may increase inflammation-related atherosclerosis and affect vascular damage response via increasing the levels of TNF-α, IRAK1, and TRAF6 (Qu et al. 2016). MiRNA-146a has been found to be downregulated in placenta of preeclampsia patients (Chen and Wang 2013).

Additionally, among preeclampsia patients, MIR146A rs2910164 CC genotype carriers showed significantly higher levels of SBP, DBP, urea, creatinine, and urinary protein compared to the GG and GC genotypes carriers. Association of this polymorphism with high blood pressure was reported in a previous study on Egyptian women with metabolic syndrome (Mehanna et al. 2015). MiRNA-146a was found to exert a role in regulation of renal inflammation in mice (Bhatt et al. 2016; Dai et al. 2016). A recent study related the expression levels of miRNA-146a with levels of plasma renalase (Dziedzic et al. 2017), a renal enzyme that plays a role in regulation of blood pressure (Desir 2011).

In the current study, preeclampsia patients with GC and CC genotypes of rs2910164 polymorphism had significantly abnormal lipid profile, which agrees with previous records in Egyptian women (Mehanna et al. 2015). MiRNA-146a was suggested to have a role in regulation of oxidized LDL accumulation via targeting toll-like receptor 4 (Yang et al. 2011).

In conclusion; this study suggests an association of the rare CC genotype of MIR146A rs2910164 polymorphism with the incidence of preeclampsia in gestational diabetes patients. However, these findings are limited by relatively small sample size. Further studies using larger sample size are required to support our findings.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interests.

Informed Consent All the participants in the study provided written informed consent following a protocol approved by the Research Ethics Committee of Faculty of Pharmacy, Suez Canal University (Code: 201709RH1). The study followed the principles of the Declaration of Helsinki.

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