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FULL PAPER

# Vascular endothelial growth factor –A (VEGF-A) and its receptor (VEGFR-2) in rheumatoid arthritis patients with type 2 diabetes mellitus

**Manar Abbas Al-Ameri*** |**Zeinab M. Al-Rubaei**

*Department of Chemistry, College of Education for Pure Sciences, Ibn Al-Haitham of the University of Baghdad, Baghdad, Iraq*

***Corresponding Author:**
Manar Abbas Al-ameri
Email: manar.alameri89@gmail.com
Tel.:+9647722229592

This study aimed to early detection of diabetes type 2 in rheumatoid arthritis (RA) patients.Thus, the present study designed to determine vascular endothelial growth factor-A (VEGF-A), vascular endothelial growth factor receptor -2 (VEGFR-2), rheumatoid factor (RF),anti-cyclic citrullinated peptide (Anti-CCP), C- reactive protein (CRP),erythrocyte sedimentation rate (ESR), glycated hemoglobin (HbA1c) and total vitamin D (Vit. D) in RA patients with and without diabetes type 2 as a complication of this disease andmake a comparison with control group in order to assess their usage asbiochemical parameters for prompt diagnostic test of RA and find correlation of VEGFR-2 with all studied parameters in all groups. The presents study included 90 subjects aged (35-55) years for all subjects and divided into three groups: (G1) control (30), (G2) RA (30) and (G3) RA with T2DM group (30). The data demonstrated a highly significant increase in RF, Anti-CCP, C-reactive protein, ESR, VEGF-A and VEGFR-2 levels in (G2) and (G3) in comparison to (G1), and a highly significant increase in G3 compared with G2 was found. Results of HbA1c showed a non-significant elevation in (G2) comparing to (G1), while there was a highly significant elevation in (G3) comparing to (G2) and (G1). Levels of Vitamin were found to be significantly lower in (G2) and (G3) when compared with controls (G1). These results revealed that these parameters could be used as biochemical markers for early diagnosis of diabetes in RA patients.

**KEYWORDS**

VEGF–A; VEGFR-2; rheumatoid arthritis with T2DM.

## Introduction

The relationship between rheumatoid arthritis (RA) and diabetes has been shown in several cases, and RA is connected to abnormalities in glucose metabolism, particularly insulin resistance, which can lead to T2DM [1]. Research has reported that individuals with RA had a greater risk of diabetes, but little is known regarding RA risk in those who already have type 2 diabetes. As a result, one of the study's objectives is to investigate the probability of incident in individuals with type 2 diabetes [2]. The cells of Th17 are engaged in the pro-inflammatory response to infections, whereas regulatory T cells mediate tolerance to self-antigens. The Treg-Th17 balance is disrupted in RA and other autoimmune disorders. In RA, enhanced glucose intake and glycolytic pathways result in a metabolic shift from a low-energy to a high-energy state [3].

Vascular endothelial growth factor (VEGF) also known as vascular permeability factor (VPF), is a homodimeric protein with 34–42 kDa in molecular weight, produced by many

types of cells, including fibroblasts, macrophages, endothelial cells, neutrophils, and T cells, many other cell types. The VEGF action is not restricted to the circulatory system; it is also involved in fetus, bone, and reproductive system growth. Synovial neovascularization and bone damage caused by high levels of VEGF in the synovial fluid and serum of RA patients have been found [4].

Vascular Endothelial Growth Factor Receptors (VEGFRs) are receptors for vascular endothelial growth factor (VEGF). Human VEGFR2 contains 1337 amino acids and the mature protein is a ~200–230 kDa glycoprotein expressed in both vascular and lymphatic endothelial cells. VEGFR-2 is a major mediator of angiogenic, mitogenic, and vascular permeability activity. VEGF gene transcription is stimulated by hypoxia, which enhanced KDR expression. As a result of elevated VEGF/KDR signalling, atherosclerosis and chronic inflammation are both exacerbated. Patients with Rheumatoid Arthritis (RA) display an increased VEGF/KDR system expression in blood and synovial fluid in response to pro-inflammatory cytokines, which has been linked to disease severity and activity. To put it another way, autoimmunity and RA formation and/or progression may be influenced by processes that govern the VEGF/KDR system [5].

## Subjects and methods

The presents study included (90) subjects aged (35-55) years for all subjects. The patients were newly diagnosed (before treatment) by rheumatologists, who were attending the Baghdad teaching hospital, and Al- Yarmuk teaching hospital, between December (2020) to August (2021). The patients were classified into three groups: G1; (30), G2 ;(30), and G3; (30). All patients were interviewed in person using a specially prepared questionnaire format that contained a complete history of the patient's medical history.

The following biochemical tests were performed: serum VEGF-A level, serum VEGFR-2, rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-ccp), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and glycated hemoglobin (HbA1c). Whole blood was used in the determination of HbA1c and ESR.

The SPSS-21 statistical software was used to analyse the data. The data were summarized using the standard deviation and mean values. T-test for difference between two independent means was used to determine the significance of the difference between various means in quantitative data. When the P-value was equal to or less than 0.05, statistical significance was evaluated [6]. Pearson's correlation was computed for the correlation between two quantitative variables, and the significance of the correlation was tested using t-test. The value of the correlation coefficient (r) is either positive direct correlation or negative inverse correlation, with a value of < 0.3 indicating no correlation, 0.3- < 0.5 indicating weak correlation, 0.5- < 0.7 indicating moderate strength, and >0.7 indicating high correlation

## Results and discussion

Serum levels of RF, Anti-CCP, CRP, ESR in the three groups G1: control, G2: rheumatoid arthritis patients and G3: rheumatoid arthritis with T2DM as a complication are shown in Table 1.

**TABLE 1** Levels of RF, Anti-CCP CRP and ESR in the three groups

| parameter | mean± SE | | | p-value | | |
|---|---|---|---|---|---|---|
| | G1 (n=30) | G2 (n=30) | G3 (n=30) | G1&G2 | G1&G3 | G2&G3 |
| **RF (IU/mL)** | 3.66±0.29 | 79.72±2.83 | 101.83±3.11 | **HS** | **HS** | **HS** |
| **Anti-CCP (U/mL)** | 18.91±0.85 | 81.77±3.60 | 103.76±3.55 | **HS** | **HS** | **HS** |
| **CRP (mg/L)** | 3.66±0.29 | 61.82±4.03 | 90.80±4.09 | **HS** | **HS** | **HS** |
| **ESR (mm/h)** | 14.93±0.48 | 74.87±2.99 | 89.43±2.72 | **HS** | **HS** | **HS** |

**HS: Highly significant at the 0.01 level

Data in Table 1 demonstrate value of serum RF levels in (G2) was (79.72±2.83) IU/mL and (G3) was (101.83 ± 3.11) IU/mL, which were significantly increased compared with serum RF in (G1) by (3.66±0.29) IU/mL. In addition, a highly significant increased level found in (G3) compared to (G2).

Rheumatoid Factors (RF) are autoantibodies that directly bind to the fraction crysallizable (Fc) component of accumulated IgG and are generated regionally by B cells in lymphoid follicles and germinal centre-like structures that arise in inflamed RA synovial.RF testing in RA patients has a sensitivity reaching up to 90% and an accuracy ranging from 48 to 92 %, according to several studies, [7].

The anti-ccp levels in Table 1 increased significantly in rheumatoid arthritis patients (G2) by (81.77± 3.60) U/ml and rheumatoid arthritis with T2DM (G3) were (103.78± 3.55) U/ml in comparison to control (G1) (18.91 ± 0.85) U/ ml. Additionally, a highly significant increase in G3 was found compared with G2. Anti-CCP auto-antibodies bind antigenic determinants that contain unusual amino-acid citrulline. Amino acid also is not integrated into protein during the synthesis process, although it can be produced by post-translational modification. Citrullination or deimination is an enzyme-catalysed process in which the positively charged NH2– group of amino-acid arginine is hydrolysed to a neutral oxygen group. Autoantibodies in RA particularly detect this oxygen group of peptidylcitrulline. The citrulline residues are essential part of the antigenic determinants recognized by the RA antibodies. Anti-CCP testing, with its high specificity early in the disease process and capacity to identify individuals who are likely to suffer serious illness and irreparable damage, is particularly useful in the diagnosis of RA [8]. A recent study demonstrated that anti-CCP in RA patients were significantly higher as compared with that of healthy control [9]. Data in Table (1) show a highly significant increase in C-reactive protein levels in (G2) (61.82±4.03) mg/L and (G3) (90.80±4.09) mg/L in comparison to (G1) (3.66±0.29) mg/L. Additionally, a highly significant elevation was seen in G3 comparing to G2.

The results of this study agree with a previous study that observed a high levels of CRP indicative of active inflammation in RA patients [10]. CRP levels were shown to be higher in RA patients with type 2 diabetes (T2DM) as compared with patients without diabetes.[11].High CRP levels in RA have also been linked to problems with how the body handles glucose, how it uses glucose, and how insulin works [12]. Furthermore, a modest but

important increase in the likelihood of impaired fasting glucose was seen [13]. A previous study discovered that a combination of prognostic indicators like inflammation, high levels of C-reactive protein, and rheumatoid factor positive might predict the likelihood of rheumatoid advancement [14]. Furthermore, pre-study findings revealed that these markers were elevated in individuals with rheumatoid arthritis. High levels of CRP, RF, and Anti-CCP in the blood have been linked to negative consequences such as chronic illness, joint deterioration, and functional impairment [15].

Table 1 similarly showed a statistically significant increase in ESR levels in (G2) (74.87±2.99) mm/hr and (G3) (89.43±2.72)mm/hr in comparison to (G1) (14.93± 0.48) mm/hr. The results of this study are in agreement with a previous study reporting that an extremely considerable rise in ESR levels in their studies [16]. Increased ESR is beneficial in assessing a variety of clinical diseases, including RA. [17]. Although the erythrocyte sedimentation rate (ESR) is not an etiologic diagnosis, it can be used frequently for inflammatory surveillance in RA patients. It is caused by the ESR method, which is straightforward, practical, convenient, cost-effective, and has significant clinical significance. Increased ESR is caused by inflammatory processes or tissue destruction in the body [18].

The current study also included the determination of the levels of HbA1c.The results of HbA1c showed a non-significant elevation in (G2) (4.84±0.11) compared with (G1)(4.81±0.09) while there are highly significant elevation in (G3)(8.66±0.21) compared with (G2) and (G1). The majority of well-conducted research show that RA is linked to T2DM development. The inflammatory reactions involved with these illnesses could explain the possible relationship between RA and incident T2DM. Chronic systemic inflammation is a key factor in the development of both RA and T2DM. RA is linked to systemic inflammation caused by pro-inflammatory cytokines including TNF- and IL-6, which cause insulin resistance, leading to T2DM by blocking insulin action [19]. Additionally, liver immune cells produce pro-inflammatory cytokines in response to inflammatory mediators secreted by adipose tissue. The development of RA has been linked to a variety of pro-inflammatory cytokines. [20]. Another research found a link between glucose metabolism unbalance and uncontrollable clinical signs in people with RA, as well as a substantial risk of T2DM [21].

Vitamin D levels were found to be significantly lower in (G2) (13.28± 0.51) and rheumatoid arthritis with T2DM (G3) (15.68± 0.43) compared with control group G1) (33.90± 0.35). Moreover, the results showed a highly significant decrease difference between (G3) compared with (G2).

In the current study, there were a significant decrease found in levels of Vitamin D in RA patients compared with the control group. The results are in agreement with pervious study, showing significantly reduced vitamin D levels in RA patients compared with healthy controls [22]. Vitamin D inhibits antibody synthesis and proliferation, as well as B-cell precursor development into plasma cells. These findings support a role for vitamin D insufficiency in the onset and progression of autoimmune inflammatory diseases, particularly RA [23]. Vitamin D's anti-inflammatory activity in synovial fluid and reversal serum level with C- reactive proteins may explain why this vitamin is so important in the progression of RA disease in those who are vitamin D deficient [24].

Data in Table 2 demonstrated the mean value of serum VEGF-A in (G2) was (127.93± 0.88) ng/L and (G3) was (152.97± 1.49) ng/L which showed a highly significant increase compared with control (G1) by (84.90± 1.26) ng/L. In other hand, the mean value of serum VEGF-A in G3 showed a highly significant increase compared with G2.

The VEGF-A has been identified as a fundamental controller of angiogenesis, and its information is now the most extensive among the VEGF family [25]. Angiogenesis is thought to play a role in the development and management of rheumatoid arthritis (RA). This vascular mechanism can increase cartilage and bone deterioration in later stages of RA. Inflammatory cells and mediators enter the joint through angiogenesis. In RA, though, the neovascular network is defective, and the joint is hypoxic. Inflammatory cytokines and hypoxia also increase VEGF expression in RA [26]. The VEGF-A protein is up-regulated in painful illness models such as chronic constriction damage and type I diabetes [27], and is raised in the serum of rheumatoid arthritis patients. Furthermore, serum VEGF levels are higher in RA patients than in osteoarthritis patients [28].

Results of Table 2 revealed a highly significant increase in VEGFR-2 with (G2) by (28.77± 0.60) ng/ml and (G3) by (39.70± 0.62) ng/ml as compared with control (G1) by (9.67±0.44) ng/mL. In addition, a highly significant increase in (G3) was found in comparison to (G2).

In this study, a significant increase was found in levels of VEGFR-2 in RA patients compared with the control group. Similar results were reported where VEGFR-2 levels in patients with RA were higher than in healthy subjects [5]. According to literature review, there are essential differences in VEGFR-2 levels with diabetes, in which no significant differences were observed between the levels of VEGFR2 in the control group and those in the group of patients with well-controlled diabetes [29].

The serum and synovial fluid VEGF concentrations are higher in rheumatoid arthritis (RA) patients than in osteoarthritis (OA) patients or normal controls, and VEGF levels are linked to RA disease activity, such as erythrocyte sedimentation rate, C-reactive protein, tender and swollen joint counts, serum rheumatoid factor, and quality of life. VEGF also plays a pro-inflammatory and anti-apoptotic effect in the pathophysiology of RA. It induces tumour necrosis factor (TNF)-α and interleukin (IL)-6 from synovial fluid mononuclear cells of RA patients [30].

**TABLE 2** Mean ±SE of serum VEGF-A and VEGFR-2 levels in three groups

| parameter | mean± SE | | | p-value | | |
|---|---|---|---|---|---|---|
| | G1 (n=30) | G2 (n=30) | G3 (n=30) | G1&G2 | G1&G3 | G2&G3 |
| **VEGF-A (ng/L)** | 84.90±1.26 | 127.93±0.88 | 152.97±1.49 | **HS** | **HS** | **HS** |
| **VEGFR-2 (ng/ml)** | 9.67 ± 0.44 | 28.77±0.60 | 39.70±0.66 | **HS** | **HS** | **HS** |

**HS: Highly significant at the 0.01 level

*Serum VEGFR-2 correlation study*

Table 3 shows the correlation between VEGFR-2 and all of the parameters investigated. For all parameters, the correlation coefficient (r) was obtained for all groups.

**TABLE 3** Correlation coefficient (r) and p-value of VEGFR-2 with all parameters studied

| Parameters | | VEGF-R2 | | |
|---|---|---|---|---|
| | | r1 | r2 | r3 |
| RF (IU/mL) | r | 0.078 | 0.111 | -0.253 |
| | P | 0.681 | 0.559 | 0.178 |
| AntiCCP (U/L) | r | 0.261 | 0.088 | -0.224 |
| | P | 0.163 | 0.646 | 0.235 |
| CRP (mg/L) | r | -0.257 | 0.058 | -0.145 |
| | P | 0.171 | 0.761 | 0.443 |
| ESR (mm/hr) | r | 0.041 | -0.017 | -0.026 |
| | P | 0.828 | 0.931 | 0.890 |
| HbA1c (%) | r | 0.002 | -0.066 | 0.043 |
| | P | 0.992 | 0.727 | 0.820 |
| Vitamin D (ng/mL) | r | -0.052 | 0.173 | 0.226 |
| | P | 0.784 | 0.360 | 0.229 |
| VEGF-A (ng/l) | r | -0.372* | 0.153 | 0.027 |
| | P | 0.043 | 0.420 | 0.888 |

*G1: Control, G2: Rheumatoid arthritis, G3: Rheumatoid arthritis with T2DM*
**Correlation is significant at the 0.05 level ** Correlation is highly significant at the 0.01 level*

Table 3 displays the correlation relation between VEGFR-2 and RF. Results illustrated a non-significant positive correlation in both G1 ($r_1$= 0.078) and G2 ($r_2$= 0.111) while a non-significant negative correlation was found in G3 ($r_3$= -0.253). Also, this study revealed a non-significant positive correlation between VEGFR-2 and anti-ccp in both G1, G2 groups ($r_1$= 0.261), ($r_2$= 0.088), respectively while there was a non- significant negative correlation in G3 ($r_3$= - 0.224). Results displayed a non-significant negative correlation in G1 and G3 between VEGFR-2 and CRP ($r_1$= - 0.257), ($r_3$= - 0.145), respectively while there was a non- significant positive correlation in G2 ($r_2$= 0.058).

Table 3 also shows a non-significant negative correlation between VEGFR-2 and ESR for G2, G3 ($r_2$= - 0.017), ($r_3$= - 0.058), respectively, while a non-significant positive correlation was observed in G1 ($r_1$= 0.041). Results also showed a non-significant positive correlation between VEGFR-2 and HbA1c in both G1 and G3 ($r_1$= 0.002), ($r_3$= 0.043) while a non- significant negative correlation was found in G2 ($r_2$= - 0.066).

According to the finding of this research, there was a statistically insignificant link between levels of VEGFR-2 and Vitamin D in the G1 group, as well as between the levels of VEGFR-2 and Vitamin D in the G2 and G3 groups. The levels of VEGFR-2 and VEGF-A in the G2 and G3 groups were shown to be unrelated ($r_2$= 0.153), ($r_3$= 0.888), according to the research while there was a significant negative correlation in G1 ($r_1$= - 0.372).

## Conclusion

Significant changes (increase or decrease) were reported here in VEGF-A, VEGFR-2, RF, Anti-CCP, CRP, ESR, HbA1c and Vitamin D total in G2 and G3 (patients groups) compared with G1 (control group). In addition, there were significant changes in G3 findings when compared with G2. The results revealed that these parameters could be used as biochemical markers for early diagnosis of diabetic in rheumatoid arthritis patients. Also, a significant positive or negative correlation of VEGFR-2 with all parameters for all groups showed good-related biomarkers with these patients so that optimal drug and treatment will be possible.

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***Orcid:***
*Manar Abbas Alameri:*
*https://orcid.org/0000-0001-8302-2464*

## References

[1] S. Lillegraven, J.D. Greenberg, G.W. Reed, K. Saunders, J.R. Curtis, L. Harrold, D.H. Solomon, *PLoS One*, **2019**, *14*, e0210459. [crossref],[Google Scholar], [Publisher]
[2] M.C. Lu, S.T. Yan, W.Y. Yin, M. Koo, N.S. Lai, *PLoS One*, **2014**, *9*, e101528.[crossref],[Google Scholar], [Publisher].
[3] U. Fearon, M.M. Hanlon, S.M. Wade, J. Fletcher, *Clin.Exp. Immun*., **2019,** *197*, 170-180.[crossref],[Google Scholar], [Publisher]
[4] H. Zhan, H. Li, C. Liu, L. Cheng, S. Yan, Y. Li,*Front. Immun*., **2021**, *12*, 1751. [crossref],[Google Scholar],[publisher].
[5] A. Paradowska-Gorycka, B. Stypinska, A. Pawlik, D. Malinowski, K. Romanowska-Prochnicka, M. Manczak, M. Olesinska. *Biomolecules*, **2019**, *9*, 355. [crossref],[Google Scholar],[Publisher].
[6] B. Sharma, *Bio Epid. Int. J*., **2018**, *1*, 3-5.[crossref],[Google Scholar],[Publisher]
[7] H.E. Kang, J.Y. Ha, J.Y. Lee, *Int. J. Mol. Sci.,* **2020,** *21*, 1382.[ crossref],[Google Scholar],[Publisher]
[8] T. Masoodi, A. Farhana, M. Saleem, A. Khaliq, S. Qayoom, A. Rashid, *Ls-An Int. J. Life Sci*., **2019**, *8*, 65-69. [crossref],[Google Scholar],[Publisher]
[9] H.J. Hassoon, W.E. Jasim, A.A.H. Abbas, *Iraqi J. Sci.*, **2020**, 2196-2203.[crossref],[Google Scholar],[Publisher]
[10] H. Jeong, S.Y. Baek, S.W. Kim, E.J. Park, J. Lee, H. Kim, C.H. Jeo, *BMJ open*, **2019**, *9*, e029861.[crossref],[GoogleScholar],[Publisher]
[11] J.E. Pope, E.H. Choy, *Semin. Arthritis Rheum.*, **2021**, *51*, 219-229. [crossref],[Google Scholar],[Publisher]
[12] F. Ursini, E. Russo, S. D'Angelo, F. Arturi, M.L. Hribal, L. D'Antona, R.D. Grembiale, *Medicine*, **2016,** *95*, e2552. [crossref],[GoogleScholar],[Publisher]
[13] P. Ruscitti, F. Ursini, P. Cipriani, F. Ciccia, V. Liakouli, F. Carubbi, R. Giacomelli, *Medicine*, **2017**, 96, e7896.[crossref],[Google Scholar],[Publisher]
[14] Z. Fang, J. Lv, J. Wang, Q. Qin, J. He, M. Wang, Q. Wang, *Front. Immunol.*, **2020**, *11*, 958. [crossref],[GoogleScholar],[Publisher]
[15] C.D.S. Carvalho, L.E.C. Andrade, S.P. Keusseyan, J.L. Rangel, J. Ferreira-Strixino, A. A. Martin, L.J. Raniero, *Rev. Bras. Eng. Bioméd.*, **2014**, *30*, 54-63.[crossref],[Google Scholar],[Publisher]
[16] F. Ursini, S. D'Angelo, E. Russo, G. Ammerata, L. Abenavoli, D. Mauro, G. De Sarro, *Rev. Rec. Clin. Trials.*, **2018**, *13*, 21522. [crossref],[GoogleScholar],[Publisher]
[17] N.M. Saptarini, M.S. Wibowo, T. Gusdinar, *Mahidol Univ. J. Pharm. Sci.*, **2016,** *43*, 55-62.[Google Scholar],[Publisher]
[18] S.C. Shapiro, *Cureus*, **2021**, *13*, e15063. [crossref],[Google Scholar],[Publisher].
[19] Y.H. Lee, G.G. Song, *J. Rheum. Dis.*, **2019**, *26*, 131-136.[crossref],[Google Scholar], [Publisher]
[20] J.H. IM, *ActaReumatol. Port.*, **2017**. [Google Scholar], [Publisher].
[21] P. Ruscitti, F. Ursini, P. Cipriani, V. Liakouli, F. Carubbi, O. Berardicurti, R. Giacomelli, *PLoSOne*, **2017**, *12*, e0181203. [crossref],[Google Scholar],[Publisher]
[22] N. Sukharani, K. Dev, F.N.U. Rahul, P. Bai, A. Ali, F.N.U. AAvinash, A. Rizwan, *Cureus*, **2021**, *13*. [crossref], [Google Scholar], [Publisher]
[23] M.L. Dupuis, M.T. Pagano, M. Pierdominici, E. Ortona, *Biol. Sex Differ.*, **2021**, *12*, 1-12. [crossref],[Google Scholar],[Publisher]
[24] D. Li, L.E. Jeffery, C. Jenkinson, S.R. Harrison, R.F. Chun, J.S. Adams, Karim Raza, M. Hewison, *J. Steroid Biochem. Mol. Biol.*, **2019**, *187*, 1-8. [crossref], [Google Scholar], [Publisher]
[25] R.S. Apte, D.S. Chen, N. Ferrara, *Cell*, **2019**, *176*, 1248-1264.[crossref], [Google Scholar], [Publisher]

[26] I.J. MacDonald, S.C. Liu, C.M. Su,Y.H. Wang, C.H. Tsai, C.H.Tang,*Int.J. Mol. Sci.*, **2018**, *19*, 2012. [crossref],[GoogleScholar],[Publisher]
[27] N. Beazley-Long, C.E. Moss, W.R. Ashby, S.M. Bestall, F. Almahasneh, A.M. Durrant, L.F. Donaldson, *BrainBeliav. Immune.*, **2018**, *74*, 49-67.[crossref],[Google Scholar],[Publisher]
[28] T.H.V. Le, S.M. Kwon, *Int.J. Mol. Sci.*, **2021,** *22*, 5387. [crossref], [GoogleScholar], [Publisher].
[29] B. Ruszkowska-Ciastek, A. Sokup, M.W. Socha, Z. Ruprecht, L. Hałas, B. Góralczyk, D. Rość, *J. Zhejiang.Univ.Sci. B*, **2014**, *15*, 575-581.[crossref],[Google Scholar],[Publisher]
[30] H.R. Kim , K.W. Kim, B.M. Kim, M.L. Cho, S.H. Lee, *PloS one*, **2015**, *10*, e0124909. [crossref],[Google Scholar],[Publisher]

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