UDC 663.974-028.27 doi: https://doi.org/10.15407/ubj97.06.055

ANGIOTENSIN, VASCULAR ENDOTHELIAL GROWTH FACTOR AND CASPASE-3 LEVELS IN BLOOD SERUM OF SMOKING STUDENTS

I. A. A. K. AL-SAMARAI[1], A. J. AL SAMER[1], H. N. MOHAMMED[2]

[1]Department of Applied Chemistry, College of Applied Science, University of Samarra, Saleh Aden, Iraq;
[2]Department of Biotechnology, College of Applied Science, University of Samarra, Saleh Aden, Iraq;
✉e-mail: israa.a@uosamarra.edu.iq

Received: 18 July 2025; **Revised:** 18 September 2025; **Accepted:** 28 November 2025

Smoking cigarettes is currently considered a widespread behavioral habit among university students due to psychological, social, and behavioral factors. Smoking is believed to impair renin-angiotensin system, blood pressure regulation, endothelial function, and cells viability, particularly in the lungs or blood vessels. The study aimed to assess the level of angiotensin, vascular endothelial growth factor (VEGF), caspase-3 and the activity of antioxidants glutathione S-transferase (GST) and superoxide dismutase (SOD) in the blood serum of students at Samarra University (Iraq). The study lasted from 20/2 /2025 to 20/4/ 2025 and involved 100 male students aged 18-28 years. The first group consisted of 30 nonsmoker students and the second included 70 smoker students, whose daily cigarette consumption ranged between 60-100 cigarettes. The results showed a significant increase in angiotensin, VEGF and caspase-3 levels, measured by ELISA, and a significant decrease in GST and SOD activity in the blood serum of smoker students compared to nonsmokers. A high negative correlation between angiotensin, GST and SOD activity in both smokers and nonsmokers, and a positive correlation between angiotensin and caspase-3 levels in smokers were observed, indicating the promising use of studied parameters as indicators of adverse effects caused by smoking.

K e y w o r d s: smoking, angiotensin, caspase-3, vascular endothelial growth factor, antioxidant markers, serum, students.

In the last period, the market quickly became saturated with vaping devices available in many flavors and forms appealing to youth [1]. Tobacco smoking is one of the most lethal drugs for its users. It is estimated that 1.1 billion smokers worldwide, approximately 80% live in low- and middle-income countries. The trend is increasing, especially among college and university students [2]. There are many factors, including gender, age, education, marital status, household income, assets, and risky behaviors, all of which significantly predict a person's likelihood of currently smoking [3]. It is well known that long-term smoking for several years causes many diseases, and thus complications increase in smokers, who are more susceptible to death [4]. Tobacco smoking represents a global public health challenge, with estimated costs of US$1.4 trillion, and is a preventable risk through reducing tobacco use [5]. In May 2018, the WHO Convention Secretariat held a meeting to discuss the potential for reducing tobacco addiction. The meeting focused primarily on reviewing research findings on the behavioral effects of reducing cigarette addiction [6]. The World Health Organization estimated in 2021 that 18.5% of the Iraqi population currently use tobacco products, therefore smoking rates among Iraqi men are about 31% compared to females by 4% [7, 8], Peers strongly influence smoking behavior in young people, and smoking is often associated with having smoker friends or parents [9]. Various genetic, socioeconomic, and environmental factors also contribute to the risk of smoking among youth and young adults [10]. Cigarette smoking is one of the world's largest avoidable risk factors for disease and death. It is linked to many diseases, including heart disease and high blood pressure [11]. Smoking has also been linked to the renin-angiotensin system, which is one of the mechanisms that control

circulatory stability by regulating blood pressure and sodium-potassium balance [12]. Cigarette smoking enhances the production of angiotensin-converting enzyme and causes significant changes in inflammation and oxidative stress. This leads to increased antioxidant activity and lipid oxidation [13]. In addition, smoking has been associated with vascular endothelial growth factor. Smoking is believed to impair endothelial function through decreased nitric oxide bioavailability, resulting from the activation of oxidative stress and inflammation. Endothelial dysfunction can be improved or enhanced through appropriate interventions, including drug therapy, dietary supplements, and lifestyle modification [14]. Smoking has also been linked to the activity of the caspase-3 enzyme, one of the main caspases responsible for programmed cell death, which is activated and forces the cell to die [15]. Therefore, it plays different roles such as proliferation and necrosis in programmed cell death to protect the organism from stress signals and pathogenic hybridization. These forms of cell death are important [16]. These enzymes act as apoptosis inducers, executors of apoptosis, and are responsible for programmed cell death [17]. Despite repeated warnings about the irreversible side effects of smoking in the public media, Cigarette consumption continues to rise in many countries, both developed and developing. It has been found that tobacco smoke and its components cause an increase in the formation of reactive oxygen species, which leads to the development of oxidative stress. This, in turn, leads to lipid peroxidation, DNA damage, and a decrease in antioxidants, resulting in numerous diseases, including infertility [18]. Free radical scavenging enzymes, namely superoxide dismutase, catalase (CAT), and glutathione peroxidase (GPx), represent the enzyme segment capable of inhibiting oxidative stress by removing highly destructive free radicals [19]. Oxidative stress is one of the indicators associated with many diseases, and its association has been found in isolated platelets, which can be protected from oxidative stress by the use of antioxidants, including L-carnitine [20]. On the other hand, a study found an increase in the activity of superoxide dismutase in patients with type 2 diabetes and a decrease in glutathione and glutathione peroxidase in the red blood cells [21]. Smoking is also linked to cancer and inflammatory immune diseases. This is because tobacco smoke contains a mixture of chemicals, including a group of reactive oxygen and nitrogen species , which can damage cellular and subcellular targets, such as lipids, proteins, and nucleic acids [22]. The current research aimed to investigate the relationship between smoking and abnormal stimulation of blood vessel growth by measuring vascular endothelial growth factor. Additionally, it sought to determine the relationship between smoking and an increased rate of programmed cell death, particularly in the lungs or blood vessels, by assessing the activity of the enzyme caspase-3. Angiotensin concentrations are measured to link smoking to the risk of high blood pressure and heart disease. The study also aimed to examine the relationship between smoking and antioxidant levels, including activities of the enzymes GST and SOD, which work to detoxify the body from oxidative substances produced by smoking.

Materials and Methods

A collection of samples. The sample for the current study were selected randomly from the College of Education and Applied Sciences, Department of Chemistry, Samarra University, Iraq. All participants were interviewed about tobacco use and were asked about the number of cigarettes they smoked per day and their exposure to secondhand smoke. Ethical approval was obtained from them to participate in this study. The study consisted of 100 samples collected from male students aged 18-28 years for the period from 2/20/2025 to 4/20/2025. The samples were divided into two groups; the first group (G1) included 30 samples of non-smoking students (as a control sample). The second group (G2) included 70 samples of male students who smoked, and whose daily smoking cigarette on the university campus ranged from 60 to 100 cigarettes. Blood samples from the test and control groups were collected between 8:00 and 9:00 a.m. after an overnight fast of 10–12 h. Blood samples were centrifuged at 3,000 rpm for 10 min. The samples were separated and serum was obtained. Then, the serums were stored at -5°C until the biochemical tests were performed (angiotensin, caspase 3, vascular endothelial growth factor, glutathione-S transferase, superoxide dismutase).

Measurement of serum biochemical parameters. Commercially available ELISA kits from Fin-Test China (catalog numbers EU3123, EH0546, EH0327, EH4706-1, and EH4260, Fine Test-China) were used to assess the activity of angiotensin, caspase-3, VEGF, SOD, and GST in serum, respectively.

Ethics approval. This study was conducted in the laboratories of the College of Applied Sciences at Samarra University and several research centers in Baghdad. Verbal consent was obtained from the study participants, along with approval from the relevant scientific department, before the study began on 5/2/2025. All procedures were carried out following the recognized ethical principles of scientific research, taking into account the privacy of the individuals involved.

Statistical analysis. Biochemical tests were analyzed in SPSS for the two groups (smokers and non-smokers) using the F-test to compare the two groups at a significance level of 0.05. The correlation between angiotensin and the studied variables was evaluated using the correlation test. The area under the curve was analyzed using Med Calc.V.20, while the figures were drawn using GraphPad Prism V.9.

Results and Discussion

The results of the current study, according to Table 1, indicate that smoking is associated with an increase in biomarkers associated with inflammation and vascular changes. The results indicate that angiotensin, caspase-3 activity, and vascular endothelial growth factor increased significantly ($P \leq 0.05$) in the blood serum of students who smoke cigarettes (G2) compared to non-smokers (G1). This indicates greater activity in the pathways of cellular apoptosis and reflects changes in vascular formation (Fig. 1, 2).

A significant decrease in SOD and GST activities in the blood serum of the smoker group compared to non-smokers ($P \leq 0.05$) was observed which indicates a weakening of the antioxidant defense system (Fig. 3).

Fig. 4-6 show the potential diagnostic significance of serum angiotensin, caspase-3, VEGF, SOD, GST. The results of ROC curve analysis showed that the area under the curve (AUC) for the angiotensin enzyme was high, reaching (1), sensitivity (100%), and specificity (100%), which indicates its efficiency in distinguishing between smoker and non-smoker students. The AUC value of caspase-3 enzyme reached a high level of diagnostic accuracy, reaching (0.997), sensitivity (100%), and specificity (%), which reflects its potential role as a biomarker for the state of programmed cells. The results of vascular endothelial growth factor showed a high predictive value, with AUC values reaching (1), sensitivity (100%), and specificity (100%), indicating its high predictive ability in assessing the vascular effect of smoking. Meanwhile, the AUC values for SOD and GST enzymes were (1), sensitivity (100%),

Table 1. Angiotensin, caspase-3, and VEGF levels in smokers and non-smokers, (mean ± SD)

Parameters	Non-smoking students (G1)	Smoking students (G2)	*P*-value
Angiotensin, ng/ml	0.991 ± 0.272	5.832 ± 3.507	>0.0001*
Caspase-3, ng/ml	3.749 ± 0.436	13.086 ± 4.285	>0.0001*
VEGF, pg/ml	382.356 ± 44.560	1506.676 ± 424.669	>0.0001*

Note. *$P \leq 0.05$

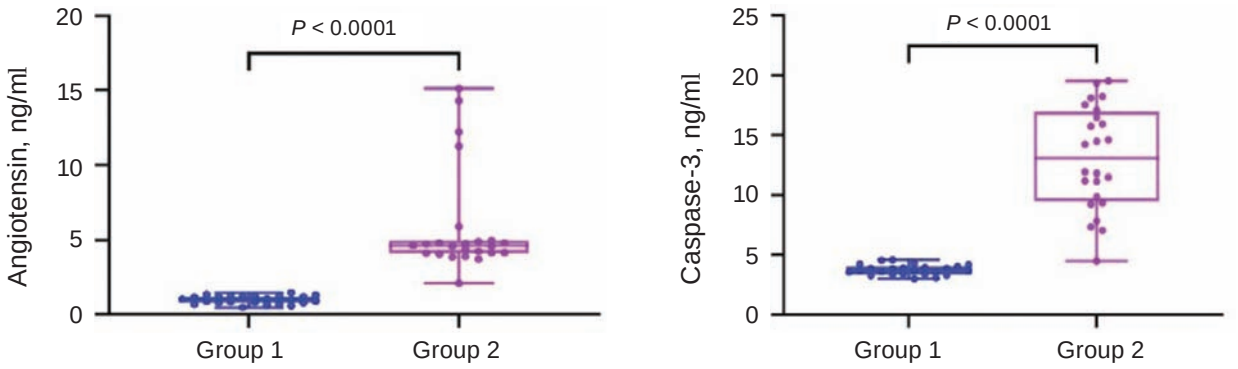

Fig. 1. Activity of angiotensin and caspase-3 in smoker and non-smoker students

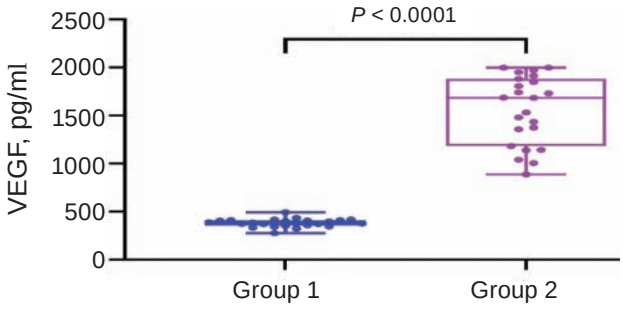

Fig. 2. Concentration of VEGF in smokers and non-smoker students

and specificity (100%), indicating the diagnostic accuracy of the effectiveness of these enzymes towards smoking.

Table 2 shows the correlation of the effectiveness of the angiotensin enzyme with the parameter studied. A high positive significant correlation was found between angiotensin activity and caspase-3. The value of the correlation coefficient was 0.408 in smoker students group, while a neactive significant relationship was found between the angiotensin and SOD, GST activity in two groups. The values of

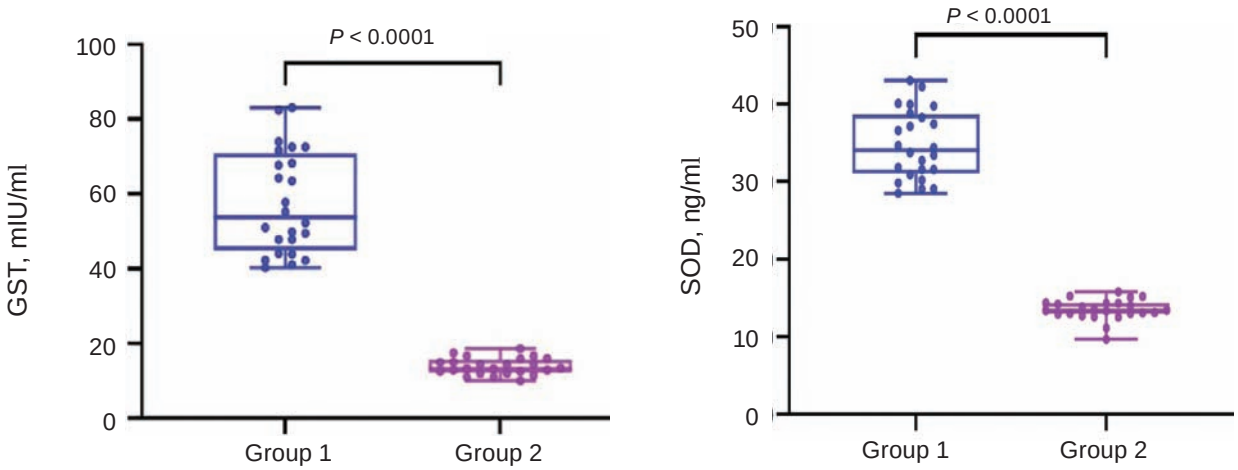

Fig. 3. GST and SOD activities in smoker and non-smoker students

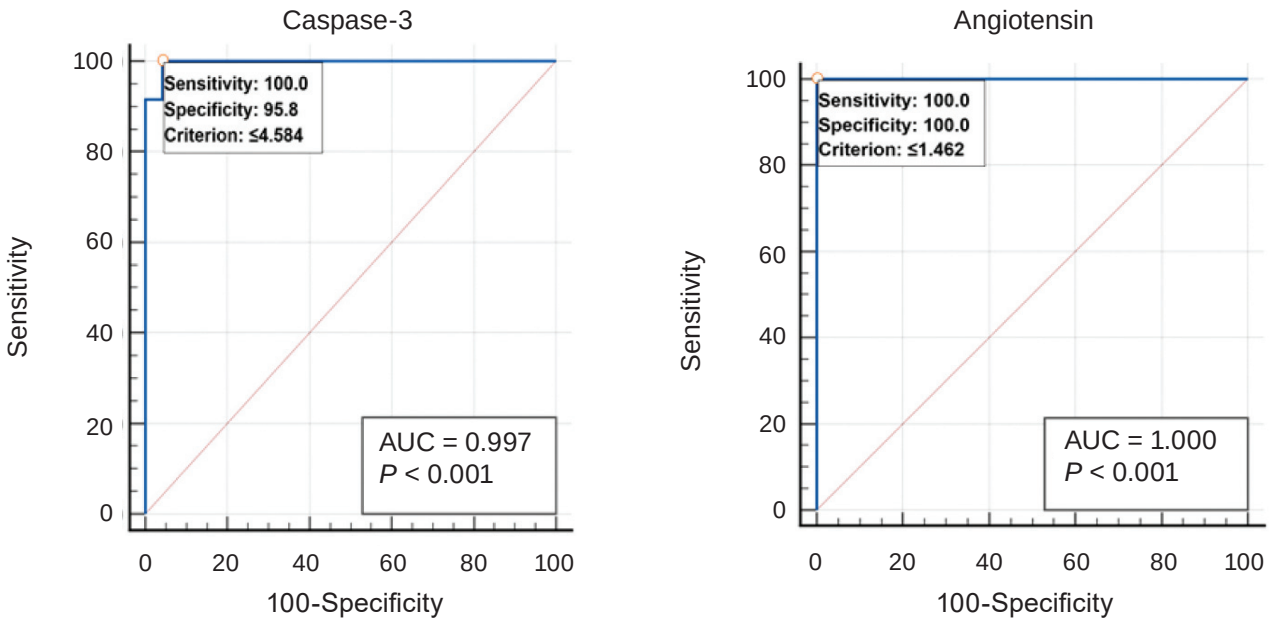

Fig. 4. The ROC of angiotensin and caspase-3 in smoker and non-smoker groups

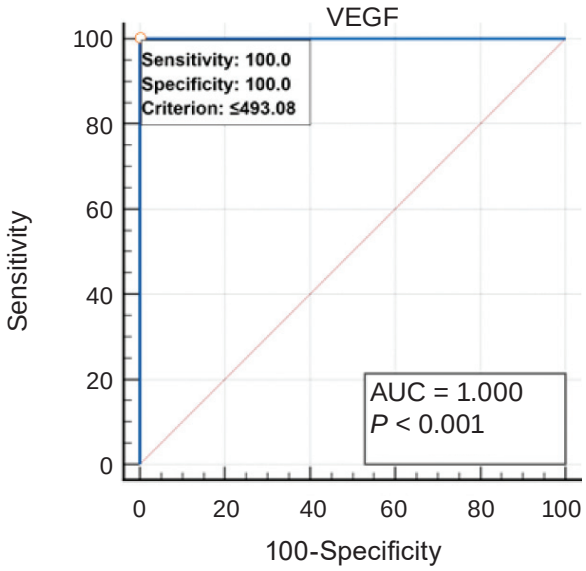

Fig. 5. The ROC of VEGF in smoker and non-smoker groups

the correlation coefficients were 0.987, 0.682,0.957, 0.489, respectively.

Discussion

Smoking, through its main component, nicotine, greatly affects the renin-angiotensin-aldosterone system, which leads to increased angiotensin activity. Therefore, the effects that accompany smoking in students may lead to an increased risk of heart disease, high blood pressure, and affect brain development. The results of the current study showed an increase in angiotensin activity in the blood serum of smoking students, which reached a value 5.832±3.507 ng/ml compared to non-smoker students, which reached a value 0.991±0.272 ng/ml. Cigarette smoking is a major risk factor for car-

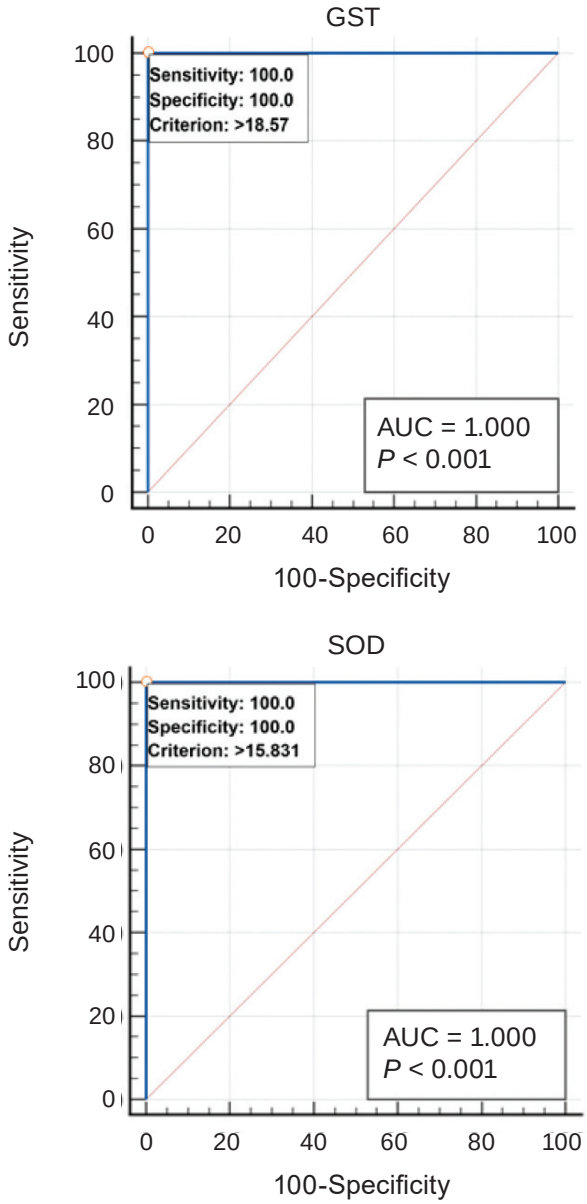

Fig. 6. The ROC of SOD and GST in smoker and non-smoker groups

Table 2. Correlation of angiotensin with biochemical parameters

Parameters	Angiotensin			
	Non-Smoking (G1)		Smoking (G2)	
	r	*P*-value	*r*	*P*-value
Caspase-3	0.191	0.372	0.408*	0.048
VEGF	0.241	0.268	0.353	0.091
SOD	-0.987**	0.000	-0.682**	0.000
GST	-0.957**	0.000	-0.489*	0.015

Note. *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

diovascular disease, as well as respiratory diseases. Although smoking rates have been gradually declining since ancient times, the advent of e-cigarettes about a decade ago has attracted a segment of former smokers, along with a new generation of users. Evidence suggests a link between nicotine and angiotensin-containing training programs, which are often among the most important biomolecules regulating heart and lung function in civil defense. Nicotine disrupts the balance in this system by stimulating ACE1 receptors, versus the ACE2/ANG(1-7)/Mas receptor axis, which represents a compensatory mechanism in this system [23]. A study in laboratory animals have shown that the renin-angiotensin system is activated by cigarettes smoke. Chronic administration of nicotine via osmotic minipumps has been shown to elevate plasma renin activity in rats fed a high-salt diet [24]. It also raises plasma angiotensin-converting enzyme activity with increased conversion of angiotensin I to angiotensin II [25-26].

The results of our current study showed that smoker students have a family history of smoking but are not at risk for chronic diseases. Therefore, continued smoking puts them at greater risk for many diseases, including cardiovascular and lung diseases. Thus, a study found a link between smoking and angiotensin-converting enzyme and its potential impact on the cardiovascular system. Therefore, smoking increases systolic and diastolic blood pressure [27]. These effects were accompanied by an increase in the concentration of angiotensin-converting enzyme by disrupting the renin-angiotensin-aldosterone system. Several epidemiological studies have revealed that serum ACE activity is abnormally elevated in patients with CKD and hypertension. It is associated with coronary artery stenosis. The renin-angiotensin-aldosterone system plays an important role in the development of cardiovascular disease [28]. Therefore, smoking may harm the RAAS system, leading to increased angiotensin activity and exacerbation of cardiovascular problems. This effect is more severe in students who smoke due to the effects of nicotine on the developing body. Therefore, it is necessary to raise awareness of the dangers of smoking, especially among young students, and to encourage them to quit smoking to avoid chronic diseases later on. Caspase-3 is one of the main enzymes responsible of carrying out programmed cell death. Therefore, it was found that its effectiveness increases in smoker students, which reached a value 13.086±4.285 ng/ml, compared to non-smoker students, which reached a value 3.749±0.436 ng/ml. A study indicated that cigarette smoking leads to damage to the vascular lining, which causes accelerated programmed cell death by increasing the enzyme caspase-3. Therefore, excessive programmed cell death may contribute to the dysfunction of the vascular lining caused by cigarettes smoke, and thus lead to many diseases, including atherosclerosis [29]. Neutrophils are the main inflammatory cells in the lungs of smokers, but little is known about how cigarettes smoke modulates their function. Neutrophils undergo caspase-3-dependent and phagocytosis-induced apoptosis. A study examined the effect of a cigarette smoke extract on human neutrophils. The study showed that the extract significantly inhibits the activity of caspase-3 without affecting the processing of procaspase-3 into its active form and that this inhibition leads to a weakening of the ability of neutrophils to phagocytose, which indicates that caspase-3 plays a non-programmed role in the function of neutrophils and that smoking contributes to a weak immune response [30]. A study also indicated that cigarette smoke extract can induce apoptosis in human gastric epithelial cells by increasing the activity of caspase-3, and that this effect occurs through the mitochondrial pathway, leading to the release of cytochrome C and the activation of caspase-3 [31]. On the other hand, vascular endothelial growth factor is a major protein in the blood vessels, so its increased levels in smoking students indicate the presence of a chronic inflammatory response resulting from smoking.

The results of the current research found that VEGF levels in the blood serum of smoking students were higher, which reached a value 1506.676±424.669 pg/ml, compared to non-smoking students, which reached a value 382.356±44.560 pg/ml. The results were consistent with the study by Sarah [32], which indicated that the inflammatory marker VEGF levels are high in smokers. The study of Higashi [33] also indicated that smoking is associated with impaired endothelial function. It is believed that smoking weakens endothelial function by reducing the bioavailability of nitric oxide, resulting from the activation of oxidative stress and inflammation. Therefore, endothelial dysfunction can be enhanced through drug therapy, dietary supplements, and lifestyle modification. A study also indicated that smokers, both healthy smokers and those with COPD, have elevated levels of VEGF in the airways, and that this elevation is associated with increased

inflammatory cells such as neutrophils and elevated levels of inflammatory cytokines such as IL-18 and TNF-α, indicating an interaction between VEGF and inflammatory stimuli [34]. Therefore, it may be concluded that smoking affects VEGF levels through several pathways, including the direct effect of nicotine, activation of inflammatory pathways, and response to hypoxia.

The results of the study showed a significant decrease in superoxide dismutase activity in the blood serum of smoking students, which reached a value 13.516±1.333 ng/ml, compared to non-smokers, which reached a value 34.780±4.439 ng/ml. Antioxidants are the body's first line of defense against the harmful effects of free radicals and may protect against some of the harmful effects of cigarette smoking. The study of Suriyaprom et al. [35] found a decrease in superoxide dismutase activity in the blood serum of smokers compared to non-smokers. But the results of study of Düken [36] showed that SOD activity was higher in long-term smokers compared to short-term smokers. The results of the study Russo [37] also indicated that acute exposure to high concentrations of free radicals may lead to inhibition of gene expression of antioxidant enzymes, while chronic and continuous exposure to free radicals may stimulate an elevated this gene expression as a compensatory mechanism. In the same context, on the other hand, the study of Mithun [38] found that cigarette smoking causes many life-threatening diseases, such as lung and cardiovascular diseases, and lung cancer. One of its most prominent health effects is oxidative damage to cell components, including proteins, lipids, and DNA. This oxidative damage is caused by reactive oxygen species found in cigarette components. One study indicated a close relationship between tobacco use and disease, including cancer, as tobacco is considered a major source of free radicals, which contribute to cellular changes that may lead to the development of cancerous tumors [39]. Cigarette smoke is a potent proinflammatory agent, altering the natural balance between antioxidants and oxidants, inducing oxidative stress in both the respiratory system and throughout the body. This persistent, systemic oxidative state is reflected within the body by increased levels of oxidative stress and biomarkers of inflammation [40]. A study also found that smoking reduces antioxidants and increases levels of oxidative stress, including malondialdehyde [41].

The results of the study also indicated a significant decrease in glutathione S-transferase activity in the blood serum of smoker students, which reached a value 13.839±2.197 mIU/ml compared to non-smokers, which reached a value 57.699±13.642 mIU/ml. A study found that all smokers had lower antioxidant capacity than non-smokers [42]. The results of the current study also indicated that the area under the curve for the studied variables was excellent, they can be suggesting important diagnostic variables in smokers, as smoking may lead to an increase in the activity of the angiotensin enzyme, which may affect the AUC value. Smoking also affects the activity of the caspase-3 enzyme, which varies depending on the type of cell and the tissue involved, indicating the need for further research on the area under the curve of the caspase-3 enzyme. Smoking has also been found to affect VEGF levels in various ways, potentially impacting angiogenesis in various tissues. It also affects the effectiveness of antioxidant enzymes, potentially impacting the body's oxidative balance. Therefore, studying the area under the curve is important for understanding changes between smokers and nonsmokers. The research results indicated a significant positive correlation between angiotensin and caspase-3. The study demonstrated that the angiotensin II type 2 receptor (AT2R) can induce apoptosis by activating caspase-3. When the study was conducted on bladder cancer cells, activation of AT2R led to increased activity of caspase-3, indicating that this pathway may be responsible for apoptosis associated with tissue damage in conditions such as chronic smoking [43]. A study also indicated that the ACE2/Ang-(1-7)Mas axis can provide protection against apoptosis induced by cigarette smoke in alveolar epithelial cells by inhibiting the pathway involving ROS, caspase-3 [44]. Therefore, it is concluded that the relationship between the two enzymes may help in developing therapeutic strategies targeting these pathways to reduce the damage caused by smoking. The results of the current study also indicated a highly significant inverse relationship between the angiotensin enzyme and antioxidants. This relationship is explained by the fact that smoking activates the RAS system, which increases the production of free radicals and reduces the effectiveness of antioxidant systems, including the enzyme superoxide dismutase and glutathione S-transferase.

Conclusion. The results indicate that increased activity of angiotensin and vascular endothelial growth factor indicate an inflammatory response and angiogenesis, while high activity of caspase-3

reflects increased apoptosis, and low levels of antioxidants indicate decreased antioxidant defense mechanisms. Therefore, smoking may enhance the occurrence of oxidative stress and thus increase chronic inflammation that leads to many diseases.

Conflct of interest. Authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

Funding. This research did not receive any financial support from any funding agency.

РІВЕНЬ АНГІОТЕНЗИНУ, ФАКТОРУ РОСТУ ЕНДОТЕЛІЮ СУДИН ТА КАСПАЗИ-3 У СИРОВАТЦІ КРОВІ СТУДЕНТІВ, ЯКІ КУРЯТЬ

I. A. A. K. Al-Samarai[1], *A. J. Al Samer*[1], *H. N. Mohammed*[2]

[1]Department of Applied Chemistry,
College of Applied Science,
University of Samarra, Saleh Aden, Iraq;
[2]Department of Biotechnology,
College of Applied Science,
University of Samarra, Saleh Aden, Iraq;
✉e-mail: israa.a@uosamarra.edu.iq

Куріння сигарет наразі вважається поширеною звичкою серед студентів університетів через психологічні, соціальні та поведінкові чинники. Вважається, що куріння погіршує роботу ренін-ангіотензинової системи, регуляцію артеріального тиску, функцію ендотелію та життєздатність клітин, особливо в легенях та судинах. Метою дослідження було оцінити рівень ангіотензину, фактору росту ендотелію судин (VEGF), каспази-3 та активність антиоксидантів глутатіон-S-трансферази (GST) і супероксиддисмутази (SOD) у сироватці крові студентів університету Самарра (Ірак). Дослідження тривало з 20 лютого 2025 року по 20 квітня 2025 року і охоплювало 100 студентів-чоловіків віком 18-28 років. Перша група складалася з 30 студентів-некурців, а друга – з 70 студентів, які щодня викурювали від 60 до 100 сигарет. Результати показали значне підвищення рівнів ангіотензину, VEGF та каспази-3, виміряних методом ELISA, а також значне зниження активності GST та SOD у сироватці крові студентів-курців порівняно з некурцями. Виявлено високу негативну кореляцію між рівнем ангіотензину, активністю GST і SOD як у курців, так і у некурців, а також позитивну кореляцію між рівнем ангіотензину і каспази-3 у курців, що вказує на перспективність використання досліджуваних параметрів як індикаторів розвитку негативних ефектів, спричинених курінням.

Ключові слова: куріння, ангіотензин, каспаза-3, фактор росту ендотелію судин, антиоксидантні маркери, сироватка, студенти.

References

1. Hasan N, Nasser NA,Hussein AD , Mohsein OA. Effect of electronic smoking (Vaping) on thyroid hormones level and lipid profile in men. *Ukr Biochem J.* 2024; 96(5): 55-64.
2. Telayneh AT, Gedefaw M, Haile D, Habtegiorgis SD, Getahun DS, Tafere Y, Assemie MA, Woyraw W, Temesgen H, Mekonnen N. Cigarette smoking prevalence and associated factors among college students, Amhara, Ethiopia. *Pan Afr Med J.* 2021; 40: 170.
3. Watanapongvanich S, Khan MSR, Putthinun P, Ono S, Kadoya Y. Financial Literacy, Financial Education, and Smoking Behavior: Evidence From Japan. *Front Public Health.* 2021; 8: 612976.
4. Varghese J, Muntode Gharde P. A Comprehensive Review on the Impacts of Smoking on the Health of an Individual. *Cureus.* 2023; 15(10): e46532.
5. Ilesanmi OS, Agwai VI, Afolabi AA. A systematic review of tobacco smoking cessation services in Africa: Practices and challenges faced by healthcare workers. *J Ideas Health.* 2021; 4(2): 371-379.
6. Donny EC, White CM. A review of the evidence on cigarettes with reduced addictiveness potential. *Int J Drug Policy.* 2022; 99: 103436.
7. Hussain Z, Sullivan R. Tobacco in post-conflict settings: the case of Iraq. *Ecancermedicalscience.* 2017; 11: 735.
8. Hajee BARB, Agha SY. Tobacco smoking and alcohol drinking among youth in Duhok, Iraq: A cross-sectional study. *J Clin Diagn Res.* 2022; 16(4): LC35-LC41.
9. Grenard JL, Dent CW, Stacy AW. Exposure to alcohol advertisements and teenage alcohol-related problems. *Pediatrics.* 2013; 131(2): e369-e379.
10. Al Sabbah H, Assaf EA, Dabeet E. Prevalence of smoking (cigarette and waterpipe) and its

association with obesity/overweight in UAE and Palestine. *Front Public Health*. 2022; 10: 963760.
11. Jareebi MA. The association between smoking behavior and the risk of hypertension: Review of the observational and genetic evidence. *J Multidiscip Healthc*. 2024; 17: 3265-3281.
12. Te Riet L, van Esch JH, Roks AJ, van den Meiracker AH, Danser AH. Hypertension: renin-angiotensin-aldosterone system alterations. *Circ Res*. 2015; 116(6): 960-975.
13. Nath D, Shivasekar M. Role of cigarette smoking on serum agiotensin-converting enzyme and its association with inflammation and lipid peroxidation. *Cureus*. 2022; 14(8): e27857.
14. Higashi Y. Smoking cessation and vascular endothelial function. *Hypertens Res*. 2023; 46(12): 2670-2678.
15. Dou H, Yu PY, Liu YQ, Zhu Y, Li FC, Wang YY, Chen XY, Xiao M. Recent advances in caspase-3, breast cancer, and traditional Chinese medicine: a review. *J Chemother*. 2024; 36(5): 370-388.
16. Tong J, Rufli S, Wong WW. Measuring caspase activity using a fluorometric assay or flow cytometry. *J Vis Exp*. 2023; (193): e64745.
17. Galluzzi L, López-Soto A, Kumar S, Kroemer G. Caspases connect cell-death signaling to organismal homeostasis. *Immunity*. 2016; 44(2): 221-231.
18. Omolaoye TS, El Shahawy O, Skosana BT, Boillat T, Loney T, du Plessis SS. The mutagenic effect of tobacco smoke on male fertility. *Environ Sci Pollut Res Int*. 2022; 29(41): 62055-62066.
19. Han L, Yang Q, Ma W, Li J, Qu L, Wang M. Protocatechuic Acid Ameliorated Palmitic-Acid-Induced Oxidative Damage in Endothelial Cells through Activating Endogenous Antioxidant Enzymes via an Adenosine-Monophosphate-Activated-Protein-Kinase-Dependent Pathway. *J Agric Food Chem*. 2018; 66(40): 10400-10409.
20. Mithun M, Rajashekaraiah V. Antioxidants as supplements during drug-induced thrombocytopenia: a comparative analysis of Vanillic acid, L-carnitine and Caripill™. *Ukr Biochem J*. 2024; 96(1): 49-59.
21. Saenko YA, Gonchar OO, Mankovska IM, Drevytska TI, Bratus LV, Mankovsky BM. Oxydative stress in type 2 diabetic patients: involvement of HIF-1 alpha AND mTOR genes expression. *Ukr Biochem J*. 2023; 95(2): 48-57.
22. Caliri AW, Tommasi S, Besaratinia A. Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. *Mutat Res Rev Mutat Res*. 2021;787:108365.
23. Oakes JM, Fuchs RM, Gardner JD, Lazartigues E, Yue X. Nicotine and the renin-angiotensin system. *Am J Physiol Regul Integr Comp Physiol*. 2018; 315(5): R895-R906.
24. Delgado GE, Siekmeier R, Krämer BK, Grübler M, Tomaschitz A, März W, Kleber ME. The renin-angiotensin-aldosterone system in smokers and non-smokers of the Ludwigshafen risk and cardiovascular health (LURIC) study. *Adv Exp Med Biol*. 2016; 935: 75-82.
25. Kitamura S. Effects of cigarette smoking on metabolic events in the lung. *Environ Health Perspect*. 1987; 72: 283-296.
26. Sugiyama Y, Yotsumoto H, Takaku F. Increase of serum angiotensin-converting enzyme level after exposure to cigarette smoke and nicotine infusion in dogs. *Respiration*. 1986; 49(4): 292-295.
27. Virdis A, Giannarelli C, Neves MF, Taddei S, Ghiadoni L. Cigarette smoking and hypertension. *Curr Pharm Des*. 2010; 16(23): 2518-2525.
28. Wei P, Yang K, Long D, Tan Y, Xing W, Li X, Wu H, Liu H. Efficacy and Safety of TCMI in Patients With Combined Coronary Heart Disease and Heart Failure: A Systematic Review and Network Meta-Analysis. *Front Pharmacol*. 2021; 12: 741261.
29. Wang J, Wilcken DE, Wang XL. Cigarette smoke activates caspase-3 to induce apoptosis of human umbilical venous endothelial cells. *Mol Genet Metab*. 2001; 72(1): 82-88.
30. Stringer KA, Tobias M, O'Neill HC, Franklin CC. Cigarette smoke extract-induced suppression of caspase-3-like activity impairs human neutrophil phagocytosis. *Am J Physiol Lung Cell Mol Physiol*. 2007; 292(6): L1572-L1579.
31. Wang HY, Shin VY, Leung SY, Yuen ST, Cho CH. Involvement of bcl-2 and caspase-3 in apoptosis induced by cigarette smoke extract in the gastric epithelial cell. *Toxicol Pathol*. 2003; 31(2): 220-226.
32. Elkot S, Elazazy O, Diab AH. Levels of vascular endothelial growth factor (VEGF) in peri-implant crevicular fluid (PICF) of smokers versus non smokers (clinical and biochemical study). *Egypt Dental J*. 2023; 69(1139): 1143.
33. Higashi Y. Smoking cessation and vascular endothelial function. *Hypertens Res*. 2023; 46(12): 2670-2678.

34. Rovina N, Papapetropoulos A, Kollintza A, Michailidou M, Simoes DC, Roussos C, Gratziou C. Vascular endothelial growth factor: an angiogenic factor reflecting airway inflammation in healthy smokers and in patients with bronchitis type of chronic obstructive pulmonary disease? *Respir Res.* 2007; 8(1): 53.
35. Suriyaprom K, Sirikulchayanonta C, Tungtrongchitr R, Namjuntra P, Phraephan S, Sornwatana T. The Relationship between Characteristics of Cigarette Smoking and Cytokine/Antioxidant Status in Thai Males. *J Med Assoc Thai*. 2020; 103(1): 38-45.
36. Diken H, Kelle M, Tümer C, Deniz B, Baylan Y, Şermet A. Effects of Cigarette Smoking on Blood Antioxidant Status in Short-Term and Long-Term Smokers. *Turk J Med Sci.* 2001; 31(6): 553-557.
37. Russo M, Cocco S, Secondo A, Adornetto A, Bassi A, Nunziata A, Polichetti G, De Felice B, Damiano S, Serù R, Mondola P, Di Renzo G. Cigarette smoke condensate causes a decrease of the gene expression of Cu-Zn superoxide dismutase, Mn superoxide dismutase, glutathione peroxidase, catalase, and free radical-induced cell injury in SH-SY5Y human neuroblastoma cells. *Neurotox Res.* 2011; 19(1): 49-54.
38. Rudrapal M, Maji S, Prajapati SK, Kesharwani P, Deb PK, Khan J, Mohamed Ismail R, Kankate RS, Sahoo RK, Khairnar SJ, Bendale AR. Protective Effects of Diets Rich in Polyphenols in Cigarette Smoke (CS)-Induced Oxidative Damages and Associated Health Implications. *Antioxidants (Basel).* 2022; 11(7): 1217.
39. Yadav U, Ahmed J, Shenoy N, Sujir N, Denny C. Effect of Smoking and Tobacco Chewing on Superoxide Dismutase Activity. *Indian J Public Health Res Dev.* 2020; 11(3):57-62.
40. Astori E, Garavaglia ML, Colombo G, Landoni L, Portinaro NM, Milzani A, Dalle-Donne I. Antioxidants in smokers. *Nutr Res Rev.* 2022;35(1):70-97.
41. Khudhur ZO, Smail SW, Awla HK, Ahmed GB, Khdhir YO, Amin K, Janson C. The effects of heavy smoking on oxidative stress, inflammatory biomarkers, vascular dysfunction, and hematological indices. *Sci Rep.* 2025; 15(1): 18251.
42. Ahmadkhaniha R, Yousefian F, Rastkari N. Impact of smoking on oxidant/antioxidant status and oxidative stress index levels in serum of the university students. *J Environ Health Sci Eng.* 2021; 19(1): 1043-1046.
43. Pei N, Mao Y, Wan P, Chen X, Li A, Chen H, Li J, Wan R, Zhang Y, Du H, Chen B, Jiang G, Xia M, Sumners C, Hu G, Gu D, Li H. Angiotensin II type 2 receptor promotes apoptosis and inhibits angiogenesis in bladder cancer. *J Exp Clin Cancer Res.* 2017; 36(1): 77.
44. Arthur G, Bradding P. New Developments in Mast Cell Biology: Clinical Implications. *Chest.* 2016; 150(3) :680-693.