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ROLE OF ARBs AND ACEIs IN THE TREATMENT OF SARS-COV2

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Abstract - The coronavirus 2 (SARS- CoV- 2) induces severe acute respiratory distress syndrome (ARDS)via the coronavirus receptor angiotensin- converting enzyme 2 (ACE2) in the host cell to facilitate entry into the lungs Over activation of the renin- angiotensin system (RAS) and the down regulation of ACE2 expression are involved in SARS- CoV induced lung injury. RAS is the main system that has a regulatory roleinmaintaining electrolyte balance, blood pressure, vascular tone and cardiovascular remodeling in the body. Angiotensin II receptor blockers (ARBs) and Inhibitors (ACEIs) are vital medications that are widely used for the treatment of cardiovascular diseases (CVDs). The question which now arises is: It is possible to continue using either ARBs or ACEIsor both medications in patients with SARS-CoV2? Both ARBs and ACEIs can facilitate COVID-19 entry into the host cell due to increase expression of ACE2. On the other hand, ARBs have a greater potential to reduce downstream pathogenicity of the SARS-CoV2 via different cell signaling pathways including free radical generation, up regulation of NF-κB pathway, toll-like receptors (TLRs) and pro-apoptotic protein by blocking the renin–angiotensin system more severely compared to the effect of ACEIs. The current hypothesis is that ARBs can perform better therapeutically compared to ACEIs in respiratory disorders such as ARDS which is induced by viral infection especially since more than 40 % of angiotensin II can be synthesized by other enzymes such as chymase, cathepsin. ARBs treatment can increase the levels of both angiotensin II (Ang II) and the ACE2 enzyme making Ang II a target substrate for hydrolysis by ACE2 into Ang 1-7 which in turn exerts anti-inflammatory, anti-apoptotic and anti-oxidant activities. These effects are achieved by the binding of Ang 1-7 to both angiotensin-type 2 receptor (AT2) and receptor mas' axis (Mas) and also by its ability to block Ang II/AT1 receptor-induced TLR4/MyD88 signaling thereby highlighting the potential therapeutic use of ARB sin preventing injury induced by COVID-19 virus. It is concluded that patients who are already on ARBs medications must continue to use them daily since ARBs have protective effects against COVID-19 virus. Moreover, ARB sexert their beneficial effects via their anti-inflammatory, anti-apoptotic, anti-oxidant and anti-fibrotic properties. On the other hand, those patients who are on ACEIs medications must change to other safe drugs since ACEIs can facilitate an increase in COVID-19 virus entry into the body as well as reducing levels and protecting effect of Ang 1-7.

Keywords: SARS-CoV2, RAS, ACEIs, ARBs, Ang II, ACE2

INTRODUCTION

The novel coronavirus (2019-nCoV) was first originated in Wuhan, China and it caused many cases of human infection, suffering and deaths in all the continents and most countries globally. It is more severe in some countries such as Brazil, China, France, India, Italy, Great Britain, Spain, Iran, USA and few others. People, especially the sick, the old, and those who are clinically and extremely vulnerable, are at higher of infection risk. Currently, around 1 million people died from the novel coronavirus (2019-nCoV and more than 25 million are infected globally. The genomic structure, binding site and symptoms of 2019-nCoV, are similar to those caused by SARS coronavirus SARS-CoV [1]. Figure 1*shows a* schematic diagram illustrating the pathogenesis of nCOVID-19in inducing host cell injury. A spike receptor-binding domain

(RBD) of 2019-nCoV recognizes angiotensin-converting enzyme 2 (ACE2) receptor on the host cell membrane which is considered as a critical step in the virus entry into the body via an endocytosis process [2]. The viral RNA is released into the cytoplasm, translates and then newly genomic RNA, nucleocapsid proteins and envelope glycoprotein are formed [3]. The virus-induced infection is due to the activation of a numbers of cell signaling pathways either directly via the virus itself or indirectly via reactive oxygen species (ROS), nuclear factor-kappa B-dependent mechanism and apoptosis [4]. In turn, the generation of such free radicals as O^-, H_2O_2, $OH^-$and peroxidation of membrane phospholipids such as malondi-aldehyde (MDA) can cause cellular injury via a disturbance of membrane phospholipids and mitochondrial respiration, leading to DNA damage and dysfunction [5]. Moreover, ROS in turn can also activate other mediators and inflammatory factors such as tumor necrotic factor (TNF-α), myocytes chemoattractant protein-1 (MCP-1] interleukin, IL-1, IL-6, and C - reactive protein (CRP) [6].

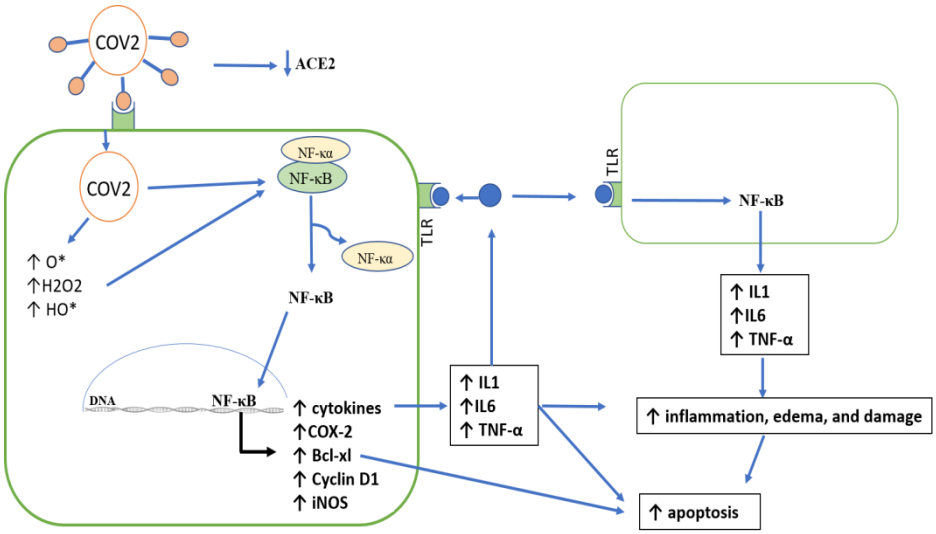

Figure (2): A schematic diagram showing the pathogenesis of nCOVID-19 and its interaction with ACE2 receptor.

Following its penetration into the cell, it induces mainly inflammation and ROS via binding to ACE2 receptor leading to the generation of free radicals, increase dissociation of NF-κB from its complex, translocation, DNA binding and gene expression of pro-apoptotic proteins, pro-inflammatory cytokines that bind to TLR on the same cell or neighboring cells to induce further NF-κB activation. Finally, all these processes can lead to injury of the host cell and subsequently, death (apoptosis), adapted from reference [6]. Figure (3) shows a schematic diagram illustrating the ACE/Ang I/AT 1 receptor and ACE2/Ang 1-7/Mas receptor pathways. The renin-angiotensin system (RAS) has a regulatory role in maintaining blood pressure as well as electrolyte and fluid in the body. Ang I is converted to Ang II by an angiotensin-converting enzyme (ACE). Thereafter, Ang II binds to G-protein-coupled receptors AT1 and AT2 receptors [7]. Activation of AT1 receptor leads to the stimulation of pro-inflammatory mediators, pro-oxidants, pro-apoptotic proteins and fibrosis in the infected cells of the body [8]. In addition, other enzymes such as cathepsin-G and chymase-Ang I can also convert angiotensinogen into Ang II [9-10]. In this system, ACE2 has negative regulatory mechanism via converting of Ang-I to Ang-1–9 and Ang-II to Ang-1–7 which binds to the Mas receptor [11]. The Mas receptor has negatively role throughout the process by reducing not only leukocyte migration and cytokine expression and release, but also inhibiting anti-fibrotic, anti-oxidant, anti-apoptotic effect [12-13]. The affinity of Ang II to ACE2 was approximately 400-fold, much more than Ang I. Therefore, any therapeutic agent(s) that can increase ACE2 level has protective effect in severe acute lung injury (SALI) that induced by SARS-COV infection [14]. In human, Ang II has the ability to increase ACE level and down-regulate ACE2 level via binding to the AT1 receptor that initiates ERK/p38 MAP kinase pathway [15].

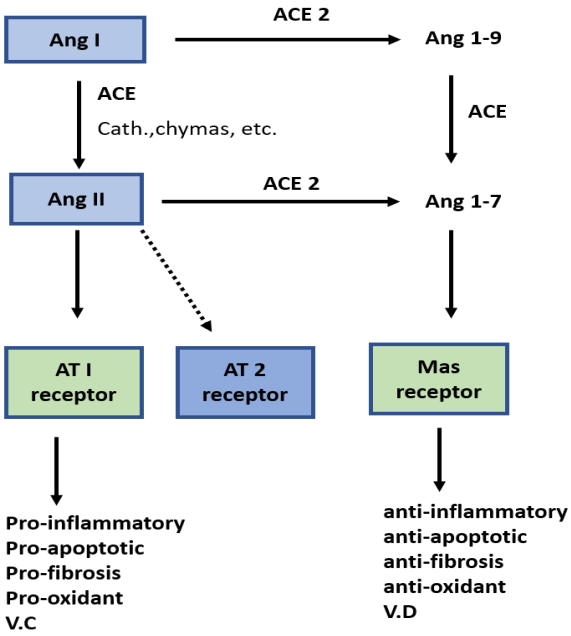

Figure (4): A schematic diagram showing the ACE/Ang I/AT 1 receptor pathway and ACE2/Ang 1-7/Mas receptor pathway

The figure illustrates where Ang I is converted to Ang II via ACE, cathepsin, chymase and Ang II bind to AT 1 receptor and to lesser extend to AT 2 receptor. However, Ang II is also converted to Ang 1-7 via ACE2 and Ang 1-7 binding to Mas receptor, taken form reference (15). Angiotensin-converting enzyme inhibitors (ACEIs) are therapeutic agents that block the ACE both in the circulating system and in tissues of the body. In addition, they can also block the breakdown of bradykinine leading to a rise in bradykinine levels which can induce adverse effects in the body [7]. ACEIs have many beneficial effects on the endothelial function in the body especially in improving vasodilatation and blood flow during hypertension by preventing the vasoconstriction action of angiotensin II. Moreover, ACEIs can also reduce other the risks associated of endothelial dysfunction and subsequently, cardiovascular diseases [8]. On the other hand, ARBs are drugs which act by inhibiting the interaction between angiotensin II and the AT1R and they are developed to overcome some adverse effects of ACEIs, especially in the elevation in bradykinine level. As such, ARBs are deemed to improve the side-effect profile of ACEI drugs [9]. Generally, the ACEIs and ARBs are effective in the management of hypertension [10], post myocardial infarction, reduce mortality after myocardial infarction in patients with heart failure and low ejection fraction and delay the progression of chronic kidney disease in diabetic and even non-diabetic patients [11-12].

Mechanistic effect of ACEIs and ARBs on SARS-Cov2 entry

Figure5shows a schematic diagram illustrating the proposed mechanisms of the protective effect of ARBs against SARS-CoV2. The common receptor for both SARS-CoV and SARS- CoV2 is ACE2which is expressed on the apical surface membrane of human airway epithelia as well as lung parenchyma [13]. ACE-2 is also expressed in the lung, kidney, testes, heart, and gastrointestinal tract [14]. ACE2 expression is reduced during SARS-CoV infections that lead to an increase in Ang II / AT1 R pathway thereby inducing host cell damage [15]. However, agents which can increase the expression of ACE2 can also facilitate the entry of the virus into host cell. Therefore, patients treated with ACEIs and ARBS will be more susceptible to the viral entry than others since these agents can increase the numbers of ACE2 receptors in lungs of the patients [16]. The hypothesis in this mini review is that ACEIs and ARBs may increase susceptibility to the virus entry and severity of the disease due to increased expression of the receptor. However, both ACEIs and ARBs have different effects on ACE2/Ang II/ Ang 1-7. ACEIs, in

clinical use, do not directly affect ACE2 activity [17], while ARBs increase messenger RNA expression as well as protein levels of ACE2 [18]. Duncan *et al*. [19] reported that ACE inhibitors had no significant effect on the level of Ang 1–7, while the level of Ang I was increased by 2.4- to 2.8-fold which was accompanied by a decrease in the level of Ang II by 54–58%. The level of ACE2 in patients who received long-term treatment with the ARBs was higher compared to untreated control patients, but this was not observed with the treatment of ACEIs. Long-term treatment of ARBs has been reported to decrease the plasma level of Ang II in hypertensive patients. This was due to increased activity of ACE2 leading to the hydrolysis of Ang II to Ang-(1–7) [20].

Anti-inflammatory and anti-oxidant role of ACEIs and ARBs

It is now well known that approximately little less than half 40% of Ang II molecule is synthesized via non-ACE pathways employing cathepsin and chymase. Therefore, ARBs have a greater potential to block the renin–angiotensin system than ACE inhibition in human subjects [21]. Furthermore, ARBs provide a theoretical additional advantage compared with ACEIs since they exert a potential effect on Ang II and Ang 1-7 via the activation of the individual receptor for AT2 and Mas, respectively. As a result of these mechanisms, ARBs are able to exert their protective anti-inflammatory, anti-oxidant, anti-apoptotic and anti-fibrotic actions in the body. Currently, there is no evidence that ACEIs can reduce plasma levels of major inflammatory mediators such as fibrinogen and CRP in hypertensive models. In contrast, ARBs seem to be highly potent as anti-inflammatory drugs compared to ACEIs since they can block AT1 receptor (22). Other beneficial effects of ARBs, over ACEIs, are their potential ability to block Ang II/AT1 receptor to induce TLR4/MyD88 signaling which in turn promotes cellular oxidative injury, apoptosis and a reduction in the release of cytokines [23]. ARBs, and to a lesser extent ACEIs, exert anti-oxidant and anti-inflammatory properties by increasing the level of ACE2 which in turn enhances Ang 1–7 level. It is well known that Ang 1–7 can induce protective effects in the body. These include its vasodilator effect, anti-inflammatory properties, endothelial protection from damage, anti-cell proliferative activity, anti-hypertrophic action and anti-fibrosis effects via it binding and subsequent activation of the Mas receptor [18]. Sukumaran *et al. [24] found that the ARBs, Telmisartan and olmesartancan exert anti-inflammatory effect in the body via a reduction of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6. In turn, these cytokines reduce the level of p38 MAPK and down-regulate the expression of PI3K and phosphor-Akt. In another study, Dandona et al. [25] investigated the effect of the ARB, valsartan on ROS generation and on the expression of NF-κB p65. They concluded valsartan inhibited ROS generation and suppress the expression of NF-κB and p65 at both cellular and plasma levels. Together, these results indicate that valsartan can induce an anti-inflammatory effect at cellular, molecular and plasma levels, Likewise, Wu et al. [26] reported that mice infected with influenza A virus and then treated with losartan showed alleviated lung edema and improved lung histopathology. These findings demonstrated a lowered lung injury scores and a reduced number of infiltrating leukocytes. The authors of the study concluded that ARBs should be considered as a potential candidate for therapies in clinical treatment of viral infected patients. Ang II regulates the production of ROS through various signaling targets such as, MAP kinases, RhoA/Rho kinase, transcription factors, protein tyrosine Phosphatase and tyrosine kinases. Activation of these redox-sensitive signaling pathways can induce cell growth and inflammation [27]. In another study, Kim et al showed that both SH-containing and non-SH-containing ACE inhibitors have superoxide anion-scavenging properties and as such, they concluded that ACEI can protect the cell against free radical-induced injury [28]. Figure (3) illustrates the cellular mechanisms where by ACEIs (A) and ARBS (B) can exert their protective effects in the body following an infection with* SARS-CoV2.

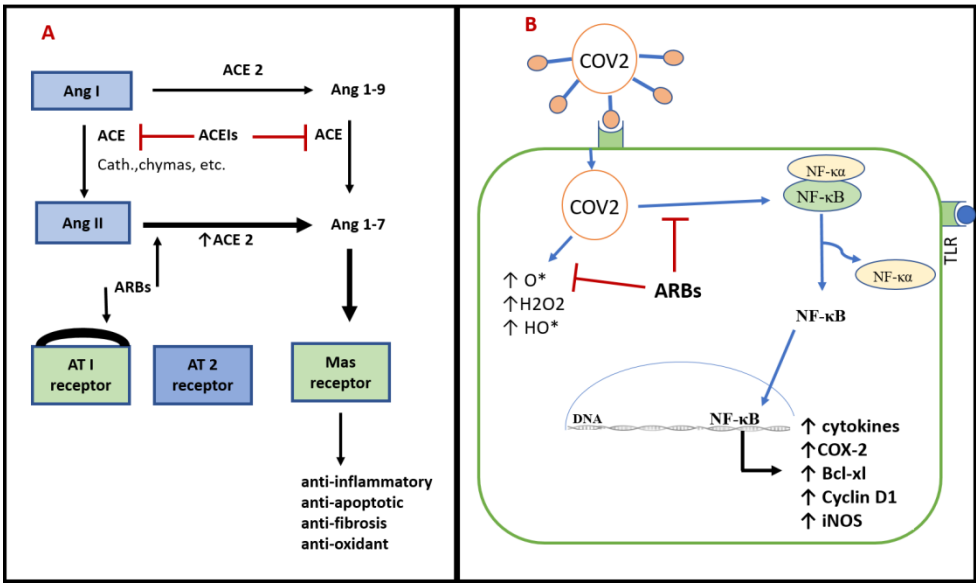

Figure (6): Schematic flow diagrams (A and B) showing the mechanisms via which ACEIs (A) and ABRs (B) can exert their protective effects against SARS-CoV2 in the body

Firstly, ARBs can block harmful AT1 receptor and increase Ang 1-7 which then binds to Mas receptor (figure 3A).Secondly, ARBs can reduce inflammation by blocking the NF-κB pathway and its downstream, as well as ROS generation, TLRs expression, and apoptosis, figure (3B).

CONCLUSION

In conclusion, the literature data reveal that ARBs can block the renin–angiotensin system in the body by .decreasing inflammation and ROS generation through different cellular mechanisms. These involve the inhibition of NF-kB, an increase in anti-oxidant activity, and the down regulation of TLRs. In addition, ARBs can also increase the level of Ang 1-7 via the ACE2 enzyme which synthesizes it from Ang II. In turn, Ang 1-7 can bind to both AT2 and Mas receptors to produce anti-inflammatory, anti-apoptotic, anti-oxidant activities. Finally, ARBs can also block the Ang II/AT1 receptor to induce TLR4/MyD88 signaling. It is concluded that ARBs are preferentially more useful than ACEIs to treat SARS-CoV2.

REFERENCES

1. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273.
2. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Military Medical Research. 2020;7(1):11-19.
3. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nature Microbiology. 2020;5(4):562-569.
4. Lin CW, Lin KH, Hsieh TH, Shiu SY, Li JY. Severe acute respiratory syndrome coronavirus 3C-like protease-induced apoptosis. FEMS Immunology and Medical Microbiology. 2006;46(3):375-380.
5. Di A, Kiya T, Gong H, Gao X, Malik AB. Role of the phagosomal redox-sensitive TRP channel TRPM2 in regulating bactericidal activity of macrophages. Journal of Cell Science. 2017;130(4):735-744.
6. Neely JR, Rovetto MJ, Oram JF. Myocardial utilization of carbohydrate and lipids. Progress in Cardiovascular Diseases. 1972;15(3):289-329.

7. Norris SL, Weinstein J, Peterson K, Thakurta S, McDonagh MS. Drug class review: direct renin inhibitors, angiotensin converting enzyme inhibitors, and angiotensin II receptor blockers: Oregon Health & Science University.; 2010.

8. Chen SX, Song T, Zhou SH, Liu YH, Wu SJ, Liu LY. Protective effects of ACE inhibitors on vascular endothelial dysfunction induced by exogenous advanced oxidation protein products in rats. European Journal of Pharmacology. 2008;584(2-3):368-375.

9. Osgood MJ, Harrison DG, Sexton KW, Hocking KM, Voskresensky IV, Komalavilas P, et al. Role of the renin-angiotensin system in the pathogenesis of intimal hyperplasia: therapeutic potential for prevention of vein graft failure? Annal of Vascular Surgery. 2012;26(8):1130-1144.

10. Low-dose captopril for the treatment of mild to moderate hypertension. I. Results of a 14-week trial. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Archives of Internal Medicine. 1984;144(10):1947-1953.

11. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet (London, England). 1993;342(8875):821-828.

12. Agodoa LY, Appel L, Bakris GL, Beck G, Bourgoignie J, Briggs JP, et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. Jama. 2001;285(21):2719-2728.

13. Jia HP, Look DC, Shi L, Hickey M, Pewe L, Netland J, et al. ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. J Virol. 2005;79(23):14614-14621.

14. Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, et al. A Novel Coronavirus Associated with Severe Acute Respiratory Syndrome. New England Journal of Medicine. 2003;348(20):1953-1966.

15. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005;11(8):875-879.

16. Sukumaran V, Veeraveedu PT, Gurusamy N, Yamaguchi K, Lakshmanan AP, Ma M, et al. Cardioprotective effects of telmisartan against heart failure in rats induced by experimental autoimmune myocarditis through the modulation of angiotensin-converting enzyme-2/angiotensin 1-7/mas receptor axis. International Journal of Biological Sciences. 2011;7(8):1077-1092.

17. RICE Gillian I, THOMAS Daniel A, GRANT Peter J, TURNER Anthony J, HOOPER Nigel M. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. Biochemical Journal. 2004;383(1):45-51.

18. Ferrario Carlos M, Jessup J, Chappell Mark C, Averill David B, Brosnihan KB, Tallant EA, et al. Effect of Angiotensin-Converting Enzyme Inhibition and Angiotensin II Receptor Blockers on Cardiac Angiotensin-Converting Enzyme 2. Circulation. 2005;111(20):2605-2610.

19. Campbell DJ, Zeitz CJ, Esler MD, Horowitz JD. Evidence against a major role for angiotensin converting enzyme-related carboxypeptidase (ACE2) in angiotensin peptide metabolism in the human coronary circulation. Journal of Hypertension. 2004;22(10):1971-1976.

20. Furuhashi M, Moniwa N, Mita T, Fuseya T, Ishimura S, Ohno K, et al. Urinary Angiotensin-Converting Enzyme 2 in Hypertensive Patients May Be Increased by Olmesartan, an Angiotensin II Receptor Blocker. American Journal of Hypertension. 2014;28(1):15-21.

21. Hollenberg Norman K, Fisher Naomi DL, Price Deborah A. Pathways for Angiotensin II Generation in Intact Human Tissue. Hypertension (Dallas, Tex : 1979). 1998;32(3):387-392.

22. Di Raimondo D, Tuttolomondo A, Butta C, Miceli S, Licata G, Pinto A. Effects of ACE-inhibitors and angiotensin receptor blockers on inflammation. Current pharmaceutical design. 2012;18(28):4385-413.

23. Lv J, Jia R, Yang D, Zhu J, Ding G. Candesartan attenuates Angiotensin II-induced mesangial cell apoptosis via TLR4/MyD88 pathway. Biochemical and Biophysical Research Communications. 2009;380(1):81-86.

24. Gava E, Samad-Zadeh A, Zimpelmann J, Bahramifarid N, Kitten GT, Santos RA, et al. Angiotensin-(1-7) activates a tyrosine phosphatase and inhibits glucose-induced signalling in proximal tubular cells. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association. European Renal Association. 2009;24(6):1766-1773.

25. Dandona P, Kumar V, Aljada A, Ghanim H, Syed T, Hofmayer D, et al. Angiotensin II Receptor Blocker Valsartan Suppresses Reactive Oxygen Species Generation in Leukocytes, Nuclear Factor-κB, in Mononuclear Cells of Normal Subjects: Evidence of an Antiinflammatory Action. The Journal of Clinical Endocrinology & Metabolism. 2003;88(9):4496-4501.

26. Yan Y, Liu Q, Li N, Du J, Li X, Li C, et al. Angiotensin II receptor blocker as a novel therapy in acute lung injury induced by avian influenza A H5N1 virus infection in mouse. Sci China Life Sci. 2015;58(2):208-211.

27. Nguyen Dinh Cat A, Montezano AC, Burger D, Touyz RM. Angiotensin II, NADPH oxidase, and redox signaling in the vasculature. Antioxid Redox Signal. 2013;19(10):1110-1120.

28. Kim JH, Kim H, Kim YH, Chung W-S, Suh JK, Kim SJ. Antioxidant effect of captopril and enalapril on reactive oxygen species-induced endothelial dysfunction in the rabbit abdominal aorta. Korean J Thorac Cardiovasc Surg. 2013;46(1):14-21.