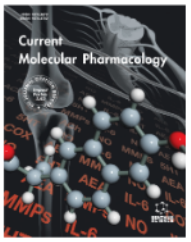
1874-4672/24

BENTHAM SCIENCE

CrossMark

Current Molecular Pharmacology

Content list available at: https://benthamscience.com/journal/cmp



MINI-REVIEW

The Role of Local Angiotensin II/Angiotensin Type 1 Receptor in Endometriosis: A Potential Target for New Treatment Approaches

Shirin Moazen[1] and Mohammad-Hasan Arjmand[2,3,*]

[1]*Department of Obstetrics and Gynecology, Clinical Research Development Unit, Hajar Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran*

[2]*Transplant Research Center, Clinical Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran*

[3]*Department of Medical Biochemistry, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

Abstract:

Endometriosis is a chronic inflammatory disorder described by the presence of functional endometrial-like tissues at extra-uterine locations that are related to chronic pelvic pain and infertility. Multiple molecular mechanisms, including inflammation, reactive oxygen species (ROS) generation, fibrotic reactions, and angiogenesis, are involved in the pathogenesis of endometriosis; however, the exact cause of this disorder still remains a matter of discussion. Recently, it has been shown that the local renin-angiotensin system (RAS) has been expressed in different tissues, like the gynecological tract, and alterations in its expression are associated with multiple pathological conditions like endometriosis. Angiotensin II (Ang II), as a main peptide of the RAS through angiotensin type 1 receptor (AT1R), upregulates signal transduction pathways such as nuclear factor kappa B (NF-κB), mitogen activation protein kinase (MAPK), and transforming growth factor beta (TGF-β) to promote inflammation, oxidative stress, and fibrogenesis. Angiotensin receptor blockers (ARBs) control high blood pressure, which is increased by excessive AT1R activity. Recently, it has been recognized that ARBs have tissue protective effects because of their anti-inflammatory and antifibrotic effects. In this review, we focused on the role of local Ang II/AT1R axis activity in endometriosis pathogenesis and justified the use of ARB agents as a potential therapeutic strategy to improve endometriosis.

Keywords: Endometriosis, Angiotensin II, Angiotensin type 1 receptor, Angiotensin receptor blocker, Inflammation, Fibrosis.

Article History	Received: March 09, 2024	Revised: May 13, 2024	Accepted: June 06, 2024

1. INTRODUCTION

Endometriosis is a common and benign gynecological disorder with dysfunctional growth of endometrial tissue, stroma, and glands outside the uterus, often with inflammatory, oxidative stress and fibrotic reactions [1]. Endometrial lesions are divided into three categories based on phenotype: deep infiltrating, ovarian endometriuma, and superficial peritoneal lesions [2]. Endometriosis has a high prevalence, and about 10% of women of reproductive age suffer from this disorder [3]. Chronic pelvic pain, pain with menstruation, and infertility with heavy economic burden are the main complications of endometriosis, which affects the quality of life of women [4]. Therefore, effective treatment is urgently needed to improve the quality of life of these patients. Recent studies have suggested that alterations in intracellular signaling pathways and specific gene expression related to inflammation and fibrosis may contribute to endometriosis; however, the exact molecular pathogenesis of endometriosis remains relatively unclear [5, 6]. Induction of pathways related to inflammation and fibrosis, such as nuclear factor kappa B (NF-κB) and transforming growth factor β, play an important role in the progression of endometriosis lesions [7, 8].

The renin-angiotensin system (RAS), as an endocrine system, plays an essential role in electrolyte balance and blood pressure hemostasis in the body. Besides the systemic RAS, local RAS is expressed throughout the human tissues, such as the gynecological tract [9, 10]. RAS contains several peptides, including renin, angiotensin I and II, angiotensin 1-7, and angiotensin converts enzyme and its receptors. Angiotensin II (Ang II), as the main peptide of the RAS, exerts its effects by binding to trans-membrane G-protein receptors named angiotensin receptor type 1&2 (AT1R and AT2R) [11]. Recently, attention has been paid to the role of the local RAS activity in ovarian and endometrial tissues, which can lead to

* Address correspondence to this author at the Transplant Research Center, Clinical Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran; Tel: +98 51 32291963;
E-mails: Arjmandmh1@mums.ac.ir, arjmandmh1@gmail.com

physiological and pathological processes, such as follicle maturation, regulation of reproduction, angiogenesis, and tumor cell proliferation [12]. In pathological conditions, it has been indicated that AT1R is highly expressed in human ovarian cancer cells and promotes tumorigenesis of endometrial carcinoma [13, 14]. Additionally, different studies have reported that Ang II with AT1R increases inflammation by increasing the generation of proinflammatory cytokines and also induces the expression of endothelial and leukocytic adhesion molecules [15]. Furthermore, Hsieh *et al*. have identified local AT1R gene polymorphism in endometriosis [16].

In this review, we discuss the role of local Ang II/AT1R dysregulation in the promotion of inflammatory fibrotic processes related to endometriosis. We also justify the use of angiotensin receptor blockers (ARBs) as a potential therapeutic strategy to improve endometriosis-related complications.

Electronic databases including PubMed, Scopus, Web of Science, and Google scholar, were used to select relevant studies in English up to 18 March 2024.

The inclusion criteria for considering qualified papers in this mini-review included a review of original articles about the role of local angiotensin II/Angiotensin type 1 receptor in endometriosis. Papers that did not mention the pathological role of renin-angiotensin receptors in endometriosis were excluded from the study. Two reviewers (MHA) and (SMD) reviewed all selected papers to extract essential data.

1.1. Role of Ang II/AT1R in Inflammatory Responses and Oxidative Stress

There is a strong association between inflammation and oxidative stress with endometriosis pathogenesis. NF-κB is a well-known pathway to participate in inflammatory responses [17]. In Previous studies, activation of NF-κB molecular mechanisms was demonstrated in endometriosis lesions and tissues. Wei *et al*. suggested that NF-κB hyper-activation increases endometriosis progression and severity [7]. As well as, Taniguchi *et al*. have shown that the NF-κB signaling pathway, through inhibition of endothelial cell apoptosis, promotes endometriosis [18].

Zhang *et al*. have reported an upregulated activation of NF-κB associated with high expression of AT1R in endometriosis tissues, which induces cell proliferation and prevents cell apoptosis [19]. AT1R induces phosphorylation of NF-κB p65 as a key molecule of the NF-κB pathway to increase the expression of inflammatory cytokines and chemokines [20]. Ekambaram *et al*. indicated that activation of the NF-κB signaling pathway through the Ang II/AT1R axis increases the calcification in vascular smooth muscle in response to inflammation. Also, Ang II/AT1R increases cell proliferation, migration, and tumoral cell invasion by NF-κB activation [21]. On the other hand, various studies have pointed out that the level of estradiol can be inversely related to the overactivity of local AT1Rs in the female reproductive tract. In stromal cells cultured from human endometrial tissue, estrogen treatment reduces the expression of AT1R, which leads to decreases in NF-κB activity. Adding tamoxifen as an estrogen receptor modulator promotes the expression levels of proteins related to the AT1R/NF-κB molecular pathway.

Furthermore, other studies have shown the modulatory effects of estrogen on AT1R expression. Kooptiwut *et al*. displayed that estradiol could attenuate the expression of AT1R mRNA levels in pancreatic β-cells [22]. Gao *et al*. have also reported that estradiol could diminish the expression of AT1R in the uterine artery [23]. These results suggested that during menstruation, a low level of the activated form of estrogen molecule may upregulate the expression of local AT1R in the endometrium, followed by the activation of downstream signaling pathways, such as NF-κB. Despite activation of NF-κB, AT1R can increase the inflammation by other molecular mechanisms. Various studies have demonstrated that AT1R increases inflammation by mitogen activation protein kinase (MAPK). MAPK complex, including extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal Kinase (JNK), and P38 MAP kinas are a serine-threonine family of protein kinases that regulate cellular responses to extracellular stress signals. Dysregulation and increased activity of MAPK complex, such as P38, increase the production of inflammatory mediators [24]. In most inflammatory cells, activated P38 MAP kinase mediates as an essential molecule for inflammatory signaling and cytokines production [25]. Different studies have shown the pathological role of MAPK complex in endometriosis [26, 27]. On the other hand, activated Ang II/AT1R leads to further stimulation of the MAPK signaling, which leads to the induction of inflammatory pathways. In this regard, Ang II by AT1R increases the proliferation of human mesangial cells and also the generation of proinflammatory cytokines by activation of MAPKs [28]. In cardiac and smooth muscle cells, AT1R promotes inflammation through MAPK signaling pathway [29]. In an *in vivo* study, it has been demonstrated that Ang-II/AT1R signaling upregulates the expression of adhesion molecules, metastasis, and inflammation through the p38/MAPK pathway in HCC cells [30]. In breast cancer, it has been indicated that the Ang II/AT1R axis is strongly associated with inflammation in the tumor microenvironment and tumorigenesis by ERK/MAPK signaling pathways [31]. Kaur *et al*. have focused on the molecular pathogenesis of endometriosis. They found that overexpression of AT1R in the endometrium and ovary increases different molecular pathways, such as MAPK complex and NF-κB to induce inflammation [32].

In addition to inflammation, oxidative stress and the production of reactive oxygen species (ROS) are also involved in the pathogenesis and exacerbation of endometriosis. Oxidative stress is the result of an imbalance between ROS production and antioxidant defense mechanisms that can lead to different pathological processes within the body. Various mechanisms are involved in causing oxidative stress in endometriosis, including phagocytosis as the result of inflammation in the peritoneal cavity [33] and activation of NF-κB that is responsible for the expression of proinflammatory cytokines and ROS, such as inducible nitric oxide [34]. Oxidative stress and an increase of free radicals contribute to the progress of endometriosis by inflammation, endometrial fragment adhesion, proliferation, and angiogenesis [35, 36]. Regarding the association between RAS and oxidative stress, AT1R activation can increase oxidative stress by

activation of NADPH oxidase in vascular cells [37], interaction with Nitric Oxide Pathway [37, 38], and mitochondrial dysfunction [39]. NADPH oxidase is found in vascular, fibroblasts, and neutrophilic cells and is a major source of ROS generation [40]. Different studies have reported that activated AT1R stimulates NADPH isoform in cells to induce oxidative stress [41].

Furthermore, Ang II/AT1R signaling transduction induces mitochondrial fragments through epidermal growth factor receptor activation. Mitochondrial fragments increase ROS production and tumor necrosis factor alpha (TNFα) signal transduction. In addition, sirtuin 3, a key regulator of mitochondrial dynamics, and superoxide dismutase have been shown to inhibit Ang/AT1R to enhance mitochondrial ROS generation [42]. Further studies are needed to investigate more precisely the role of AT1R molecular signaling in causing inflammation and oxidative damage in female reproductive tissues. The effects of RAS signaling on the induction of inflammation and oxidative stress in endometriosis lesions are summarized in Fig. (**1**).

1.2. The Association between AT1R and Transforming Growth Factor β (TGF-β) in Endometriosis

In addition to inflammatory reactions, fibrotic reactions with different degrees according to the type of endometriosis lesions are involved in the pathogenesis of the disorder. Fibrosis is described as an abnormal accumulation of the extracellular matrix (ECM) around inflamed and injured cells and tissues like endometrium and ovary [43]. Activation of different cells, such as macrophages, platelets, adherent fibroblasts, and profibrotic molecules like TGF-β, are involved in the biology of fibrosis [43, 44]. TGF-β released from immune cells and fibroblasts is the main profibrotic cytokine that induces cell proliferation, migration, and ECM deposition [45]. Three isoforms of TGF-β are distributed all over the body, but TGF-β1 is the main molecule for the progress of inflammation and fibrosis. Different studies have indicated the role of TGF-β1 in the development of endometriosis lesions. Young *et al*. have reported that women with endometriosis have high levels of TGF-β in peritoneal fluids compared with women without endometriosis [46]. Zhang *et al*. demonstrated that induction of the TGF-β/SMAD signaling pathway in ovarian endometrioma lesions leads to an increase in the cell's proliferation, collagen deposition, and promotion of fibrosis [47]. Guo *et al*. showed that TGF-β, through the increase of epithelial mesangial transition and smooth muscle metaplasia in endometriotic epithelial and stromal cells, increases the fibrotic process in endometriosis [48].

Recently, it has been observed that fibrotic effects of Ang II/AT1R are associated with activation of TGF-β1 signaling [49, 50]. Ang II/AT1R through ERK/P38 MAPK complex activates SMAD molecular signaling by phosphorylating SMAD2/3 [51]. In this way, various studies have demonstrated the link between AT1R and TGF-β signaling pathways in fibrotic conditions. Everett *et al*. showed that increased expression of TGF-β1 is mediated by AT1R in cardiac hypertrophy [52]. Ichihara *et al*. indicated that mice with a lack of AT1R have suppressed levels of TGF-β1 and collagen I and III with no cardiac hypertrophy [53]. Experiments on human atrial tissue showed that stimulation of tissue with Ang II increases the TGF-β expression by AT1R activation [54]. In another study, it was displayed that Ang II/AT1R increases the development of renal fibrosis by inducing the activation of the TGF-β1/SMAD signaling pathway [55]. It is demonstrated that Ang II/AT1R activation by TGF-β/Smad2/3 and NF-κB signaling pathway increases epithelial mesangial transition to promote Tubulointerstitial and renal fibrosis [56, 57]. Upregulated AT1Rs modulate TGF-β expression in human hypertrophic scars [58]. In a clinical study in patients with hypertrophic scars and keloids, it has been shown that Ang II/AT1R increases the expression of TGF-β and profibrotic

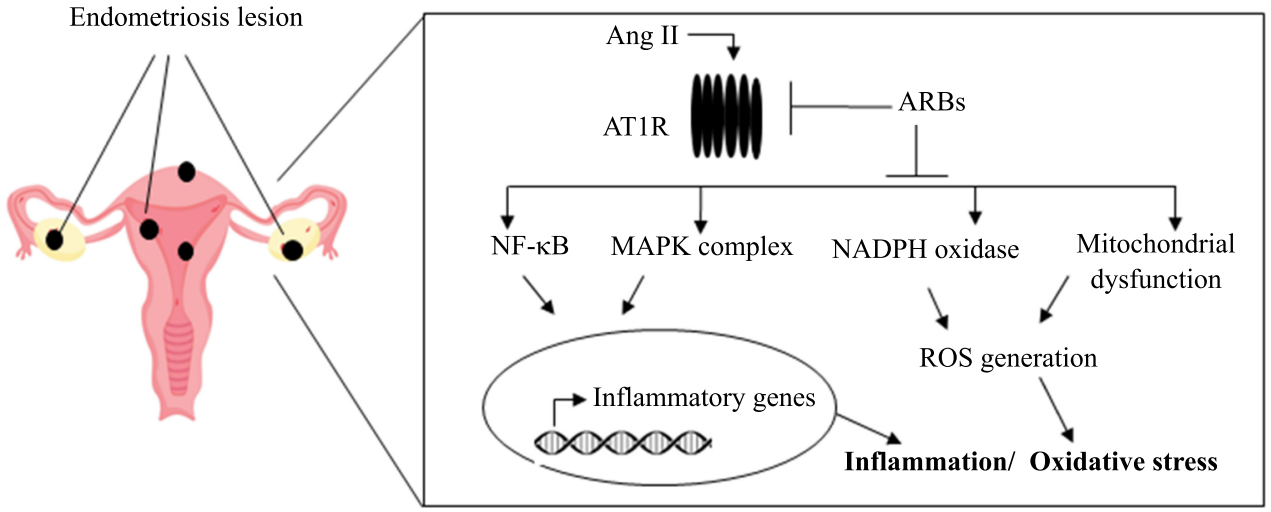


Fig. (1). Ang II/AT1R activation stimulates different intracellular molecular mechanisms to induce inflammation and oxidative stress. Ang II: angiotensin II, AT1R: angiotensin type 1 receptor, ARB: angiotensin receptor blocker, NF-κB: nuclear factor kappa B, MAPK: mitogen activation protein kinase, ROS: reactive oxygen species.

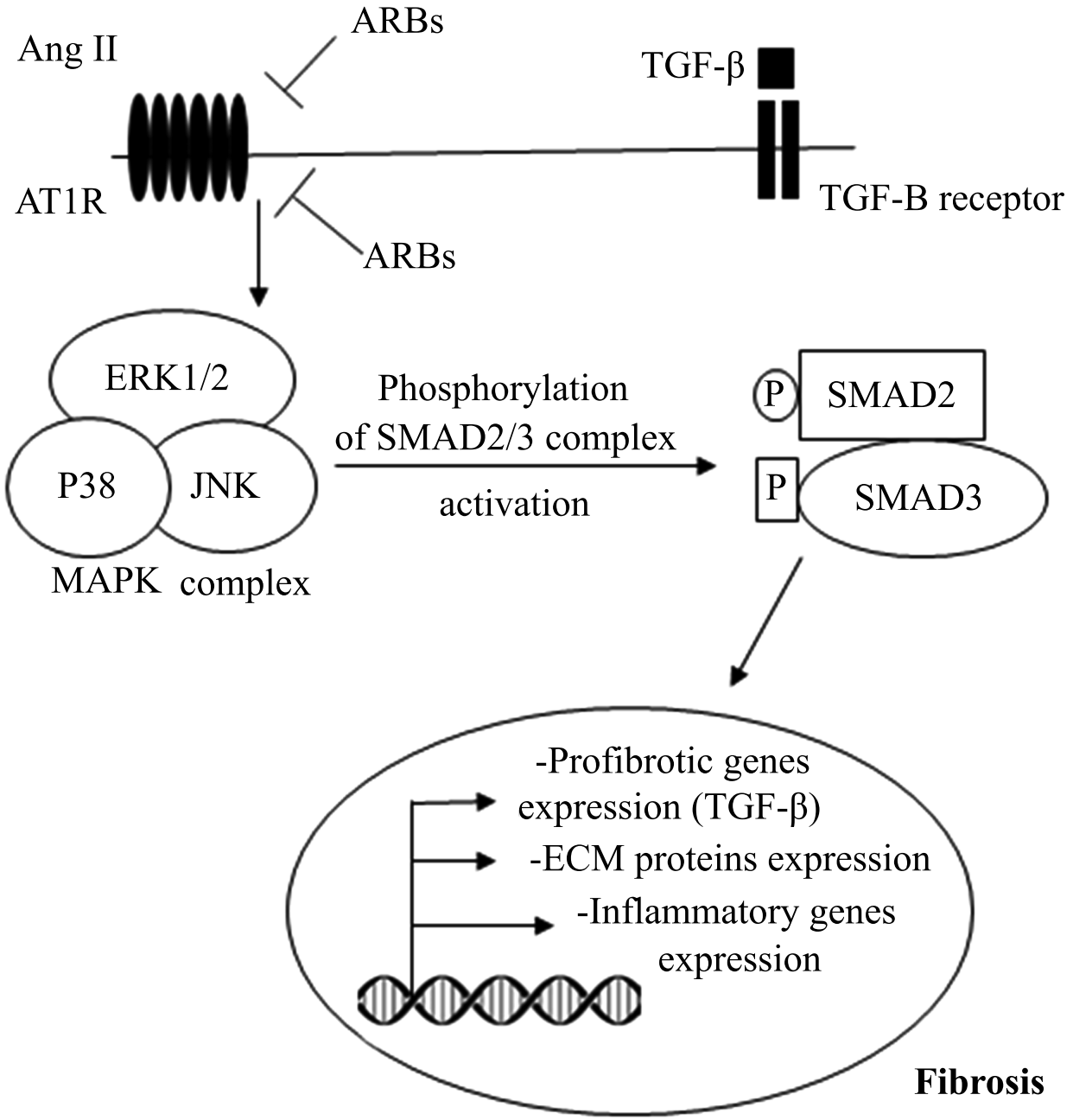


Fig. (2). Ang II/AT1R axis through MAPK complex stimulates the TGF-β/SMAD signaling pathway by inducing the phosphorylation of SMAD2/3. SMAD complex inter the nucleus and increases the expression of a wide range of genes related to inflammation and fibrosis. Ang II: angiotensin II, AT1R: angiotensin type 1 receptor, ARB: angiotensin receptor blocker, c-Jun N-terminal Kinase (JNK), extracellular signal-regulated kinase 1/2 (ERK1/2), ECM: extracellular matrix, MAPK: mitogen activation protein kinase, TGF-β: transforming growth factor beta.

molecules to develop fibrosis, and using Losartan reduces scar scores in patients [59]. Queisser *et al*. reported that Losartan administration through inhibition of AT1R reduces the expression of TGF-β1 and, as a result, liver fibrosis [60]. These results showed that Ang II by AT1R signaling pathway upregulates TGF-β/SMAD signaling pathways to promote fibrogenesis, and inhibition of AT1R by ARBs reduces the expression of profibrotic molecules and fibrosis in different organs. The interaction of Ang II/AT1R with increasing TGF-β/SMAD signaling pathway is shown in Fig. (**2**).

1.3. Therapeutic Potential of AT1R Blockers in the Reduction of Inflammation and Fibrosis

ARBs are progressed to control high blood pressure connected with excessive peripheral AT1R activity. Recently it was recognized that ARBs decrease inflammation and fibrotic pathways and have major useful effects on metabolism [61, 62]. In addition, using ARBs has tissue-protective effects

because of their anti-inflammatory and antioxidant properties [63]. Administration of ARBs ameliorated NF-κB activation and expression of proinflammatory cytokines like TNF-α and interleukin 6 (IL6) promoted by the Ang II/AT1R axis in cultured cells [64]. Arjmand *et al*. demonstrated that intraperitoneal administration of Telmisartan, a type of ARB, reduces inflammation and fibrosis scores in rats with abdominal surgeries [65]. Candan *et al*. reported that Irbesartan, as an ARB, reduces acute kidney injury through the downregulation of NF-κβ in animal models [66]. Induced peritoneal endometriosis in rat model indicated that using oral Losartan decreased the area of experimental endometriosis by plasma inflammatory factors, such as TNF-α, C reaction protein (CRP), and pentraxin-3 [67]. Nenicu *et al*. reported that Telmisartan, by inhibition of AT1Rs and upregulation of Peroxisome proliferator-activated receptor gamma (PPAR-γ) in endometriosis-like lesions, reduces the expression of some angiogenic and inflammatory genes [68]. Losartan regulates the generation of pro-inflammatory cytokines *via* T and B cells by inhibiting MAPK signaling and NF-κB [69]. ARBs reduced CRP, TNF-α, and erythrocyte sedimentation rate (ESR) in patients with arthritis rheumatoid [70, 71]. These findings suggested that ARBs have the potential to reduce inflammation in different pathological conditions.

Furthermore, it has been reported that ARBs have the potential to reduce fibrosis in different organs. In a study, it has been shown that ARBs have a beneficial effect on attenuating peritoneal fibrosis in patients undergoing long-term peritoneal dialysis [72]. Recently, Losartan was indicated to decrease fibrosis in a rat model of Crohn's disease [73]. Despite different animal studies, various clinical data show that ARB therapy has beneficial effects in improving liver fibrosis related to hepatitis C [74, 75]. Colmenero *et al*. reported that the administration of Losartan to patients with liver fibrosis improves liver function and reduces the expression of fibrogenic genes [76]. Nenicu *et al*. showed that using 100 micro/molar Telmisartan in induced peritoneal endometriosis rat models significantly reduces the expression of fibrotic genes like TGF-β to improve endometriosis-like lesions [68]. Also, they found that 200 μM Telmisartan completely suppressed vascularization and blood perfusion of endometriosis-like lesions. This evidence suggests that ARBs are useful for blocking AT1R activities, thus holding great promise in preventing inflammatory and fibrotic conditions that occur in endometriosis.

CONCLUSION

The presence of local RAS spreads beyond the classically detected renal and cardiovascular systems and has been indicated in almost the whole body, like the female reproductive tract. Recently, it has come to light that dysregulation of local Ang II/AT1R upregulates molecular pathways, such as NF-κB and TGF-β/SMAD, to induce inflammation and fibrosis in a multitude of conditions, including endometriosis lesions. These reports together point out that AT1R blockers may have therapeutic potential to prevent endometriosis and its complications in females.

AUTHORS' CONTRIBUTIONS

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AT1R	=	Angiotensin type 1 receptor
ARBs	=	Angiotensin receptor blockers
JNK	=	c-Jun N-terminal Kinase
ECM	=	Extracellular matrix
MAPK	=	Mitogen activation protein kinase
NF-κB	=	Nuclear factor kappa B
PPAR-γ	=	Peroxisome proliferator-activated receptor gamma
RAS	=	Renin-angiotensin system
ROS	=	Reactive oxygen species
TGF-β	=	Transforming growth factor beta
TNF-α	=	Tumor necrosis factor-alpha

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Clement, P.B. The pathology of endometriosis: A survey of the many faces of a common disease emphasizing diagnostic pitfalls and unusual and newly appreciated aspects. *Adv. Anat. Pathol.,* **2007**, *14*(4), 241-260. [http://dx.doi.org/10.1097/PAP.0b013e3180ca7d7b] [PMID: 17592255]

[2] Zondervan, K.T.; Becker, C.M.; Missmer, S.A. Endometriosis. *N. Engl. J. Med.,* **2020**, *382*(13), 1244-1256. [http://dx.doi.org/10.1056/NEJMra1810764] [PMID: 32212520]

[3] Sarria-Santamera, A.; Orazumbekova, B.; Terzic, M.; Issanov, A.; Chaowen, C.; Asúnsolo-del-Barco, A. Systematic review and meta-analysis of incidence and prevalence of endometriosis. *Healthcare,* **2020**, *9*(1), 29. [http://dx.doi.org/10.3390/healthcare9010029] [PMID: 33396813]

[4] As-Sanie, S.; Black, R.; Giudice, L.C.; Gray Valbrun, T.; Gupta, J.; Jones, B.; Laufer, M.R.; Milspaw, A.T.; Missmer, S.A.; Norman, A.; Taylor, R.N.; Wallace, K.; Williams, Z.; Yong, P.J.; Nebel, R.A. Assessing research gaps and unmet needs in endometriosis. *Am. J. Obstet. Gynecol.,* **2019**, *221*(2), 86-94. [http://dx.doi.org/10.1016/j.ajog.2019.02.033] [PMID: 30790565]

[5] Diao, R.; Wei, W.; Zhao, J.; Tian, F.; Cai, X.; Duan, Y.G. CCL 19/ CCR 7 contributes to the pathogenesis of endometriosis *via*PI 3K/Akt pathway by regulating the proliferation and invasion of ESC s. *Am. J. Reprod. Immunol.,* **2017**, *78*(5), e12744. [http://dx.doi.org/10.1111/aji.12744] [PMID: 28856757]

[6] Pazhohan, A.; Amidi, F.; Akbari-Asbagh, F.; Seyedrezazadeh, E.; Farzadi, L.; Khodarahmin, M.; Mehdinejadiani, S.; Sobhani, A. The Wnt/β-catenin signaling in endometriosis, the expression of total and

active forms of β-catenin, total and inactive forms of glycogen synthase kinase-3β, WNT7a and DICKKOPF-1. *Eur. J. Obstet. Gynecol. Reprod. Biol.,* **2018**, *220*, 1-5. [http://dx.doi.org/10.1016/j.ejogrb.2017.10.025] [PMID: 29107840]

[7] Wei, X.; Shao, X. Nobiletin alleviates endometriosis *via* down-regulating NF-κB activity in endometriosis mouse model. *Biosci. Rep.,* **2018**, *38*(3), BSR20180470. [http://dx.doi.org/10.1042/BSR20180470] [PMID: 29871974]

[8] Soni, U.K.; Chadchan, S.B.; Kumar, V.; Ubba, V.; Khan, M.T.A.; Vinod, B.S.V.; Konwar, R.; Bora, H.K.; Rath, S.K.; Sharma, S.; Jha, R.K. A high level of TGF-B1 promotes endometriosis development *via* cell migration, adhesiveness, colonization, and invasiveness. *Biol. Reprod.,* **2019**, *100*(4), 917-938. [http://dx.doi.org/10.1093/biolre/ioy242] [PMID: 30423016]

[9] Herr, D.; Bekes, I.; Wulff, C. Local renin-angiotensin system in the reproductive system. *Front. Endocrinol.,* **2013**, *4*, 150. [http://dx.doi.org/10.3389/fendo.2013.00150] [PMID: 24151488]

[10] Li, X.F.; Ahmed, A. Expression of angiotensin II and its receptor subtypes in endometrial hyperplasia: A possible role in dysfunctional menstruation. *Lab. Invest.,* **1996**, *75*(2), 137-145. [PMID: 8765314]

[11] Kurdi, M.; Mello, W.C.D.; Booz, G.W. Working outside the system: An update on the unconventional behavior of the renin–angiotensin system components. *Int. J. Biochem. Cell Biol.,* **2005**, *37*(7), 1357-1367. [http://dx.doi.org/10.1016/j.biocel.2005.01.012] [PMID: 15833268]

[12] Vinson, G.P.; Teja, R.; Ho, M.M.; Hinson, J.P.; Puddefoot, J.R. The role of the tissue renin-angiotensin system in the response of the rat adrenal to exogenous angiotensin II. *J. Endocrinol.,* **1998**, *158*(2), 153-159. [http://dx.doi.org/10.1677/joe.0.1580153] [PMID: 9771458]

[13] Park, Y.A.; Choi, C.H.; Do, I.G.; Song, S.Y.; Lee, J.K.; Cho, Y.J.; Choi, J.J.; Jeon, H.K.; Ryu, J.Y.; Lee, Y.Y.; Kim, T.J.; Bae, D.S.; Lee, J.W.; Kim, B.G. Dual targeting of angiotensin receptors (AGTR1 and AGTR2) in epithelial ovarian carcinoma. *Gynecol. Oncol.,* **2014**, *135*(1), 108-117. [http://dx.doi.org/10.1016/j.ygyno.2014.06.031] [PMID: 25014541]

[14] Watanabe, Y.; Shibata, K.; Kikkawa, F.; Kajiyama, H.; Ino, K.; Hattori, A.; Tsujimoto, M.; Mizutani, S. Adipocyte-derived leucine aminopeptidase suppresses angiogenesis in human endometrial carcinoma *via* renin-angiotensin system. *Clin. Cancer Res.,* **2003**, *9*(17), 6497-6503. [PMID: 14695154]

[15] MacKenzie, A. Endothelium-derived vasoactive agents, AT1 receptors and inflammation. *Pharmacol. Ther.,* **2011**, *131*(2), 187-203. [http://dx.doi.org/10.1016/j.pharmthera.2010.11.001] [PMID: 21115037]

[16] Hsieh, Y.Y.; Chang, C.C.; Chen, S.Y.; Chen, C.P.; Lin, W.H.; Tsai, F.J. XRCC1 399 * Arg-related genotype and allele, but not XRCC1 His107Arg, XRCC1 Trp194Arg, KCNQ2, AT1R, and hOGG1 polymorphisms, are associated with higher susceptibility of endometriosis. *Gynecol. Endocrinol.,* **2012**, *28*(4), 305-309. [http://dx.doi.org/10.3109/09513590.2011.631624] [PMID: 22084859]

[17] López-Novoa, J.M.; Nieto, M.A. Inflammation and EMT: An alliance towards organ fibrosis and cancer progression. *EMBO Mol. Med.,* **2009**, *1*(6-7), 303-314. [http://dx.doi.org/10.1002/emmm.200900043] [PMID: 20049734]

[18] Taniguchi, F.; Uegaki, T.; Nakamura, K.; Mon, K.Y.; Harada, T.; Ohbayashi, T.; Harada, T. Inhibition of IAP (inhibitor of apoptosis) proteins represses inflammatory status *via* nuclear factor□kappa B pathway in murine endometriosis lesions. *Am. J. Reprod. Immunol.,* **2018**, *79*(1), e12780. [http://dx.doi.org/10.1111/aji.12780] [PMID: 29105884]

[19] Zhang, Z.; Yuan, Y.; He, L.; Yao, X.; Chen, J. Involvement of angiotensin II receptor type 1/NF□κB signaling in the development of endometriosis. *Exp. Ther. Med.,* **2020**, *20*(4), 3269-3277. [http://dx.doi.org/10.3892/etm.2020.9071] [PMID: 32855697]

[20] Orejudo, M.; Rodrigues-Diez, R.R.; Rodrigues-Diez, R.; Garcia-Redondo, A.; Santos-Sánchez, L.; Rández-Garbayo, J.; Cannata-Ortiz, P.; Ramos, A.M.; Ortiz, A.; Selgas, R.; Mezzano, S.; Lavoz, C.; Ruiz-Ortega, M. Interleukin 17A participates in renal inflammation associated to experimental and human hypertension. *Front. Pharmacol.,* **2019**, *10*, 1015. [http://dx.doi.org/10.3389/fphar.2019.01015] [PMID: 31572188]

[21] Ekambaram, P.; Lee, J.Y.L.; Hubel, N.E.; Hu, D.; Yerneni, S.; Campbell, P.G.; Pollock, N.; Klei, L.R.; Concel, V.J.; Delekta, P.C.; Chinnaiyan, A.M.; Tomlins, S.A.; Rhodes, D.R.; Priedigkeit, N.; Lee, A.V.; Oesterreich, S.; McAllister-Lucas, L.M.; Lucas, P.C. The CARMA3–Bcl10–MALT1 signalosome drives nfκb activation and promotes aggressiveness in angiotensin II receptor–positive breast cancer. *Cancer Res.,* **2018**, *78*(5), 1225-1240. [http://dx.doi.org/10.1158/0008-5472.CAN-17-1089] [PMID: 29259013]

[22] Kooptiwut, S.; Wanchai, K.; Semprasert, N.; Srisawat, C.; Yenchitsomanus, P. Estrogen attenuates AGTR1 expression to reduce pancreatic β-cell death from high glucose. *Sci. Rep.,* **2017**, *7*(1), 16639. [http://dx.doi.org/10.1038/s41598-017-15237-4] [PMID: 29192236]

[23] Gao, H.; Yallampalli, U.; Yallampalli, C. Protein restriction to pregnant rats increases the plasma levels of angiotensin II and expression of angiotensin II receptors in uterine arteries. *Biol. Reprod.,* **2012**, *86*(3), 68. [http://dx.doi.org/10.1095/biolreprod.111.095844] [PMID: 22088913]

[24] Kaminska, B. MAPK signalling pathways as molecular targets for anti-inflammatory therapy—from molecular mechanisms to therapeutic benefits. *Biochim. Biophys. Acta. Proteins Proteomics,* **2005**, *1754*(1-2), 253-262. [http://dx.doi.org/10.1016/j.bbapap.2005.08.017] [PMID: 16198162]

[25] Kyriakis, J.M.; Avruch, J.J.P.r. Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. *Physiol. Rev.,* **2001**, *81*(2), 807-869. [http://dx.doi.org/10.1152/physrev.2001.81.2.807]

[26] Kajihara, H. New insights into the pathophysiology of endometriosis: from chronic inflammation to danger signal. *Gynecol. Endocrinol.,* **2011**, *27*(2), 73-79. [http://dx.doi.org/10.3109/09513590.2010.507292]

[27] Santulli, P. MAP kinases and the inflammatory signaling cascade as targets for the treatment of endometriosis. *Expert Opin. Ther. Targets,* **2015**, *19*(11), 1465-1483. [http://dx.doi.org/10.1517/14728222.2015.1090974]

[28] Zhang, A.; Ding, G.; Huang, S.; Wu, Y.; Pan, X.; Guan, X.; Chen, R.; Yang, T. c-Jun NH_2-terminal kinase mediation of angiotensin II-induced proliferation of human mesangial cells. *Am. J. Physiol. Renal Physiol.,* **2005**, *288*(6), F1118-F1124. [http://dx.doi.org/10.1152/ajprenal.00220.2004] [PMID: 15701817]

[29] Eguchi, S.; Dempsey, P.J.; Frank, G.D.; Motley, E.D.; Inagami, T. Activation of MAPKs by angiotensin II in vascular smooth muscle cells. Metalloprotease-dependent EGF receptor activation is required for activation of ERK and p38 MAPK but not for JNK. *J. Biol. Chem.,* **2001**, *276*(11), 7957-7962. [http://dx.doi.org/10.1074/jbc.M008570200] [PMID: 11116149]

[30] Feng, L.H.; Sun, H.C.; Zhu, X.D.; Zhang, S.Z.; Li, X.L.; Li, K.S.; Liu, X.F.; Lei, M.; Li, Y.; Tang, Z.Y. Irbesartan inhibits metastasis by interrupting the adherence of tumor cell to endothelial cell induced by angiotensin II in hepatocellular carcinoma. *Ann. Transl. Med.,* **2021**, *9*(3), 207. [http://dx.doi.org/10.21037/atm-20-5293] [PMID: 33708834]

[31] Zhao, Y.; Chen, X.; Cai, L.; Yang, Y.; Sui, G.; Fu, S. Angiotensin II/angiotensin II type I receptor (AT1R) signaling promotes MCF□7 breast cancer cells survival *via* PI3□kinase/Akt pathway. *J. Cell. Physiol.,* **2010**, *225*(1), 168-173. [http://dx.doi.org/10.1002/jcp.22209] [PMID: 20458733]

[32] Kaur, K.K.; Allahbadia, G.J.A.i.R.S. An update on pathophysiology and medical management of endometriosis. *Adv. Reprod. Sci.,* **2016**, *4*(2), 53-73. [http://dx.doi.org/10.4236/arsci.2016.42008]

[33] Zeller, J.M.; Henig, I.; Radwanska, E.; Dmowski, W.P. Enhancement of human monocyte and peritoneal macrophage chemiluminescence activities in women with endometriosis. *Am. J. Reprod. Immunol. Microbiol.,* **1987**, *13*(3), 78-82. [http://dx.doi.org/10.1111/j.1600-0897.1987.tb00097.x] [PMID: 3605484]

[34] Viatour, P.; Merville, M.P.; Bours, V.; Chariot, A. Phosphorylation of NF-κB and IκB proteins: Implications in cancer and inflammation. *Trends Biochem. Sci.,* **2005**, *30*(1), 43-52. [http://dx.doi.org/10.1016/j.tibs.2004.11.009] [PMID: 15653325]

[35] Lebovic, D.I.; Mueller, M.D.; Taylor, R.N. Immunobiology of endometriosis. *Fertil. Steril.,* **2001**, *75*(1), 1-10. [http://dx.doi.org/10.1016/S0015-0282(00)01630-7] [PMID: 11163805]

[36] González-Ramos, R.; Donnez, J.; Defrère, S.; Leclercq, I.; Squifflet, J.; Lousse, J.C.; Van Langendonckt, A. Nuclear factor-kappa B is constitutively activated in peritoneal endometriosis. *Mol. Hum. Reprod.,* **2007**, *13*(7), 503-509.

[http://dx.doi.org/10.1093/molehr/gam033] [PMID: 17483545]

[37] Griendling, K.K.; Minieri, C.A.; Ollerenshaw, J.D.; Alexander, R.W. Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. *Circ. Res.,* **1994**, *74*(6), 1141-1148.
[http://dx.doi.org/10.1161/01.RES.74.6.1141] [PMID: 8187280]

[38] Laursen, J.B.; Rajagopalan, S.; Galis, Z.; Tarpey, M.; Freeman, B.A.; Harrison, D.G. Role of superoxide in angiotensin II-induced but not catecholamine-induced hypertension. *Circulation,* **1997**, *95*(3), 588-593.
[http://dx.doi.org/10.1161/01.CIR.95.3.588] [PMID: 9024144]

[39] Dikalov, S.I.; Nazarewicz, R.R.; Bikineyeva, A.; Hilenski, L.; Lassègue, B.; Griendling, K.K.; Harrison, D.G.; Dikalova, A.E. Nox2-induced production of mitochondrial superoxide in angiotensin II-mediated endothelial oxidative stress and hypertension. *Antioxid. Redox Signal.,* **2014**, *20*(2), 281-294.
[http://dx.doi.org/10.1089/ars.2012.4918] [PMID: 24053613]

[40] Sharma, P. Reactive oxygen species, oxidative damage, and antioxidative defense mechanism in plants under stressful conditions. *J. Bot.,* **2012**, *2012*
[http://dx.doi.org/10.1155/2012/217037]

[41] Bataller, R.; Schwabe, R.F.; Choi, Y.H.; Yang, L.; Paik, Y.H.; Lindquist, J.; Qian, T.; Schoonhoven, R.; Hagedorn, C.H.; Lemasters, J.J.; Brenner, D.A. NADPH oxidase signal transduces angiotensin II in hepatic stellate cells and is critical in hepatic fibrosis. *J. Clin. Invest.,* **2003**, *112*(9), 1383-1394.
[http://dx.doi.org/10.1172/JCI18212] [PMID: 14597764]

[42] Dikalova, A.E.; Itani, H.A.; Nazarewicz, R.R.; McMaster, W.G.; Flynn, C.R.; Uzhachenko, R.; Fessel, J.P.; Gamboa, J.L.; Harrison, D.G.; Dikalov, S.I. Sirt3 impairment and SOD2 hyperacetylation in vascular oxidative stress and hypertension. *Circ. Res.,* **2017**, *121*(5), 564-574.
[http://dx.doi.org/10.1161/CIRCRESAHA.117.310933] [PMID: 28684630]

[43] Henderson, N.C.; Rieder, F.; Wynn, T.A. Fibrosis: From mechanisms to medicines. *Nature,* **2020**, *587*(7835), 555-566.
[http://dx.doi.org/10.1038/s41586-020-2938-9] [PMID: 33239795]

[44] Eming, S.A.; Martin, P.; Tomic-Canic, M. Wound repair and regeneration: Mechanisms, signaling, and translation. *Sci. Transl. Med.,* **2014**, *6*(265), 265sr6.
[http://dx.doi.org/10.1126/scitranslmed.3009337] [PMID: 25473038]

[45] Hu, H.H.; Chen, D.Q.; Wang, Y.N.; Feng, Y.L.; Cao, G.; Vaziri, N.D.; Zhao, Y.Y. New insights into TGF-β/Smad signaling in tissue fibrosis. *Chem. Biol. Interact.,* **2018**, *292*, 76-83.
[http://dx.doi.org/10.1016/j.cbi.2018.07.008] [PMID: 30017632]

[46] Young, V.J.; Brown, J.K.; Maybin, J.; Saunders, P.T.K.; Duncan, W.C.; Horne, A.W. Transforming growth factor-β induced Warburg-like metabolic reprogramming may underpin the development of peritoneal endometriosis. *J. Clin. Endocrinol. Metab.,* **2014**, *99*(9), 3450-3459.
[http://dx.doi.org/10.1210/jc.2014-1026] [PMID: 24796928]

[47] Zhang, Q.; Duan, J.; Liu, X.; Guo, S.W. Platelets drive smooth muscle metaplasia and fibrogenesis in endometriosis through epithelial–mesenchymal transition and fibroblast-to-myofibroblast transdifferentiation. *Mol. Cell. Endocrinol.,* **2016**, *428*, 1-16.
[http://dx.doi.org/10.1016/j.mce.2016.03.015] [PMID: 26992563]

[48] Guo, S.W.; Ding, D.; Geng, J.G.; Wang, L.; Liu, X. P-selectin as a potential therapeutic target for endometriosis. *Fertil. Steril.,* **2015**, *103*(4), 990-1000.e8.
[http://dx.doi.org/10.1016/j.fertnstert.2015.01.001] [PMID: 25681855]

[49] Dobaczewski, M.; Chen, W.; Frangogiannis, N.G. Transforming growth factor (TGF)-β signaling in cardiac remodeling. *J. Mol. Cell. Cardiol.,* **2011**, *51*(4), 600-606.
[http://dx.doi.org/10.1016/j.yjmcc.2010.10.033] [PMID: 21059352]

[50] Schultz, J.E.J. TGF-beta1 mediates the hypertrophic cardiomyocyte growth induced by angiotensin II. *J. Clin. Invest.,* **2002**, \ *109*(6), 787-796.

[51] Murphy, A.M.; Wong, A.L.; Bezuhly, M. Modulation of angiotensin II signaling in the prevention of fibrosis. *Fibrogenesis Tissue Repair,* **2015**, *8*(1), 7.
[http://dx.doi.org/10.1186/s13069-015-0023-z] [PMID: 25949522]

[52] Everett, A.D.; Tufro-McReddie, A.; Fisher, A.; Gomez, R.A. Angiotensin receptor regulates cardiac hypertrophy and transforming growth factor-beta 1 expression. *Hypertension,* **1994**, *23*(5), 587-592.
[http://dx.doi.org/10.1161/01.HYP.23.5.587] [PMID: 8175166]

[53] Ichihara, S.; Senbonmatsu, T.; Price, E., Jr; Ichiki, T.; Gaffney, F.A.; Inagami, T. Angiotensin II type 2 receptor is essential for left ventricular hypertrophy and cardiac fibrosis in chronic angiotensin II-induced hypertension. *Circulation,* **2001**, *104*(3), 346-351.
[http://dx.doi.org/10.1161/01.CIR.104.3.346] [PMID: 11457756]

[54] Kupfahl, C.; Pink, D.; Friedrich, K.; Zurbrügg, H.R.; Neuss, M.; Warnecke, C.; Fielitz, J.; Graf, K.; Fleck, E.; Regitz-Zagrosek, V. Angiotensin II directly increases transforming growth factor β1 and osteopontin and indirectly affects collagen mRNA expression in the human heart. *Cardiovasc. Res.,* **2000**, *46*(3), 463-475.
[http://dx.doi.org/10.1016/S0008-6363(00)00037-7] [PMID: 10912457]

[55] Lin, S.L.; Chen, R.H.; Chen, Y.M.; Chiang, W.C.; Lai, C.F.; Wu, K.D.; Tsai, T.J. Pentoxifylline attenuates tubulointerstitial fibrosis by blocking Smad3/4-activated transcription and profibrogenic effects of connective tissue growth factor. *J. Am. Soc. Nephrol.,* **2005**, *16*(9), 2702-2713.
[http://dx.doi.org/10.1681/ASN.2005040435] [PMID: 15987746]

[56] Zhuo, J.L.; Kobori, H.; Li, X.C.; Satou, R.; Katsurada, A.; Navar, L.G. Augmentation of angiotensinogen expression in the proximal tubule by intracellular angiotensin II *via* AT $_{1a}$ /MAPK/NF-κB signaling pathways. *Am. J. Physiol. Renal Physiol.,* **2016**, *310*(10), F1103-F1112.
[http://dx.doi.org/10.1152/ajprenal.00350.2015] [PMID: 26864937]

[57] Carvajal, G. Angiotensin II activates the Smad pathway during epithelial mesenchymal transdifferentiation. *Kidney Int.,* **2008**, *74*(5), 585-595.
[http://dx.doi.org/10.1038/ki.2008.213]

[58] Liu, H.W.; Cheng, B.; Yu, W.L.; Sun, R.X.; Zeng, D.; Wang, J.; Liao, Y.X.; Fu, X.B. Angiotensin II regulates phosphoinositide 3 kinase/Akt cascade *via* a negative crosstalk between AT1 and AT2 receptors in skin fibroblasts of human hypertrophic scars. *Life Sci.,* **2006**, *79*(5), 475-483.
[http://dx.doi.org/10.1016/j.lfs.2006.01.031] [PMID: 16522324]

[59] Fang, Q.Q.; Wang, X.F.; Zhao, W.Y.; Ding, S.L.; Shi, B.H.; Xia, Y.; Yang, H.; Wu, L.H.; Li, C.Y.; Tan, W.Q. Angiotensin-converting enzyme inhibitor reduces scar formation by inhibiting both canonical and noncanonical TGF-β1 pathways. *Sci. Rep.,* **2018**, *8*(1), 3332.
[http://dx.doi.org/10.1038/s41598-018-21600-w] [PMID: 29463869]

[60] Queisser, N.; Happ, K.; Link, S.; Jahn, D.; Zimnol, A.; Geier, A.; Schupp, N. Aldosterone induces fibrosis, oxidative stress and DNA damage in livers of male rats independent of blood pressure changes. *Toxicol. Appl. Pharmacol.,* **2014**, *280*(3), 399-407.
[http://dx.doi.org/10.1016/j.taap.2014.08.029] [PMID: 25204689]

[61] Zhang, Y.-Y. Antifibrotic roles of RAAS blockers: Update. *Adv. Exp. Med. Biol.,* **2019**, *1165*, 671-691.
[http://dx.doi.org/10.1007/978-981-13-8871-2_33]

[62] AlQudah, M.; Hale, T.M.; Czubryt, M.P.J.M.B. Targeting the renin-angiotensin-aldosterone system in fibrosis. *Matrix Biol.,* **2020**, *91-92*, 92-108.
[http://dx.doi.org/10.1016/j.matbio.2020.04.005]

[63] Taguchi, I.; Toyoda, S.; Takano, K.; Arikawa, T.; Kikuchi, M.; Ogawa, M.; Abe, S.; Node, K.; Inoue, T. Irbesartan, an angiotensin receptor blocker, exhibits metabolic, anti-inflammatory and antioxidative effects in patients with high-risk hypertension. *Hypertens. Res.,* **2013**, *36*(7), 608-613.
[http://dx.doi.org/10.1038/hr.2013.3] [PMID: 23425956]

[64] Alique, M.; Sánchez-López, E.; Rayego-Mateos, S.; Egido, J.; Ortiz, A.; Ruiz-Ortega, M. Angiotensin II, *via* angiotensin receptor type 1/nuclear factor-κB activation, causes a synergistic effect on interleukin-1-β-induced inflammatory responses in cultured mesangial cells. *J. Renin Angiotensin Aldosterone Syst.,* **2015**, *16*(1), 23-32.
[http://dx.doi.org/10.1177/1470320314551564] [PMID: 25354522]

[65] Arjmand, M.H.; Zahedi-Avval, F.; Barneh, F.; Mousavi, S.H.; Asgharzadeh, F.; Hashemzehi, M.; Soleimani, A.; Avan, A.; Fakhraie, M.; Nasiri, S.N.; Mehraban, S.; Ferns, G.A.; Ryzhikov, M.; Jafari, M.; Khazaei, M.; Hassanian, S.M. Intraperitoneal administration of telmisartan prevents postsurgical adhesion band formation. *J. Surg. Res.,* **2020**, *248*, 171-181.
[http://dx.doi.org/10.1016/j.jss.2019.10.029] [PMID: 31923833]

[66] Candan, B. Irbesartan restored aquaporin-1 levels *via* inhibition of NF-kB expression in acute kidney injury model. *Nefrología,* **2023**, *44*(2), 119-312.
[http://dx.doi.org/10.1016/j.nefro.2023.11.005]

[67] Cakmak, B.; Cavusoglu, T.; Ates, U.; Meral, A.; Nacar, M.C.; Erbaş, O. Regression of experimental endometriotic implants in a rat model with the angiotensin II receptor blocker losartan. *J. Obstet. Gynaecol. Res.,* **2015**, *41*(4), 601-607.
[http://dx.doi.org/10.1111/jog.12558] [PMID: 25302540]

[68] Nenicu, A.; Körbel, C.; Gu, Y.; Menger, M.D.; Laschke, M.W. Combined blockade of angiotensin II type 1 receptor and activation of peroxisome proliferator-activated receptor- by telmisartan effectively inhibits vascularization and growth of murine endometriosis-like lesions. *Hum. Reprod.,* **2014**, *29*(5), 1011-1024. [http://dx.doi.org/10.1093/humrep/deu035] [PMID: 24578472]

[69] Wang, X.; Chen, X.; Huang, W.; Zhang, P.; Guo, Y.; Körner, H.; Wu, H.; Wei, W. Losartan suppresses the inflammatory response in collagen-induced arthritis by inhibiting the MAPK and NF-κB pathways in B and T cells. *Inflammopharmacology,* **2019**, *27*(3), 487-502. [http://dx.doi.org/10.1007/s10787-018-0545-2] [PMID: 30426454]

[70] Price, A.; Lockhart, J.C.; Ferrell, W.R.; Gsell, W.; McLean, S.; Sturrock, R.D. Angiotensin II type 1 receptor as a novel therapeutic target in rheumatoid arthritis: *In vivo* analyses in rodent models of arthritis and ex vivo analyses in human inflammatory synovitis. *Arthritis Rheum.,* **2007**, *56*(2), 441-447. [http://dx.doi.org/10.1002/art.22335] [PMID: 17265479]

[71] Perry, M.E.; Chee, M.M.; Ferrell, W.R.; Lockhart, J.C.; Sturrock, R.D. Angiotensin receptor blockers reduce erythrocyte sedimentation rate levels in patients with rheumatoid arthritis. *Ann. Rheum. Dis.,* **2008**, *67*(11), 1646-1647. [http://dx.doi.org/10.1136/ard.2007.082917] [PMID: 18854516]

[72] Kolesnyk, I.; Noordzij, M.; Dekker, F.W.; Boeschoten, E.W.; Krediet, R.T. A positive effect of AII inhibitors on peritoneal membrane function in long-term PD patients. *Nephrol. Dial. Transplant.,* **2008**, *24*(1), 272-277. [http://dx.doi.org/10.1093/ndt/gfn421] [PMID: 18676349]

[73] Wengrower, D.; Zanninelli, G.; Latella, G.; Necozione, S.; Metanes, I.; Israeli, E.; Lysy, J.; Pines, M.; Papo, O.; Goldin, E. Losartan reduces trinitrobenzene sulphonic acid-induced colorectal fibrosis in rats. *Can. J. Gastroenterol.,* **2012**, *26*(1), 33-39. [http://dx.doi.org/10.1155/2012/628268] [PMID: 22288068]

[74] Yoshiji, H.; Noguchi, R.; Kojima, H.; Ikenaka, Y.; Kitade, M.; Kaji, K.; Uemura, M.; Yamao, J.; Fujimoto, M.; Yamazaki, M.; Toyohara, M.; Mitoro, A.; Fukui, H. Interferon augments the anti-fibrotic activity of an angiotensin-converting enzyme inhibitor in patients with refractory chronic hepatitis C. *World J. Gastroenterol.,* **2006**, *12*(42), 6786-6791. [http://dx.doi.org/10.3748/wjg.v12.i42.6786] [PMID: 17106926]

[75] Li, J.J.; Xue, X.D. [Protection of captopril against chronic lung disease induced by hyperoxia in neonatal rats]. *Zhongguo Dang Dai Er Ke Za Zhi,* **2007**, *9*(2), 169-173. [PMID: 17448318]

[76] Colmenero, J.; Bataller, R.; Sancho-Bru, P.; Domínguez, M.; Moreno, M.; Forns, X.; Bruguera, M.; Arroyo, V.; Brenner, D.A.; Ginès, P. Effects of losartan on hepatic expression of nonphagocytic NADPH oxidase and fibrogenic genes in patients with chronic hepatitis C. *Am. J. Physiol. Gastrointest. Liver Physiol.,* **2009**, *297*(4), G726-G734. [http://dx.doi.org/10.1152/ajpgi.00162.2009] [PMID: 19628656]