Saudi Pharmaceutical Journal (2011) **19**, 29–34

King Saud University

Saudi Pharmaceutical Journal

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Anti-inflammatory activity of telmisartan in rat models of experimentally-induced chronic inflammation: Comparative study with dexamethasone

Waleed K.G. Al-Hejjaj [a], Intesar T. Numan [b], Raghdan Z. Al-Sa'ad [c], Saad A. Hussain [b,*]

[a] *Department of Pharmacology, College of Pharmacy, University of Basrah, Iraq*
[b] *Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, Iraq*
[c] *Department of Pharmacy, Babylon Directorate of Health, Babylon, Iraq*

Received 22 June 2010; accepted 4 October 2010
Available online 4 November 2010

KEYWORDS

Telmisartan;
PPARγ;
Chronic inflammation

Abstract Recently, significant progress has been made through the application of peroxisome proliferator activated receptor-γ (PPAR-γ) agonists as anti-inflammatory drugs that are efficacious, relatively free of side effects, and can be used effectively for a long time. The present study was designed to evaluate the dose–response relationship of the anti-inflammatory activity of telmisartan in rat models of chronic inflammation. The study protocol includes four stages: First stage: 48 rats were allocated into eight groups, each containing six rats, for the study of the anti-inflammatory activity of different doses of telmisartan in rat model of formaldehyde-induced chronic inflammation. Second stage: six rats were used to study the anti-inflammatory activity of telmisartan (1.5 mg/kg) in combination with dexamethasone (0.5 mg/kg) in the same model. Third stage: 48 rats were allocated into eight groups, each containing six rats, for the study of the anti-inflammatory activity of telmisartan in rat model of cotton pellet-induced granuloma. Fourth stage: six rats were used to study the anti-inflammatory activity of telmisartan (1.5 mg/kg) when used as adjuvant with dexamethasone (0.5 mg/kg) in the same model. Telmisartan in a dose-dependent pattern (0.1, 0.2. 0.4, 0.6, 1.5, 3 mg/kg) significantly suppressed inflammation in rat models of formaldehyde-induced

* Corresponding author. Tel.: +964 7901712624.
E-mail address: saad_alzaidi@yahoo.com (S.A. Hussain).

Peer review under responsibility of King Saud University.
doi:10.1016/j.jsps.2010.10.004

Production and hosting by Elsevier

chronic inflammation and cotton pellet-induced granuloma. When combined with dexamethasone, telmisartan (1.5 mg/kg body weight) significantly suppressed inflammation in both models, which is significantly higher than all of the effects produced by other approaches of treatment when telmisartan used alone. In conclusion, telmisartan decreased formaldehyde-induced chronic inflammation and cotton-pellet induced granuloma in rats in a dose-dependent pattern. Therefore, it may be considered as a potential treatment for chronic inflammatory conditions in human.

1. Introduction

Angiotensin II, the central product of the renin–angiotensin system, induces oxidative stress and inflammation by activating the angiotensin II type 1 (AT1) receptor (Welch, 2008). Telmisartan is a highly selective AT1-receptor antagonist approved for treatment of hypertension. On the other hand, telmisartan acts as a partial agonist on the nuclear peroxisome proliferator-activated receptor-γ (PPAR-γ) that has been reported to exert anti-oxidative and anti-inflammatory effects (Benson et al., 2004). Recently, telmisartan has been reported to have additional peroxisome proliferator-activated receptor-gamma (PPAR-γ) partial agonist activity which regulates metabolic and inflammatory pathways, and improves left ventricular functions (Benson et al., 2004; Schupp et al., 2004). It has also been demonstrated to have beneficial effect on post-infarct ventricular remodeling (Geng et al., 2006). With these dual actions, telmisartan provides additional beneficial pleiotropic effects such as anti-inflammatory, antioxidative and antiproliferative effects in atherosclerosis and myocardial infarction (Imayama et al., 2006; Takaya et al., 2006). On the other hand, telmisartan does not have adverse effects like fluid retention and edema of clinically used full PPAR-γ agonists such as pioglitazone and rosiglitazone (Goebel et al., 2006). Also, candisartan and telmisartan significantly attenuated gastric mucosal lesions induced by cold-restraint stress and indomethacin in nondiabetic rats (Pavel et al., 2008; Morsy et al., 2009). Although telmisartan has the potential to interfere with the inflammatory reaction cascade, the dose–response relationship in animal models of inflammation and comparative study with other anti-inflammatory agents is not clear enough to establish the required dose for this effect. Therefore, the present study was designed to investigate the dose–response relationship of the anti-inflammatory activity of telmisartan in animal models of chronic inflammation.

2. Experimental

2.1. General

Telmisartan powder (Boehringer Ingelheim, Germany) was dissolved in distilled water to produce a stock solution of 0.4 mg/ml, from which different doses were prepared according to the body weight of the animals. Sprague–Dawley rats weighing 180–220 g of both sexes were purchased from the National Centre for Drug Research and Quality Control, Baghdad. They were kept in the animal house of the Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, at 25 ± 2 °C and light:dark cycle of 12:12 h for 1 week before starting experiments. Animals were provided with standard rodent pellet diet and the food was withdrawn 12 h before the experiment, though water was allowed *ad libitum*. All experiments were performed according to the guidelines of laboratory animals care and the ethical guidelines for the investigations on experimental animals. In the present study, 108 rats were allocated into 18 groups (six rats each) and the study protocols were divided into four stages: First stage: 48 rats were used, and allocated into eight groups for the study of the anti-inflammatory activity of telmisartan in rat model of formaldehyde-induced chronic inflammation. Second stage: six rats were used to study the anti-inflammatory activity of the maximum effective dose of telmisartan obtained from first stage when used in combination with dexamethasone (0.5 mg/kg) (American reagent, USA) in rat model of formaldehyde-induced chronic inflammation. Third stage: 48 rats allocated into eight groups for the study of the anti-inflammatory activity of telmisartan in rat model of cotton pellet-induced granuloma. Fourth stage: six rats were used for the study of the anti-inflammatory activity of the maximum effective dose of telmisartan when used in combination with dexamethasone (0.5 mg/kg) in rat model of cotton pellet-induced granuloma.

2.2. Formalin-induced chronic inflammation

The anti-inflammatory effect of telmisartan in chronic inflammation was evaluated by formalin-induced paw edema (Chau, 1989). In this model, chronic inflammation was induced by injecting 0.1 ml of 2% formalin (Al-Jubail, Saudi Arabia) into the sub-plantar area of the right hind paw of ether anaesthetized rats. All drugs including telmisartan (0.1, 0.2, 0.4, 0.6, 1.5, and 3 mg/kg body weight), dexamethasone 1 mg/kg and distilled water 2 ml/kg were given 30 min prior to formalin injection and continued for seven consecutive days. All drugs and the vehicle were given orally once daily using oral gavage needle. In this model, the increase in paw edema was measured by vernier caliper method (Joseph et al., 2005). In vernier caliper method, the paw thickness was measured before and 6 days after induction of inflammation by using vernier caliper. The difference in paw thickness after and before induction of inflammation was calculated and presented as mean increase in paw thickness (mm). The ability of the anti-inflammatory drug to suppress paw inflammation was expressed as a percentage of inhibition of paw edema (Duffy et al., 2001).

2.3. Cotton pellet-induced granuloma

The anti-inflammatory activity of telmisartan was evaluated using cotton pellets-induced granuloma according to the method of Winter and Porter (1957). Cotton pellets weighing 10 ± 1 mg were sterilized in an autoclave for 30 min at 120 °C under 15 Ib pressure. Four pellets were implanted subcutaneously (s.c.) into the ventral region, two on either side, in

Table 1 Effects of different doses of telmisartan and its combination with dexamethasone on paw thickness and inhibition of paw edema (%) in formaldehyde-induced chronic inflammation in rats.

Treatment groups	Mean paw thickness (mm) at zero time	Mean paw thickness (mm) after 7 days	Mean increase in paw thickness (mm) after 7 days	Inhibition of paw edema (%)
Distilled water	3.22 ± 0.07	7.00 ± 0.05*	3.78 ± 0.09[a]	–
Telmisartan 0.1 mg/kg	3.28 ± 0.06	5.86 ± 0.10*	2.58 ± 0.11[b]	16.28
Telmisartan 0.2 mg/kg	3.14 ± 0.1	5.42 ± 0.02*	2.28 ± 0.10[c]	22.71
Telmisartan 0.4 mg/kg	3.12 ± 0.04	5.28 ± 0.01*	2.16 ± 0.04[c]	24.71
Telmisartan 0.6 mg/kg	3.13 ± 0.05	5.17 ± 0.03*	2.04 ± 0.06[c]	26.14
Telmisartan 1.5 mg/kg	3.15 ± 0.09	4.74 ± 0.05*	1.58 ± 0.10[d]	32.42
Telmisartan 3 mg/kg	3.20 ± 0.08	4.24 ± 0.04*	1.04 ± 0.09[e]	39.42
Telmisartan 1.5 mg/kg + 0.5mg/kg dexamethasone	3.19 ± 0.05	3.80 ± 0.05*	0.61 ± 0.07[f]	45.71
Dexamethasone 1 mg/kg	3.21 ± 0.06	3.27 ± 0.06	0.05 ± 0.08[g]	53.42

Data are expressed as mean ± standard error; $n = 6$ animals in each group; *significantly different compared to control ($P < 0.05$); values with non-identical superscripts (a, b, c, d, e, f, g) were considered significantly different ($P < 0.05$).

each rat under light ether anesthesia. All drugs doses and vehicle were administered as mentioned before for seven consecutive days before the day of cotton pellet implantation. On 8th day the animals were anaesthetized and the pellets together with the granuloma tissues were carefully removed and made free from extraneous tissues. The wet pellets were weighed for the determination of wet weight, and then dried in an incubator at 60 °C for 18 h until a constant weight obtained (all the exudates dried); after that the dried pellets were weighed again. The exudate amount (mg) was calculated by subtracting the constant dry weight of pellet from the immediate wet weight of pellet. The granulation tissue formation (dry weight of granuloma) was calculated after deducting the weight of cotton pellet (10 mg) from the constant dry weight of pellet and taken as a measure of granuloma tissue formation. The percent inhibitions of exudate and granuloma tissue formation were determined.

2.4. Statistical analysis

All results were expressed as mean ± SEM. The significance of differences between treated groups was determined using Student's *t*-test and one-way analysis of variance (ANOVA). *P*-values < 0.05 were considered significant.

3. Results

3.1. Anti-inflammatory activity in formalin-induced chronic inflammation

In Table 1, all telmisartan doses (0.1, 0.2, 0.4, 0.6, 1.5, and 3 mg/kg body weight) significantly reduced the increases in paw thickness (in a dose-dependent pattern) compared to controls, with maximum effect produced by 1.5 mg/kg (32.2%) and 3.0 mg/kg (39.42%), respectively. Meanwhile, 1 mg/kg dexamethasone significantly inhibited the increases in paw thickness compared to controls (53.42%). Telmisartan (1.5 mg/kg body weight), when administered with dexamethasone (0.5 mg/kg body weight), resulted in 45.71% decrease in paw edema, which was significantly higher than all of the effects produced by telmisartan alone. In Fig. 1, the dose–response relationship of

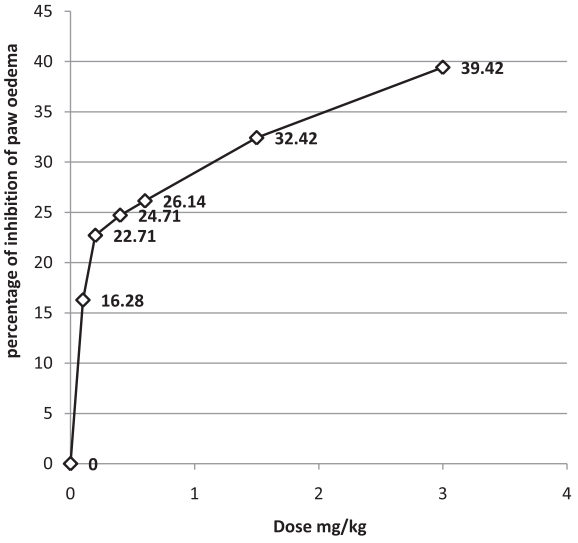

Figure 1 Dose–response relationship of the effect of telmisartan on percent inhibition of paw edema in formaldehyde-induced chronic inflammation in rats.

the anti-inflammatory activity of telmisartan was found to be relatively linear within the dose ranges utilized in this study, with best linearity between 0.6 and 3 mg/kg.

3.2. Anti-inflammatory activity in cotton pellet-induced granuloma

Table 2 shows that all telmisartan doses significantly decreased the formation of inflammatory exudate (in a dose-dependent pattern) compared to controls, with the maximum effect produced by 1.5 mg/kg (34.01%) and 3 mg/kg (47.47%). Meanwhile, 1 mg/kg of dexamethasone significantly inhibited exudate formation compared to controls, and the largest effect was produced by dexamethasone (49.04%). Telmisartan (1.5 mg/kg body weight) in combination with dexamethasone (0.5 mg/kg body weight) resulted in (48.30%) decrease in exudate formation, which was significantly higher than all of the effects produced by telmisartan alone. In Fig. 2, the dose–

Table 2 Effects of different doses of telmisartan and its combination with dexamethasone on mean weight of exudates and inhibition of exudates (%) in cotton pellet-induced chronic inflammation in rats.

Treatment groups	Mean weight of exudates (mg)	% inhibition of exudate
Distilled water	108.5 ± 0.84	–
Telmisartan 0.1 mg/kg	100.4 ± 0.31*[a]	7.47
Telmisartan 0.2 mg/kg	91.0 ± 0.09*[b]	16.13
Telmisartan 0.4 mg/kg	89.8 ± 0.12*[b]	17.24
Telmisartan 0.6 mg/kg	74.9 ± 0.20*[c]	30.97
Telmisartan 1.5 mg/kg	71.6 ± 0.05*[d]	34.01
Telmisartan 3 mg/kg	57.0 ± 0.26*[e]	47.47
Telmisartan 1.5 mg/kg + 0.5 mg/kg dexamethasone	56.1 ± 0.15*[f]	48.30
Dexamethasone 1 mg/kg	55.3 ± 0.12*[g]	49.04

Data are expressed as mean ± standard error; $n = 6$ animals in each group; *significantly different compared to control ($P < 0.05$); values with non-identical superscripts (a, b, c, d, e, f, g) were considered significantly different ($P < 0.05$).

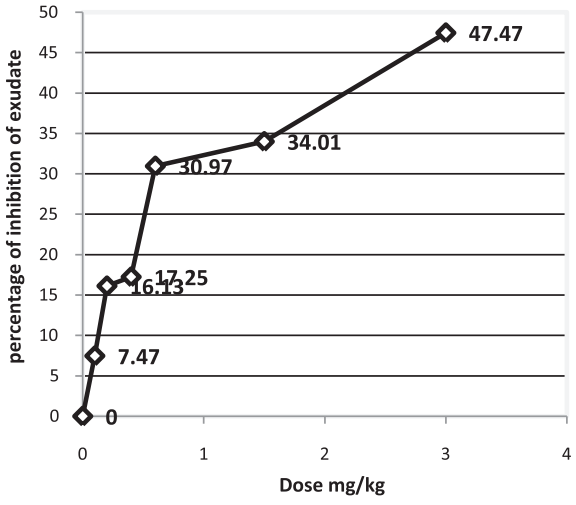

Figure 2 Dose–response relationship of the effect of telmisartan on exudate inhibition (%) in cotton pellet-induced granuloma in rats.

response relationship of the anti-inflammatory activity (in terms of attenuation of inflammatory exudate formation) of telmisartan was found to be relatively linear within the dose ranges utilized in this study. Meanwhile, telmisartan significantly decreased the formation of granuloma (in a dose-dependent pattern) compared to control, with the maximum effect produced by the dose 3.0 mg/kg (58.74%). Meanwhile, 1 mg/kg dexamethasone significantly inhibited the formation of granuloma compared to controls; the maximum effect was produced by dexamethasone (71.43%) (Table 3). Adjunct use of telmisartan (1.5 mg/kg body weight) with dexamethasone (0.5 mg/kg body weight) resulted in 68.26% decrease in the formation of granuloma, which was significantly higher than all of the effects produced by telmisartan alone. In Fig. 3, the dose–response relationship of the anti-inflammatory activity (in terms of attenuation of granuloma formation) of telmisartan was found to be relatively linear within the dose ranges utilized in the present study, with best linearity shown between 0.6 and 3 mg/kg.

4. Discussion

In the present study, formaldehyde- and cotton pellet-induced inflammatory reactions similar to that reported during arthritis, and these animal models, are standard for the evaluation of therapeutic agents with suspected anti-arthritic activity (Okoli et al., 2008). As telmisartan significantly inhibited inflammatory reactions in this model of inflammation, it can be proposed that this agent may possess anti-proliferative and anti-arthritic activities. Tissue injury induces a cascade of cellular reactions in the lesion area, accompanied with the release of pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, IL-8 and other substances, which is then followed by subsequent inflammatory reactions (Hua et al., 1996). Prostaglandins such

Table 3 Effects of different doses of telmisartan and its combination with dexamethasone on mean weight of dry granuloma and inhibition of granuloma (%) in formaldehyde-induced chronic inflammation in rats.

Treatment groups	Mean dry weight of granuloma (mg)	Granuloma inhibition (%)
Distilled water	31.5 ± 0.16	–
Telmisartan 0.1 mg/kg	21.8 ± 0.17*[a]	30.8
Telmisartan 0.2 mg/kg	19.1 ± 0.02*[b]	39.37
Telmisartan 0.4 mg/kg	18.2 ± 0.03*[b]	42.23
Telmisartan 0.6 mg/kg	17.1 ± 0.02*[c]	45.72
Telmisartan 1.5 mg/kg	14.7 ± 0.04*[d]	53.34
Telmisartan 3 mg/kg	13.0 ± 0.03*[d]	58.74
Telmisartan 1.5 mg/kg + 0.5 mg/kg dexamethasone	10.00 ± 0.15*[e]	68.26
Dexamethasone 1 mg/kg	9.0 ± 0.12*[e]	71.43

Data are expressed as mean ± standard error; $n = 6$ animals in each group; *significantly different compared to control ($P < 0.05$); values with non-identical superscripts (a, b, c, d, e) were considered significantly different ($P < 0.05$).

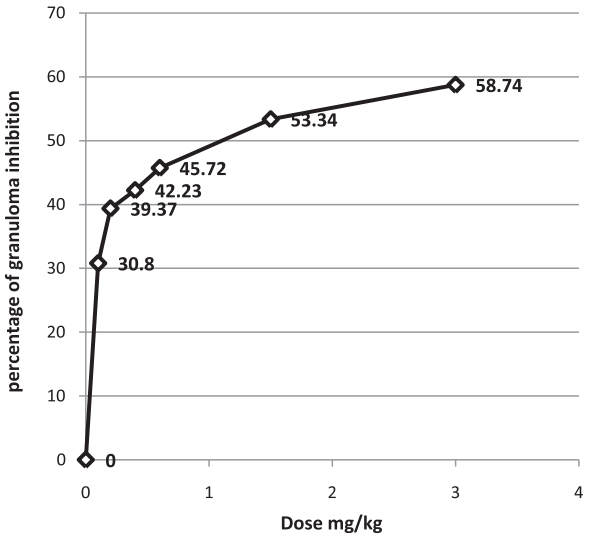

Figure 3 Dose–response relationship of the effect of telmisartan on granuloma inhibition (%) in cotton pellet-induced granuloma in rats.

as PGE_1 and PGE_2, which are produced at elevated levels in inflamed tissues like rheumatoid synovium, increase local blood flow and potentiate the effects of mediators such as bradykinin that induce vasopermeability (Yoshida et al., 2006). Meanwhile, many studies suggested that activation of PPAR-γ with many classes of ligands (including telmisartan) may decrease production of the hypertrophic prostanoids PGE2, with consequent amelioration or modulation of some component of inflammation (Norihiro et al., 2006). Telmisartan, the selective AT1 receptor antagonist, was proved effective in reducing the generation of reactive oxygen species and pro-inflammatory mediators. The antioxidant and anti-inflammatory effects of telmisartan are related to its ability to prevent the activation of nuclear factor-κB signaling pathway which promotes the transcription of NADPH oxidase, tumor necrosis factor-α and inducible nitric oxide synthase genes (Takaya et al., 2006; Morishima et al., 2009). This is in agreement with the present results which revealed that telmisartan treatment significantly prevented the formation of inflammatory edema due to challenge with formalin, and suppressed both exudate and granulation tissue formation as a result of subcutaneous cotton pellet implantation. Other mechanisms independent of AT1 receptor blockade are responsible for the antioxidant and anti-inflammatory activities of telmisartan. The drug acts as a partial agonist at the PPar-γ (Benson et al., 2004). Activation of this receptor induces catalase gene expression and inhibits nuclear factor-κB, thus combating oxidative stress and down regulating most of the pro-inflammatory responses (Blessing et al., 2008). In addition, the anti-inflammatory effect of telmisartan observed in the present study can be attributed to its PPAR-γ agonist activity. The fact that expression of PPAR-γ was modulated during the course of many inflammatory disorders represents the solid base for the use of highly effective PPAR-γ ligands for the aim of attenuation and/or modulation of the course of inflammation. Altered expression of PPAR-γ was observed in several other inflammatory disorders. For instance, PPAR-γ expression was shown to be reduced in many pathological conditions of inflammatory bases including atherosclerotic tissues (Klotz et al., 2005), in peripheral blood mononuclear cells from patients with multiple sclerosis (Kitamura et al., 1999) and in alveolar macrophages from patients with allergic asthma (Benayoun et al., 2001). Meanwhile, ligand activation of PPAR-γ down regulates the transcription of genes encoding inflammatory molecules, inflammatory cytokines, growth factors, proteolytic enzymes, adhesion molecules, and chemotactic factors (Koji et al., 2007; Qingping et al., 2009). Such finding gives a hope for conducting trials to evaluate the anti-inflammatory activity of potent PPAR-γ activators, including telmisartan and other ARBs, when the safety concern of these agents was completely resolved. Therefore, a possible involvement of PPAR-γ in the attenuation of inflammatory response afforded by telmisartan in animal models of chronic inflammation utilized in the present study cannot be excluded. However, this needs to be confirmed by further investigations.

5. Conclusion

In conclusion, telmisartan, in a dose-dependent pattern, was effective in attenuating formaldehyde-induced paw edema and cotton-pellet-induced granuloma in rat models of chronic inflammation, and therefore it could be investigated as a potential treatment for chronic inflammatory conditions in humans.

Acknowledgment

The authors gratefully thank the College of Pharmacy, University of Baghdad, for supporting the present work.

References

Benayoun, L., Letuve, S., Druilhe, A., Boczkowski, J., et al., 2001. Regulation of peroxisome proliferator-activated receptor γ expression in human asthmatic airways: relationship with proliferation, apoptosis, and airway remodeling. Am. J. Respir. Crit. Care Med. 164, 1487–1494.

Benson, S.C., Pershadsingh, H.A., Ho, C.I., Chittiboyina, A., et al., 2004. Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARγ-modulating activity. Hypertension 43, 993–1002.

Blessing, E., Preusch, M., Kranzhofer, R., Kinscherf, R., et al., 2008. Antiatherosclerotic properties of telmisartan in advanced atherosclerotic lesions in apolipoprotein E deficient mice. Atherosclerosis 199, 295–303.

Chau, T.T., 1989. Analgesic testing in animal models. In: Pharmacological Methods in the Control of Inflammations. Alan R Liss, Inc., New York, pp. 195–212.

Duffy, J.C., Dearden, J.C., Rostron, C., 2001. Design, synthesis and biological testing of a novel series of anti-inflammatory drugs. J. Pharm. Pharmacol. 53, 1505–1514.

Geng, D.F., Wu, W., Jin, D.M., Wang, J.F., Wu, Y.M., 2006. Effect of peroxisome proliferators-activated receptor gamma ligand rosiglitazone on left ventricular remodeling in rats with myocardial infarction. Int. J. Cardiol. 113, 86–91.

Goebel, M., Clemenz, M., Unger, T., 2006. Effective treatment of hypertension by AT(1) receptor antagonism: the past and future of telmisartan. Expert Rev. Cardiovasc. Ther. 4, 615–629.

Hua, X., Chen, P., Fox, A., Myers, R., 1996. Involvement of cytokines in lipopolysaccharide-induced facilitation of CGRP release from capsaicin-sensitive nerves in the trachea: studies with interleukin-1β and tumor necrosis factor-α. J. Neurosci. 16 (15), 4742–4748.

Imayama, I., Ichiki, T., Inanaga, K., Ohtsubo, H., et al., 2006. Telmisartan down regulates angiotensin II type 1 receptor through activation of peroxisome proliferator-activated receptor gamma. Cardiovasc. Res. 72, 184–190.

Joseph, S.M., George, M.C., Nair, J.R., et al., 2005. Effect of feeding cuttlefish liver oil on immune function, inflammatory response and platelet aggregation in rats. Curr. Sci. 88 (3), 507–510.

Kitamura, Y., Shimohama, S., Koike, H., Kakimura, J., et al., 1999. Increased expression of cyclooxygenases and peroxisome proliferator-activated receptor in Alzheimer's disease brains. Biochem. Biophys. Res. Commun. 254, 582–586.

Klotz, L., Schmidt, M., Giese, T., Sastre, M., et al., 2005. Pro-inflammatory stimulation and Pioglitazone treatment regulate PPAR levels in peripheral blood mononuclear cells from healthy controls and multiple sclerosis patients. J. Immunol. 175, 4948–4955.

Koji, F., Masato, Y., Koichiro, W., Hironori, M., 2007. Telmisartan, an angiotensin II type 1 receptor blocker, controls progress of nonalcoholic steatohepatitis in rats. Springer Science 10, 3455.

Morishima, M., Wang, Y., Akiyoshi, Y., Miyamoto, S., Ono, K., 2009. Telmisartan, an angiotensin II type 1 receptor antagonist, attenuates T-type Ca^{2+} channel expression in neonatal rat cardiomyocytes. Eur. J. Pharmacol. 609, 105–112.

Morsy, M., Ashour, O., Amin, E., Rofaeil, R., 2009. Gastroprotective effects of telmisartan on experimentally-induced gastric ulcers in rats. Pharmazie 64, 590–594.

Norihiro, N., Yuichi, O., Kanako, I., Takashi, U., Yoshiaki, K., et al., 2006. Angiotensin II type 1 receptor-mediated inflammation is required for choroidal neovascularization. Arterioscler. Thromb. Vasc. Biol. 26, 2252–2259.

Okoli, C., Akah, P., Onuoha, N., Okoye, T., Nwoye, A., Nworu, C., 2008. *Acanthus montanus*: an experimental evaluation of the antimicrobial, anti-inflammatory and immunological properties of a traditional remedy for furuncles. BMC Complement Altern. Med. 8, 27–37.

Pavel, J., Benicky, J., Murakami, Y., Sanchez-Lemus, E., Saavedra, J.M., 2008. Peripherally administered angiotensin II AT1 receptor antagonists are anti-stress compounds *in vivo*. Ann. N.Y. Acad. Sci. 1148, 360–366.

Qingping, T., Ryohei, M., Toshihiro, I., Ikuyo, I., et al., 2009. Inhibition of TNF-α induced interleukin-6 expression by Telmisartan through cross-talk of PPAR-γ with NFκB and CCAAT/Enhancer-binding protein-β. Hypertension 53, 798–799.

Schupp, M., Janke, J., Clasen, R., Unger, T., Kintscher, U., 2004. Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity. Circulation 109, 2054–2057.

Takaya, T., Kawashima, S., Shinohara, M., Yamashita, T., et al., 2006. Angiotensin II type 1 receptor blocker telmisartan suppresses superoxide production and reduces atherosclerotic lesion formation in apolipoprotein E-deficient mice. Atherosclerosis 186, 402–410.

Welch, W.J., 2008. Angiotensin II-dependent superoxide: effects on hypertension and vascular dysfunction. Hypertension 52, 51–56.

Winter, A., Porter, C., 1957. Effect of alteration in side chain upon anti-inflammatory and liver glycogen activities in hydrocortisone esters. J. Am. Pharm. Assoc. 46, 515–519.

Yoshida, T., Yamagishi, S., Nakamura, K., Matsui, T., Imaizum, T., et al., 2006. Telmisartan inhibits AGE-induced C-reactive protein production through downregulation of the receptor for AGE via PPAR-γ activation. Diabetologia 49, 3094–3099.