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Naderali, Mohammad M.; Itua, Imose; Abubakari, Abdul-Razak; Naderali, Ebrahim K.

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Research Article

Short-Term Therapy with Rosiglitazone, a PPAR- γ Agonist, Improves Metabolic Profile and Vascular Function in Nonobese Lean Wistar Rats

Mohammad M. Naderali,¹ Imose Itua,² Abdul-Razak Abubakari,² and Ebrahim K. Naderali²

¹ Calderstones School, Harthill Road, Liverpool L18 3HS, UK

² Department of Health Sciences, Liverpool Hope University, Hope Park, Liverpool L16 9JD, UK

Correspondence should be addressed to Ebrahim K. Naderali, naderae@hope.ac.uk

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A number of preclinical and clinical studies have reported blood-pressure-lowering benefits of thiazolidinediones in diabetic subjects and animal models of diabetes. This study was designed to further elucidate vascular effects of rosiglitazone, on healthy nonobese, lean animals. Adult male Wistar rats were randomized and assigned to control and rosiglitazone-treated groups and were dosed daily with either vehicle or rosiglitazone (10 mg kg⁻¹ day⁻¹) by oral gavage for 5 days. Compared with control group, rosiglitazone treatment significantly reduced plasma levels of triglycerides (>240%) and nonesterified free fatty acids (>268%) (both, $P < 0.001$). There were no changes in vascular contractility to KCl or noradrenaline between two groups. However, rosiglitazone therapy improved carbamylcholine-induced vasorelaxation ($93 \pm 3\%$ versus control 78 ± 2 , $P < 0.01$) an effect which was abolished by L-NAME. There was no difference in sodium nitroprusside-induced vasorelaxation between the control and rosiglitazone-treated animals. These results indicate that short-term rosiglitazone therapy improves both metabolic profile and vascular function in lean rats. The vascular effect of rosiglitazone appears to be mediated by alteration in NO production possibly by activation of endothelial PPAR γ . This increased NO production together with improved lipid profile may explain mechanism(s) of blood-pressure-lowering effects of thiazolidinediones on both human and experimental animals.

1. Introduction

Metabolic syndrome (syndrome X), known as a cluster of insulin resistance, abnormal glucose tolerance, abdominal obesity, dyslipidaemia, and arterial disease [1], is associated with substantially increased risk of cardiovascular disease resulting in increased morbidity and premature mortality. Insulin resistance is thought to be the primary abnormality in syndrome X. The increased cardiovascular disorders seen in syndrome X are thought to be consequences of at least (a) alterations in direct effects of insulin on vascular smooth muscle proliferation [2], (b) indirect effects *via* activation of the sympathetic nervous system [3], and (c) resistance to vasodilator effects of insulin [4].

The role of endothelium in the regulation of vascular tone by producing various vasoactive mediators which

include nitric oxide (NO) and endothelin, both of which acting on the underlying vascular smooth muscle to modulate arterial contractility, is well understood. Impaired endothelium-dependent vasorelaxation has been demonstrated in obesity, type 2 diabetes, and hypertension [5–7] with the most striking abnormality being attenuation of acetylcholine-induced NO-dependent vasodilatation.

Thiazolidinediones (TZDs), such as pioglitazone and rosiglitazone, are effective in the management of type 2 diabetes mellitus. They bind to the nuclear peroxisome proliferator-activated receptor- γ (PPAR- γ), and consequential improvements in insulin resistance and glucose metabolism are principally attributed to decreased free fatty acid concentrations [8, 9]. They improve metabolic abnormalities in animal models of insulin resistance and type 2 diabetes [5, 10] and in human subjects with type

2 diabetes mellitus [11, 12]. A variety of studies have suggested that thiazolidinediones may also have independent beneficial effects on the vasculature. These included lowering of blood pressure in fatty Zucker rats [13], genetically obese diabetic rats [14], diet-induced hypertensive rats [15], and, Dahl salt-sensitive rats [16]. Moreover, TZDs have been reported to reduce vascular adverse remodeling, and preserve intramyocardial vascularization in renovascular hypertensive rats (2K1C model) [17] as well as direct vasorelaxant effect and endothelial protective effects on arteries from obese Zucker rats [18, 19]. Similar studies in human subjects with type 2 diabetes mellitus have reported endothelial function improvement [20, 21]. Therefore, it appears that TZDs have a significantly positive effects on vascular function.

On examination of the effects of the TZD on metabolic and/or cardiovascular function, a vast majority of the animal or human studies are performed on well-established disease status. Thus, it is not possible to extrapolate if an early intervention by TZD's would also have a significant effect on cardiovascular function in prediabetic status. Hence, this study was designed to evaluate vascular effects of acute (5 day) administration of rosiglitazone in chowfed male Wistar rats. In this study, resistance arteries were deployed to measure vascular function, as these vessels represent endothelial function throughout the vasculature and are believed to be involved in determining the increase in peripheral resistance that leads to the development of hypertension [22].

2. Material and Methods

2.1. Animals. Adult (12-week-old) male Wistar rats ($n = 20$) were randomized and assigned to a control group ($n = 10$, 300.2 ± 5.4 g) and a rosiglitazone-treated group ($n = 10$, 302.5 ± 4.9 g). All animals had free access to standard laboratory pelleted diet (CRM Biosure, Cambridge, UK) and water. They were housed in pairs under controlled environmental conditions ($19\text{--}22^\circ\text{C}$; $30\text{--}40\%$ humidity) and a 12-hour light/dark cycle (lights on at 08:00 h). All animals were dosed at 08:00 daily for 5 days with either vehicle (1% carboxymethyl cellulose at 3 mL kg^{-1} body weight) or rosiglitazone ($10\text{ mg kg}^{-1}\text{ day}^{-1}$) by oral gavage.

The rats were killed 2 hours after last dose by CO_2 inhalation. Blood was removed by cardiac puncture into cold heparinized tubes and hematocrit levels were measured. The gonadal and perirenal fat pads and the gastrocnemius muscle were dissected and weighed. Plasma was immediately separated by centrifugation before being frozen for later measurements of nonesterified free fatty acids (NEFA) and triglycerides (TG), using commercially available diagnostic kits (Roche & Sigma Diagnostics, resp.).

2.2. Assessment of Vascular Function. Four third-order mesenteric arteries ($<250\ \mu\text{m}$ diameter, 2 mm lengths) were carefully dissected from each animal. Each artery was freed of fat and connective tissue and mounted on two $40\ \mu\text{m}$ diameter stainless-steel wires in an automated myograph (Cambustion, Cambridge, UK), based on the principle of the Mulvany myograph. The vessels (in duplicate) were

incubated in a 5 mL organ bath containing physiological salt solution (PSS; composition [in mM]: NaCl 119, KCl 4.7, CaCl_2 2.5, MgSO_4 1.17, NaHCO_3 25, KH_2PO_4 1.18, EDTA 0.026 and glucose 5.5) gassed with 95% O_2 and 5% CO_2 at 37°C .

After 30 min equilibration, the length-tension characteristics for each vessel were determined as described previously [23]. The computer also calculated the target tension that each vessel should develop in response to a maximal stimulus. Arteries were then allowed a further 30 min to equilibrate before being depolarized twice with high-potassium physiological salt solution (KPSS, 125 mM), in which NaCl in normal PSS was replaced by an equimolar concentration of KCl. Any vessel failing to reach its predetermined target tension in response to vasoconstriction with KCl (125 mM) was discarded. Cumulative concentration-response curves to either KCl (10–125 mM) or noradrenaline (NA, 0.5–6 μM) were then carried out.

2.3. Assessment of Endothelium-Dependent and -Independent Vascular Relaxation. Changes in endothelial-dependent and -independent vascular functions were assessed by observing any alterations in vascular reactivity to carbamylcholine (CCh), and sodium nitroprusside (SNP) in NA-precontracted arteries. Arteries were contracted with a supramaximal concentration of NA (8 μM). When contraction reached a plateau after 2 minutes, concentration-response curves were carried out to either CCh or SNP (for both, 10 nM–100 μM). Vascular responses to CCh were measured in absence or presence of L-NAME (100 μM).

2.4. Reagents. Noradrenaline, carbamylcholine, sodium nitroprusside (SNP), N(G)-nitro-L-arginine methyl ester (L-NAME), rosiglitazone, and carboxymethyl cellulose were all obtained from Sigma Chemicals (UK). Noradrenaline, CCh, SNP, and L-NAME were all dissolved in double distilled water. Both noradrenaline and SNP were kept away from light throughout the experiment. All water-soluble solutions were freshly made on the day of the experiment.

2.5. Data Interpretation and Statistical Analyses. Vasoconstriction in response to NA and KCl were expressed as absolute force generated. Vasorelaxation responses to CCh and SNP were calculated as the percentage reduction from the maximal tension generated in response to the supramaximal concentration of NA (8 μM). Data are expressed as mean \pm S.E.M. Statistical significance was tested using repeated-measures ANOVA or the Mann-Whitney test, as appropriate. Results were considered statistically significant at the $P < 0.05$ levels.

3. Results

3.1. Body Weight and Metabolic Data. There were no significant differences in body weight ($P = 0.399$), and perirenal fat pad mass ($P = 0.239$), and gastrocnemius muscle mass ($P = 0.659$) between two experimental groups (Table 1).

TABLE 1: Physiological and metabolic characteristics of the 2 experimental groups. Data are mean \pm SEM.

	Controls (<i>n</i> = 10)	Rosiglitazone (<i>n</i> = 10)
Body weight (g)		
(i) Initial	300.2 \pm 5.4	302.7 \pm 4.9
(ii) Final	325.5 \pm 5.6	339.9 \pm 8.7
Gonadal fat-pad mass (g)	1.13 \pm 0.06	1.47 \pm 0.09 ^a
Perirenal fat-pad mass (g)	1.12 \pm 0.08	1.31 \pm 0.12
Gastrocnemius muscle mass (g)	1.86 \pm 0.05	1.92 \pm 0.06
Fat/lean ratio*	1.23 \pm 0.07	1.45 \pm 0.08
Plasma triglycerides (mM)	1.34 \pm 0.11	0.50 \pm 0.04 ^b
Plasma NEFA (mM)	0.20 \pm 0.01	0.08 \pm 0.00 ^b
Total cholesterol	2.33 \pm 0.10	2.40 \pm 0.96
HDL cholesterol	0.92 \pm 0.08	1.01 \pm 0.08
LDL cholesterol	2.12 \pm 0.20	2.66 \pm 0.17
Hematocrit	45.9 \pm 0.2	41.8 \pm 0.5 ^b

* Fat/Lean ratio = sum of white fat pad masses/gastrocnemius muscle mass; ^a*P* < 0.01, ^b*P* < 0.001 versus controls.

However, compared with control groups, rosiglitazone-treated animals, had significantly higher gonadal fat pad mass (*P* < 0.01), and lower hematocrit (*P* < 0.001) (Table 1). The increase in gonadal fat pad mass in turn translated to an increase in fat/lean ratio in rosiglitazone-treated animals, compared with their counterpart control group. However, this increase in fat/lean ratio was not statistically significant from that of control group (*P* = 0.0830) (Table 1).

Rosiglitazone significantly lowered plasma levels of triglycerides (>240%) and NEFA (>268%) (for both, *P* < 0.001) than control animals; however, it had no effects on plasma levels of total cholesterol, LDL, and HDL.

3.2. Vascular Responses. There were no significant differences in arterial diameter between two groups in this study.

3.3. Contractile Responses. There were no significant differences in KCl-induced arterial contraction between the two groups. KCl concentration-response curves in both groups produced similar maximal contractile generated forces (control: 7.29 \pm 0.50 versus rosiglitazone-treated: 7.23 \pm 0.38 mN). Similar outcome was also seen with NA-induced contractility. NA-induced contractile curves were similar between control and rosiglitazone-treated animals, producing comparable maximal contractions between two groups (control: 13.99 \pm 1.21 versus rosiglitazone-treated: 13.33 \pm 0.89) (Figure 1).

3.4. Endothelium-Dependent Relaxation. Arteries from rosiglitazone-treated rats showed significant (*P* < 0.001) increase in vasorelaxation response to CCh compared with that of control animals (rosiglitazone-treated: 93 \pm 3% versus control 78 \pm 2 (Figure 2(a)). However, this

improved vasorelaxation in arteries from rosiglitazone-treated animals was abolished in the presence of L-NAME (rosiglitazone-treated: 73 \pm 2% versus control 77 \pm 2 (Figure 2(b)).

3.5. Endothelium-Independent Relaxation. The shapes of concentration response curves to SNP were almost identical in both groups. Moreover, there were no significant differences in maximum SNP-induced vasorelaxation between the two groups (rosiglitazone-treated: 88 \pm 2% versus control 91 \pm 2% (Figure 3).

4. Discussion

Rosiglitazone, a thiazolidinedione insulin-sensitizing agent which acts by stimulating PPAR- γ , has been shown to improve endothelial function in both human and animals [20, 24, 25]. Despite reports of expression and function of PPAR γ in rat and human vascular smooth muscle cells [26], studies in human and rodents have failed to show a direct vasorelaxant effect of rosiglitazone [27].

The beneficial vascular effects of rosiglitazone involve vasorelaxation but not vasoconstriction mechanism(s). In fact, it is reported that rosiglitazone had no effect on contractile responses to NA, but markedly increased sensitivity to Acetylcholine- (ACh-) induced vasorelaxation [28]. Interestingly similar effects of rosiglitazone were seen in this study, where five-day rosiglitazone treatment did not alter contractile responses to NA or KCl, while it significantly improved CCh-induced vasorelaxation indicating a role for rosiglitazone in improving endothelial function which may involve upregulation of Akt/eNOS pathways [29].

Although rosiglitazone improved CCh-induced vasorelaxation, it failed to significantly affect SNP-induced vasorelaxation suggesting that rosiglitazone does not influence vasorelaxation *via* smooth muscle cyclic guanosine monophosphate (cGMP) pathway. Interestingly a recent study reported blunting of rosiglitazone effects in lowering blood pressure and vasorelaxation in animals lacking endothelial but not smooth muscle PPAR γ (SM22Cre/flox mice) [30], indicating that beneficial effects of rosiglitazone are mediated *via* activation of specific endothelial PPAR γ receptors. Moreover, in streptozotocin- (STZ-) induced diabetic rats rosiglitazone significantly reversed blunting of ACh-induced vasorelaxation [31], further highlighting role of PPAR γ agonists in protecting endothelial function. Similar effects have also been described on genetically modified mice where regulation of blood pressure and heart rate under stressed conditions are consequence of activation of endothelial PPAR γ receptors [32]. Furthermore, stress-induced (transplantation-induced) endothelial dysfunction is completely restored by rosiglitazone [33] highlighting improvement of endothelial function by activation of PPAR γ receptors.

In our study, the increased CCh-induced vasorelaxant effect of rosiglitazone therapy was abolished in the presence of L-NAME. This is in agreement with a previous study

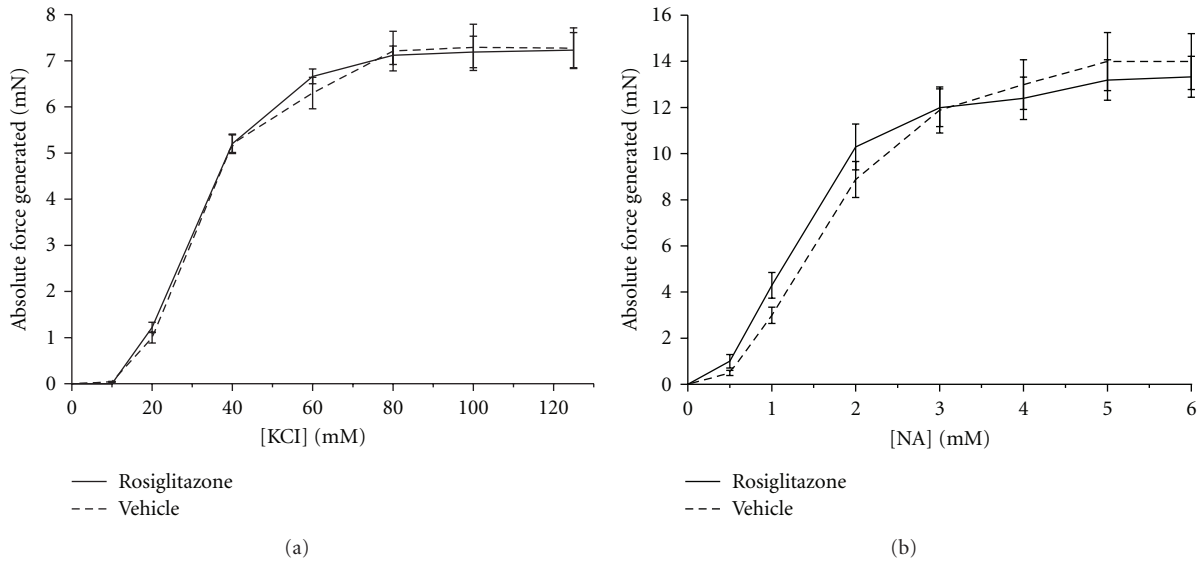


FIGURE 1: The effects of (a) KCl (10–125 mM) and (b) noradrenaline (NA; 0.5–6 μ M) on arteries from 5-day rosiglitazone-treated and untreated control animals. There were no significant differences between the two groups. Data represent mean \pm S.E.M.

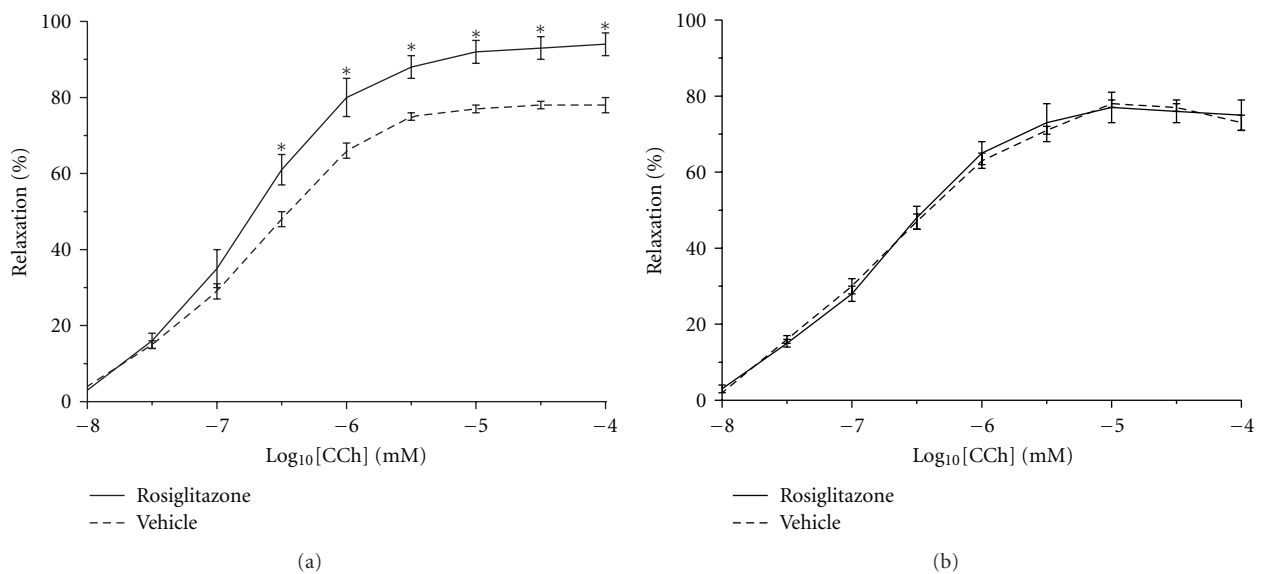


FIGURE 2: Relaxation curves for carbamylcholine (CCh) on arteries from 5-day rosiglitazone-treated and untreated control animals in (a) absence or (b) presence of L-NAME. Arteries were first precontracted with NA (8 μ M). When contraction reached a plateau after 2 minutes, concentration-response curves to CCh were carried out in the presence or absence of L-NAME (100 μ M). Data represent mean \pm S.E.M. The concentration-response curves between untreated controls and rosiglitazone-treated animals differ significantly (by ANOVA, * $P < 0.01$) in the absence of L-NAME but not in the presence of L-NAME.

where presence of L-NAME blocked ACh-induced relaxation in pioglitazone-treated STZ-diabetic rats [34]. Taken together, these data suggest that PPAR γ activation improves endothelial function, thereby facilitating production and/or release of nitric oxide (NO) vasorelaxant. Although we did not measure NO levels in this study, others have shown an increased basal nitric oxide release in TZD-treated STZ-diabetic rats suggesting inhibition of NO breakdown and/or increase of basal and agonist-stimulated production of NO

by pioglitazone [35] and rosiglitazone [36], leading to attenuated endothelial-dependent vasorelaxation.

Rosiglitazone treatment had no effects on total body weight and gastrocnemius muscle mass. Measurements of fat pad masses indicated an increase in gonadal but not in perirenal fat pad mass suggesting selective changes in adiposity in response to rosiglitazone therapy. The importance of this selective increase in fat pad remains to be elucidated. However, in agreement with previous reports

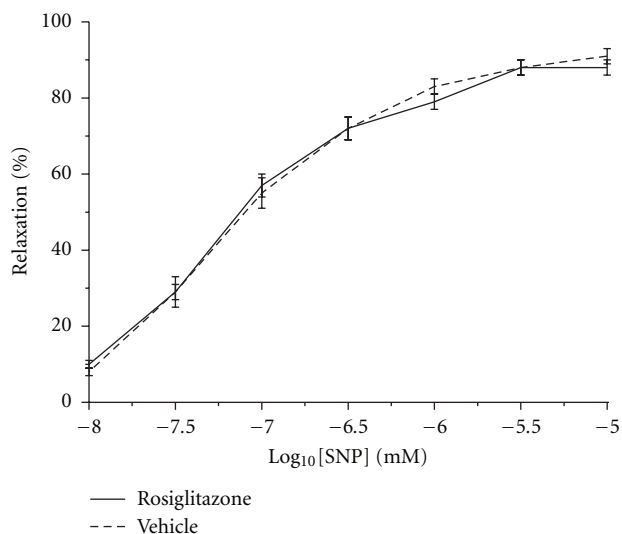


FIGURE 3: Relaxation curves for sodium nitroprusside (SNP) on arteries from 5-day rosiglitazone-treated and untreated control animals. NA ($8\ \mu\text{M}$)-precontracted arteries were subjected to increasing concentration of SNP. There were no significant differences between the two groups. Data represent mean \pm S.E.

on diabetic animal models, rosiglitazone treatment in this study significantly improved lipid profile of nonobese, lean, nondiabetic animals by reducing plasma levels of NEFA and triglyceride, perhaps by diverting circulating lipids to gonadal fat pad deposition. However, this hypothesis requires further investigation. Rosiglitazone's effects on adipocytes also include increase in adiponectin production [37] which has been shown to have cardioprotective effects [37]. Therefore, it is plausible to suggest that increase in adiponectin together with improved lipid profile may contribute to beneficial effects of rosiglitazone on vascular function.

The potential side effects of thiazolidinediones include oedema and haemodilution at least partially due to an adipose-tissue-selective activation of PKC and vascular permeability [38]. In this study, rosiglitazone treatment significantly reduced red blood cell packed volume (haematocrit). It is possible that lowering haematocrit is a secondary response to rosiglitazone-induced vasodilatation, which in turn activates renin-angiotensin system (RAS) [39] with subsequent haemodilution as a consequence of sodium and water retention. What is important to note is that despite significant beneficial effects of TZD's as an antidiabetic agents, recent reports have highlighted significant increase in cardiac related morbidity and mortality, in particular on development of heart failure in human subjects with type 2 diabetes mellitus [40–42]. However, there are contrasting reports underlining importance of rosiglitazone as a cardioprotective agent in postmyocardial infarction [37]. These conflicting reports suggest existence of multifactorial elements of TZD's effects on cardiovascular function and hence, their use should be tailored for each individual patient in question.

In summary, short-term rosiglitazone therapy improves both metabolic profile and vascular function in lean nondiabetic rats. The beneficial effect of rosiglitazone on vascular reactivity is mediated by activation of endothelial PPAR γ receptors leading to increased NO synthesis and production. This increased NO production may, at least in part, explain mechanism(s) of blood-pressure-lowering effects of thiazolidinediones on both human and animals models. Moreover, improved vasorelaxant effect seen by rosiglitazone therapy in this study appears to be a class effect shared with other thiazolidinedione compounds.

Conflict of Interests

The authors have declared that there is no conflict of interests.

Acknowledgment

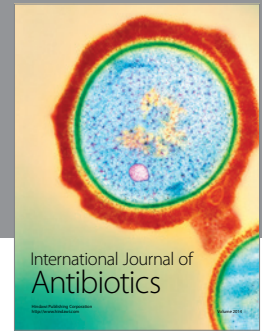
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