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Original article

# Curcumin and nanocurcumin differentially activate TRPV1 channels in non-pregnant and pregnant middle uterine artery of *Capra hircus*

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**Abstract**

The purpose of our study was to assess the differential activity of TRPV1 channels to curcumin and nanocurcumin in middle uterine artery (MUA) obtained from non-pregnant (NP) and pregnant (P) C*apra hircus (Ch).* MUA rings were mounted in an automatic organ bath containing 20 ml MKHS, maintained at pH 7.4. Vasorelaxation of curcumin (CUR) and nanocurcumin (NCUR) in presence and absence of TRPV1 antagonists in PE-precontracted MUA were elicited. The responses were recorded isometrically by highly sensitive isometric force transducer automatic organ bath connected to powerlab and analysed using Lab chart 7.1.3 software.The maximal vasorelaxation in PE-precontracted ED + MUA rings with curcumin and nanocurcumin (1pM-100 µM) was NP 42.58%, 40.36% and P *Ch* 55.49%, 44.09%, respectively. Capsazepine (CAPZ), and ruthenium red (RR) attenuated curcumin-induced vasorelaxation (CVR) to 27.81 ± 0.42%, 13.77 ± 1.78 % in NP and to 24.17 ± 0.26%, 29.24 ± 0.81% in P *Ch*, respectively. Similarly, CAPZ and RR attenuated nanocurcumin-induced vasorelaxation (NCVR) to 24.54 ± 0.94%, 25.61 ± 2.33% in NP and to 23.95 ± 0.45%, 34.05 ± 1.32% in P *Ch*. (i) The vasorelaxation of MUA of *Ch* is mediated by curcumin and nanocurcumin *via* differential activation of TRPV1 channel, (ii) Sensitivity of TRPV1 to curcumin is significantly greater than nanocurcumin in MUA of both NP and P *Ch*, (iii) Curcumin and nanocurcumin could be useful to control hypertension during pregnancy.

**Key words:** Curcumin, nanocurcumin, TRPV1, uterine artery, pregnancy

## 1. Introduction

Hypertension is considered to be a major contributing factor to several cardiovascular illnesses, including coronary heart disease, ischemia, and hemorrhagic stroke (Zhuang *et al*., 2016). Hypertensive disorders during pregnancy include gestational hypertension and preeclampsia which are the major causes of maternal and fetal morbidity and mortality, affecting 5-10% of pregnancies (Wang *et al*., 2013). The process of vasodilation is a critical event involves signalling pathways at the level of both endothelium and vascular smooth muscle within the uterine artery. Interaction between neurotransmitters and neuropeptides in the uterine artery is an important factor in the regulation of uterine blood flow (Jovanovic *et al*., 2000). Failure of these changes to occur reduces uteroplacental perfusion and contributes to pregnancy complications such as gestational hypertension and intrauterine growth restriction (Powe *et al*., 2011).

Transient receptor potential vanilloid receptor 1 (TRPV1) is a polymodal nociceptor model of the TRPV subfamily which can be activated by capsaicin, noxious heat, extracellular protons, vanilloids or voltage dependent depolarization and various lipids (Caterina and Julius, 2001). TRPV1 is distributed along the vascular system and is involved in regulation of vasoconstriction or vasodilatation (Sharma *et al*., 2013). TRPV1 channels plays a complex multi functional role in regulating pathways of inflammatory pain in female reproductive tract (FRT), present on presumed nociceptive axons in rat vagina (Liao and Smith, 2011) and human cervix (Tingaker *et al*., 2008). Furthermore, estrogen enhances pain evoked by uterine distention *via* a TRPV1 receptor dependent mechanism (Yan *et al*., 2007). The most important functions in different organ systems include pain perception, attenuation of inflammatory pain conditions and modulation of the receptor activity (Gonza´lez-Muniz, 2005). TRPV1 induced vasorelaxation may be mediated by release of relaxing factors *via* activation of endothelial TRPV1 channel, which mediates an increased $Ca^{2+}$ influx and subsequent phosphorylation of phosphorylated levels of protein kinase A (PKA) and endothelial NO synthase (eNOS), followed by release of cAMP and NO. Endothelial TRPV1 is a potential therapeutic target in the management of hypertension and related vascular diseases (Yang *et al*., 2010).

Curcumin (diferuloylmethane) is a hydrophobic polyphenol, is a principal active constituent of turmeric (*Curcuma longa*). It plays a crucial beneficial and pleiotropic regulatory role in various pathological conditions including cancer, cardiovascular disease, Alzheimers disease, inflammatory disorders, neurological disorders (Yallapu *et al*., 2015). The vanilloid moiety of curcumin is considered important for activation of the transient receptor potential vanilloid

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1 (TRPV1), which plays an important role in nociception (Yeon *et al*., 2010). Curcumin induced vasodilation in rat aorta (Sasaki *et al*., 2003), porcine coronary arteries (Xu *et al*., 2007), rabbit basilar arteries (Ahn *et al*., 2009), goat ruminal artery (Dash and Parija, 2013) and rat mesenteric arteries (Zhang *et al*., 2017). TRPV1 activity in the presence of curcumin was reported in mice jejunum (Zhi *et al*., 2013), dinitrobenzene sulfonic acid-induced colitis in mice (Martelli *et al*., 2007), Human embryonic kidney (HEK) 293 cells (Yeon *et al*., 2010) and ulcerative colitis in rat model (Yang *et al*., 2017).

For centuries, curcumin has showed incredible therapeutic benefits in various diseases. Despite phenomenal advances, the clinical implication of curcumin is hindered due to low solubility, poor bioavailability and pharmacokinetics. However, these obstacles can be overcome by encapsulating or by loading curcumin into nanoformulations. The bioavailability and efficient delivery of curcumin can be made possible in the form of nanocurcumin which preserves the properties of curcumin and ascertains that it reaches the affected tissue (Shang *et al*., 2014). In numerous *in vitro* and *in vivo* studies, nanoformulations of curcumin showed better therapeutic benefits over the native curcumin (Gupta *et al*., 2013).

Information regarding the vasodilator role of curcumin and nanocurcumin in uterine artery *via* activation of TRPV1 channels is lacking. The present work has been primarily designed to carry out functional characterization to identify the role of TRPV1 channels by assessing the vasorelaxation effect of curcumin and nanocurcumin in uterine artery of *C. hircus*.

## 2. Materials and Methods

### 2.1 Ethical guidelines

This work has been approved by institutional animal ethical committee (Registration No: 433/CPCSEA/CVS vide ID.No.1586(6)/ CVS/dt.03.05.2016 for conducting randomized animal tissue experiments.

### 2.2 Drugs and chemicals

Phenylephrine, Capsazepine were obtained from Sigma-Aldrich, USA and ruthenium red from MP Biochemicals, India. Curcumin and nanocurcumin gifted by Dr. B.P. Mohanty. All the solutions were prepared in triple distilled water except capsazepine, prepared in 70% ethanol, curcumin and nanocurcumin in 0.5 N NaOH and PBS.

### 2.3 Preparation of middle uterine artery and functional study

Non-pregnant and pregnant uterus with broad ligament intact along with uterine artery were obtained in an aerated ice-cold (4-6°C) Modified Krebs-Henseleit Saline (MKHS) solution (mM): NaCl 118, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, $NaHCO_3$ 11.9, $KH_2PO_4$ 1.2 and Dextrose 11.1, (pH 7.4). Secondary branch of uterine artery supplied to the uterine horn carefully cleared of fascia and connective tissue in MKHS solution under continuous aeration. The arteries were cut into segments of circular rings measuring 1.5-2 mm in length were then mounted between two fine stainless steel L-shaped hooks and kept under a resting tension of 1.5 gm in a thermostatically controlled (37.0 ± 0.5ºC) automatic organ bath (Pan Lab) of 20 ml capacity bubbled with carbogen (95% $O_2$ + 5% $CO_2$). The change of isometric tension was measured by a highly sensitive isometric force transducer (Model: MLT0201, AD instrument, Australia) and analysed using chart 7.1.3 software.

### 2.4 Experimental protocol

#### 2.4.1 Effect of curcumin or nanocurcumin (1pM to 100 μM)-induced vasorelaxation in PE (10 μM)-precontracted MUA rings in absence or presence of ruthenium red or capsazepine (10 μM)

Curcumin or nanocurcumin (1pM to 100 μM)-induced vasorelaxation in PE (10 μM)-precontracted MUA rings was elicited by cumulative addition of curcumin or nanocurcumin at an interval of 4 min in endothelium intact (ED +) rings. To examine the sensitivity of TRPV1 channel, the arterial rings were preincubated with non specific TRPV1 channel blocker ruthenium red (10 μM) or specific TRPV1 channel blocker capsazepine (10 μM) for a period of 30 min prior to PE-induced contraction. The concentration-related contractile response curves (CRCs) of curcumin or nanocurcumin were elicited and shift of the CRCs were compared with non treated control. The CRC response curves of curcumin or nanocurcumin induced relaxation in absence or presence of ruthenium red or capsazepine were plotted and $pIC_{50}$ was calculated. The $pIC_{50}$ and shift of the CRC response curves were compared for each set of experiments.

### 2.5 Statistical analysis

The data were expressed as percentage of the maximum relaxation to agonist obtained in the absence of antagonist (control) and analyzed by the interactive non-linear regression through the computer program Graph Pad Prism (Graph Pad Prism Software, San Diego, CA, USA). $R_{max}$ / $R_{Bmax}$, mean threshold concentration and $-logIC_{50}/pIC_{50}$ were calculated through Graph Pad Prism. Graph Pad Quick Calcs't' test was used to calculate the *p* value to determine the level of significance and to analyse the data. '*p*' value < 0.05 was considered statistically significant.

## 3. Results

### 3.1 Effect of capsazepine or ruthenium red on curcumin-induced vasorelaxation in PE-precontracted MUA rings of NP and P *Ch*

Table 1 presents the $pIC_{50}$ and $R_{max}$ of curcumin and nanocurcumin in presence of either specific TRPV1 blocker capsazepine or non specific TRPV1 blocker ruthenium red. In MUA of NP *Ch*, CVR curve was shifted to right with significant ($p$<0.001) decrease in $R_{Bmax}$ (27.81 ± 0.42%) and $pIC_{50}$ value (10.05 ± 0.21) in presence of capsazepine and significant ($p$<0.001) decrease in $R_{Bmax}$ (13.77 ± 1.78) and $pIC_{50}$ (6.87 ± 0.14) in presence of ruthenium red as compared to NP control (Figure 1A). In MUA of P *Ch*, CVR curve was shifted to right with significant ($p$<0.001) decrease in $R_{Bmax}$ (24.17 ± 0.26%) and $pIC_{50}$ value (8.28 ± 0.15) in presence of capsazepine and significant ($p$<0.001) decrease in $R_{Bmax}$ (29.24 ± 0.81%) and $pIC_{50}$ value (7.04 ± 0.14) in presence of ruthenium red as compared to *p* control (Figure 1B).

### 3.2 Effect of capsazepine or ruthenium red on nanocurcumin induced vasorelaxation in PE-precontracted MUA rings of NP and P *Ch*

In MUA of NP *Ch*, NCVR curve ($R_{max}$ 40.36 ± 2.38%; $pIC_{50}$ 8.83 ± 0.12) was shifted to right with significant ($p$<0.001) decrease in $R_{Bmax}$ (24.54 ± 0.94%) and $pIC_{50}$ value (7.28 ± 0.18) in presence of

capsazepine and significant ($p$<0.001) decrease in $R_{Bmax}$ (25.61 ± 2.33) and non-significant increase in $pIC_{50}$ (9.15 ± 0.10) in presence of Ruthenium red (Figure 2A). In MUA of P *Ch*, NCVR curve $R_{max}$ 44.09 ± 3.41%; $pIC_{50}$ 6.05 ± 0.09) was shifted to right with significant ($p$ < 0.001) decrease in $R_{Bmax}$ (23.95 ± 0.45%) and $pIC_{50}$ value (8.88 ± 0.12) presence of capsazepine, and significant (P<0.05) decrease in $R_{Bmax}$ (34.05 ± 1.32%) and significant ($p$<0.001) increase in $pIC_{50}$ value (9.63 ± 0.13) in presence of ruthenium red (Figure 2B).

**Table 1:** Curcumin/Nanocurcumin (1pM - 100 µM) induced vasorelaxation on phenylephrine (10 µM) - precontracted MUA rings in absence (control) or presence of capsazepine (CAPZ, 10 µM), ruthenium red (RR, 10 µM) in MUA of Non-pregnant (NP)/Pregnant (P) *C. hircus* (*Ch*).

| | | CURCUMIN | | | NANOCURCUMIN | | |
|---|---|---|---|---|---|---|---|
| | | CON | CAPZ | RR | CON | CAPZ | RR |
| NP | $R_{max}/R_{Bmax}$ (%) | 42.58 ± 1.84 | 27.81 ± 0.42[a] | 13.77 ± 1.78[a] | 40.36 ± 2.38 | 24.54 ± 0.94[a] | 25.61 ± 2.33[a] |
| | –LOG $IC_{50}$ | 8.83 ± 0.10 | 10.05 ± 0.21[a] | 6.87 ± 0.14[a] | 8.83 ± 0.12 | 7.28 ± 0.18[a]5 | 9.15 ± 0.10 |
| P | $R_{max}/R_{Bmax}$ (%) | 55.49 ± 1.69 | 24.17 ± 0.26[a] | 29.24 ± 0.81[a] | 44.09 ± 3.41 | 23.95 ± 0.45[a] | 34.05 ± 1.32[b] |
| | –LOG $IC_{50}$ | 9.17 ± 0.10 | 8.28 ± 0.15[a] | 7.04 ± 0.14[a] | 6.05 ± 0.09 | 8.88 ± 0.12[a] | 9.63 ± 0.13[a] |

[a]($p$<0.001), [b]($p$<0.05) represents level of significance between data of each row (treated) compared with the data of control, (CON). Values are represented as mean ± SEM, (n = 6). SEM = standard error of mean.

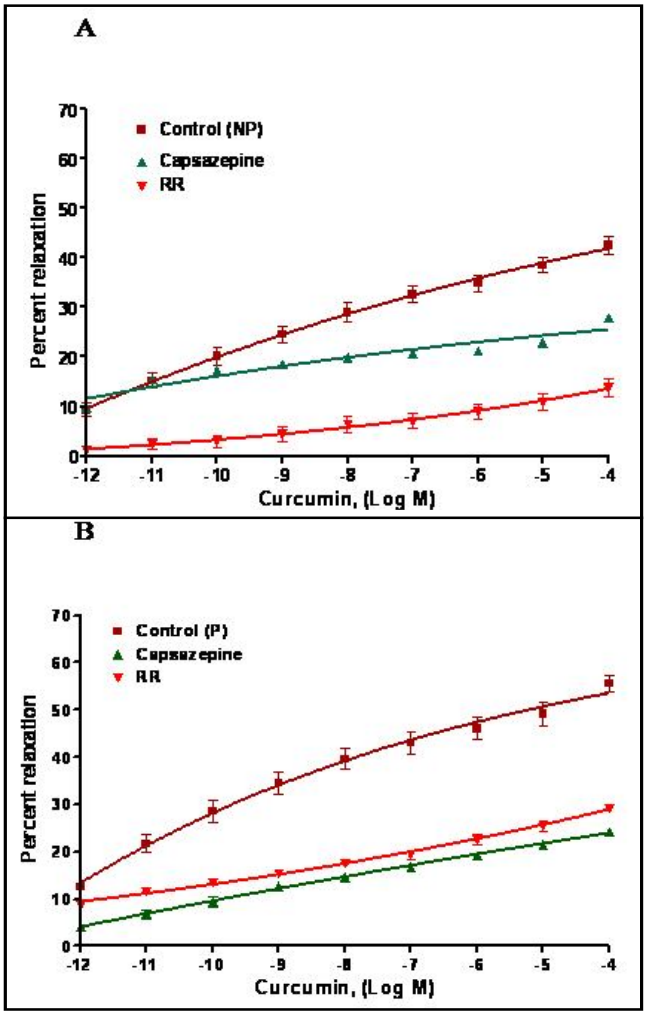


**Figure 1:** Curcumin (1pM-100 µM) induced concentration response curve elicited in absence (control) or in presence of capsazepine (10 µM) or ruthenium red (RR, 10 µM), in MUA ring of **A**. NP *Ch*. **B**. P *Ch*.

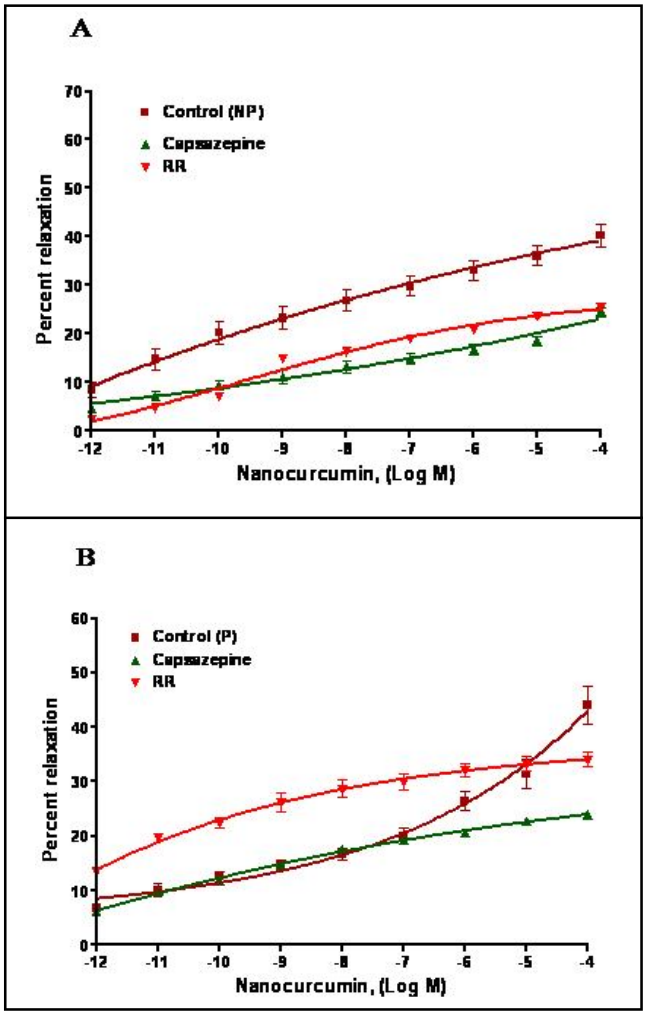


**Figure 2:** Nanocurcumin (1pM-100 µM) induced concentration response curve elicited in and absence (control) or in presence of capsazepine (10 µM) or ruthenium red (RR, 10 µM), in MUA ring of **A**. NP *Ch*. **B**. P *Ch*

## 4. Discussion

The salient findings are: (i) The maximal vasorelaxation obtained from CVR curve elicited in PE- precontracted ED + MUA rings was greater in P *Ch* (55.49%) than that of NP *Ch* (42.58%). capsazepine and ruthenium red reduced the maximal curcumin vasorelaxation elicited in PE-precontracted rings to 27.81%, 13.77% in NP and to 24.17%, 29.24% in P *Ch*. (ii) The maximal vasorelaxation obtained from NCVR curve elicited in PE-precontracted ED+ MUA rings was almost identical in P (44.09%) than NP *Ch* (40.36%). Capsazepine and ruthenium red reduced the maximal nanocurcumin vasorelaxation elicited in PE-precontracted rings to 24.54%, 25.61% in NP and to 23.95%, 34.05% in P *Ch*.

According to the World Health Organization, cardiovascular diseases are the leading cause of death worldwide. Among these, arterial hypertension has a high prevalence and is associated with other conditions, such as myocardial infarction and stroke (Nguelefack *et al*., 2007). In addition, the etiology of hypertension has been associated with vascular endothelial dysfunction, which is characterized by an uncoupling between the release of endothelial factors such as NO, $PGI_2$ and EDHF, as well as effects on endothelium-dependent contractile mechanisms, and the associated change in vascular smooth muscle tone (Brunner *et al*., 2005). In rat mesenteric arteries, *in vivo* and *in vitro* experimental data suggests that long-term activation of TRPV1 can actually increase the PKA, endothelial eNOS and plasma levels of NO metabolites, increase endothelium-dependent relaxation, thereby lowering blood pressure in hypertensive rats demonstrating endothelial TRPV1 as a potential candidate therapeutic target in the management of hypertension and related vascular diseases (Yang *et al*., 2010). Capsazepine, a synthetic analogue of capsaicin used widely as a pharmacological tool to assess the role of TRPV1 in inflammatory hyperalgesia (Watanabe *et al*., 2015). Ruthenium red, a water soluble polycationic dye, blocks the pore of the capsaicin-operated cation channel TRPV1 thus interfering with all polymodal ways of TRPV1 activation (Pierre *et al*., 2009). TRPV1 channel blocker ruthenium red has been reported to inhibit TRPV1 mediated vasorelaxation in human coronary artery at 0.1mM by 94%, rat skin saphenous nerve preparation at 50 μM, rat mesenteric artery at 3 μM by about 40% (Bautista *et al*., 2005) and goat superior mesentric artery at 10 μM by about 83% (Mohanty *et al*., 2016).

Pregnancy is a collective event of anatomical, physiological and molecular alternation of elevated uterine blood flow. During pregnancy local blood vessels dilate 10 to 20-fold to meet the requirements of the fetoplacental unit and the enlarging myometrial mass. This is achieved through a profound decrease in uterine vascular resistance and structural remodelling of the uterine artery wall (Osol *et al*., 2009).The importance of curcumin/nanocurcumin in traditional/folk medicine (Aggarwal and Harikumar, 2009) and their ability to induce vasorelaxation motivated us to investigate the importance of curcumin/nanocurcumin in ameliorating hypertension during pregnancy. Evidence suggests that the pleiotropic effects of curcumin are dependent on its capacity of interacting and regulation of multiple molecular targets. Thus, due to its efficacy and regulation of multiple targets, as well as its safety for human use, curcumin has received considerable interest as a potential therapeutic agent for the prevention and/or treatment of various malignant diseases, arthritis, allergies, Alzheimer's disease and an alternative therapy for uterine leiomyoma (Tsuiji *et al*., 2011).

In the present study we observed that capsazepine and ruthenium red reduced the maximal curcumin vasorelaxation elicited in PE - precontracted rings to 27.81%, 13.77%, in NP and to 24.17%, 29.24% in P *Ch*. This clearly suggest that curcumin activates TRPV1 channels that contribute in part to its vasorelaxation and sensitivity of TRPV1 channels to curcumin is increased by about 2 fold in MUA of P than NP *Ch*.

In the mouse jejunum showed that, the mesenteric afferent nerve response to ramp distension was attenuated by curcumin and such effects disappeared in TRPV1-knockout mice. Curcumin potently inhibited capsaicin-induced rise in intracellular calcium and inward currents in mouse or rat DRG neurons. Curcumin inhibit visceral nociception *via* antagonizing TRPV1 and may be a promising lead for the treatment of functional gastrointestinal diseases (Zhi *et al*., 2013). Oral administration of curcumin ameliorated dinitrobenzene sulfonic acid-induced colitis in mice and such effect was completely abolished by TRPV1 antagonist capsazepine. TRPV1 might be the target through which curcumin exerted its effects on visceral sensitivity and colonic inflammation (Martelli *et al*., 2007). Similarly, oral administration of curcumin alleviated visceral hyperalgesia in dextran sulfate sodium-induced colitis in rats. The anti-hyperalgesic effect is partially through down regulating the colonic expression and phosphorylation of TRPV1 on the afferent fibers projected from peptidergic and non-peptidergic nociceptive neurons of dorsal root ganglion (Yang *et al*., 2017).
Capsazepine and ruthenium red reduced the $r_{max}$ (40.36% and 44.09%) of NCVR elicited in PE-precontracted rings to 24.54%, 25.61% in NP and to 23.95%, 34.05% in P *Ch*. This result clearly indicates that vasorelaxation to NC is partly mediated by capsaicin sensitive TRPV1 channels in MUA rings of NP *Ch*. Increased sensitivity of NCVR to capsazepine in MUA of P *Ch* suggests increased function or expression of TRPV1.

## 5. Conclusion

Our study demonstrates for the first time that (i) Curcumin and Nanocurcumin-induced vasorelaxation occurs *via* TRPV1 channel activation in uterine artery of *C. hircus*, (ii) TRPV1 exhibited a differential sensitivity to curcumin and nanocurcumin and that is increased with vascular remodeling in pregnancy and (iii) Increased sensitivity of TRPV1 to curcumin with vascular remodeling in pregnancy could be due to increased expression of TRPV1.

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### Conflict of interest

We declare that we have no conflict of interest.

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