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NANOCURCUMIN SELECTIVELY ACTIVATES ENDOTHELIAL NITRIC OXIDE IN MIDDLE UTERINE ARTERY OF GOAT (*CAPRA HIRCUS*)

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Keywords:

Nanocurcumin, Uterine artery, Vasorelaxation, Nitric oxide, Pregnancy

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ABSTRACT: Objective: The present study is designed to investigate vasorelaxation mechanisms of Nanocurcumin in the middle uterine artery (MUA) of both non-pregnant (NP) and pregnant (P) *Capra hircus* (*Ch*). **Methods:** MUA rings were mounted in an automatic organ bath and the contractile response was recorded isometrically by highly sensitive force transducer connected to a power lab data acquisition system. Nanocurcumin (1 pM-100 µM) vasorelaxation response (NCVR) was elicited in PE-precontracted rings either in the absence or presence of different blockers. **Results:** The maximal vasorelaxation (R_{max}) to Nanocurcumin in phenylephrine-precontracted endothelium intact MUA rings of NP (40.36 ± 2.38%) and of P (44.09 ± 3.41%) was reduced to 22.93 ± 0.80% and 25.37 ± 2.2% in endothelium-denuded MUA rings of NP and P *Ch*. L-NAME, Indomethacin and L-NAME + Indomethacin inhibited NCVR by significantly decreasing the R_{max} to 17.65%, 28.42%, 17.95% in NP and to 27.34%, 39.06%, 24.50% in P *Ch*. The ODQ and carbenoxolone/18β Glycyrrhetinic acid did not inhibit the R_{max} of NCVR. **Conclusion:** Nanocurcumin potentially dilates the MUA of both NP and PCh. The endothelial L-NAME sensitive eNOS is activated by Nanocurcumin and it has the potential to increase blood flow to the uterus and fetus. Additionally, it could also be useful in the effective treatment of hypertensive disorders such as pre-eclampsia.

INTRODUCTION: Hypertension is the most common health disorder of pregnancy and is reported to complicate up to 10% of pregnancies and is associated with increased maternal and neonatal morbidity and mortality [1]. NO maintains vascular tone by relaxing vascular smooth muscle cells [2].

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Myo-endothelial gap junctions connect endothelial cells and smooth muscle cells. The hyper-polarization in smooth muscle cells is basically conducted from the endothelial cells through myoendothelial gap junctions since smooth muscle and endothelial cells are coupled [3].

Connexins play specific roles in estradiol-17β-treatment-regulated uterine function and in placental development during early gestation [4]. During normal pregnancy, there is an increased production of NO, PGI_2 and EDHF but in preeclampsia, there is increased release of placental cytokines that inhibit the production of endothelium-derived relaxing factors and thereby

decrease smooth muscle relaxation [5]. Curcumin, a hydrophobic polyphenol extracted from the rhizomes of *Curcuma longa* (Zingiberaceae). Curcumin has been used as traditional medicine, beauty aid, cooking spice, and a coloring agent for centuries in India [6]. Several studies have demonstrated the beneficial effects of Curcumin, including antidepressant, antioxidant, anti-inflammatory, antibacterial, and anti-cancer activities [7]. Curcumin shows to improve endothelial function and also been reported to have numerous therapeutic effects in the treatment of cardiovascular diseases [8]. The pleiotropic effects of Curcumin are dependent on its capacity of interacting and regulation of multiple molecular targets. 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 treatment of various malignant diseases, arthritis, allergies, Alzheimer's disease and alternative therapy for uterine leiomyoma [9-11].

Despite its enormous curative potential, low water-solubility, chemical instability, rapid metabolism, short half-life, and poor oral bioavailability are some of the major factors which restrict the utilization of Curcumin [12]. However, to improve its bioavailability, the nano-formulation of Curcumin is an emerging novel substitute. The different types of nano-carriers were utilized for Curcumin nano-particle formulation. Nanoparticles (10-200 nm), can improve the circulation time of the loaded therapeutic molecule and improve its residence at the pathological site by enhancing permeation and retention (EPR) effect [13]. Recent reports suggested that nano-curcumin as a chemopreventive agent against malignant tumor proliferation in different organs [14]. It may be a promising lead in reducing hypertension. Administration of nano-curcumin in proper doses can reduce hypertension during pregnancy, and this could be one of the potential adjuncts for the treatment of pre-eclampsia.

Information on the vasodilator role of nano-curcumin is lacking in the uterine artery of any species. Our present research would explore the relative potential of nano-curcumin to cause vasodilatation in MUA of non-pregnant and pregnant goat model. Further, the functional involvement of eNOS-NO-cGMP, COX-PGI_2, sGC, and hyperpolarizing factors were examined to establish the mechanism of vasorelaxation to nano-curcumin in MUA of NP and P *Ch*.

MATERIALS AND METHODS:

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

Chemicals: Nanocurcumin (Gifted by Dr. B.P. Mohanty, CIFRI, ICAR, India), 18 β Glychrrhetinic Acid (MP Biochemicals, India), N^G –nitro-L-arginine methyl ester (L-NAME), 1H-[1, 2, 4] oxadiazolo [4, 3-a] quinoxaline-1one (Cayman Chemical, USA) and Carbenoxolone (Sigma, USA) were employed in this study. All the solutions were prepared fresh in triple-distilled water except for 18βGA, ODQ which were dissolved in dimethyl sulfoxide (DMSO) and indomethacin, which was dissolved in ethanol. Nanocurcumin was prepared in 0.5 N NaOH and PBS.

Middle Uterine Artery Preparation: Both 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 to the laboratory. Secondary branches of uterine artery supplied to the uterine horn carefully cleared of fascia and connective tissue were cut into segments of circular rings measuring 1.5-2 mm in length.

The arterial rings 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 ± 0.5 ºC) automatic organ bath (Pan Lab) of 20 mL capacity bubbled with carbogen (95% O_2 + 5% CO_2). Endothelium denuded (ED-) rings were prepared by the cotton swab method. The change of isometric tension was measured by a highly sensitive isometric force transducer (Model: MLT0201, AD instrument, Australia) and analyzed using chart 7.1.3 software.

Nanocurcumin- Induced Concentration Related Response in PE-Precontracted ED +/ ED- MUA Rings: After obtaining a plateau tension induced by PE (10 µM), Nanocurcumin (1 pM-100 µM) was added to bath cumulatively with an increment of 1.0 log unit at 4 min interval. Net tension (gm) at

each concentration of nano-curcumin was recorded. The concentration-related response curves of nano-curcumin were elicited and the shift of the CRCs was compared between ED + and ED - groups. Rmax/R_{Bmax}, mean threshold concentration, and pIC_{50}, were calculated for MUA rings for non-pregnant and pregnant groups.

Nanocurcumin-Induced Vasorelaxation in Presence of L-NAME or Indomethacin or L-NAME and Indomethacin or ODQ or Carbenoxolone or 18 β Glycyrrhetinic Acid in PE-Precontracted MUA Rings: In order to examine nano-curcumin (1 pM-100 µM) induced vaso-relaxation involving EDRF and EDHF pathways, the arterial rings were pre-incubated with 10 µ of L-NAME or Indomethacin or L-NAME and Indomethacin or ODQ for a period of 15 min and Carbenoxolone or 18 β Glycyrrhetinic acid for a period of 30 min prior to PE pre contraction.

Curcumin was added with an increment of 1.0 log unit in a cumulative manner into the bath at 4 min interval after attaining a plateau contraction induced by PE. The concentration-related response curves of nano-curcumin were elicited and the shift of the CRCs was compared with non-treated control. Rmax/R_{Bmax}, mean threshold concentration, and pIC_{50}, were calculated for MUA rings of NP and P *Ch*.

Data Analysis: The data was expressed as a 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 (GraphPad Prism Software, San Diego, CA, USA). Rmax/R_{Bmax}, mean threshold concentration and $-\log IC_{50}/pIC_{50}$ were calculated through GraphPad Prism. GraphPad Quick Calcs 't' test was used to calculate the P-value to determine the level of significance and to analyze the data. A 'p' value < 0.05 and <0.001 were considered statistically significant.

RESULTS AND DISCUSSION: Table 1 presents the R_{max} and pIC_{50} of nanocurcumin in MUA of NP and P *Ch*. Nanocurcumin inhibited PE- induced sustained contraction in both NP and P *Ch* in a concentration-dependent manner. NCVR curve (R_{max} 40.36 ± 2.38%; pIC_{50} 8.83 ± 0.12) elicited in ED + rings was shifted to right with significant ($p<0.001$) decrease in R_{max} (22.93 ± 0.80%) and significant ($p<0.05$) decrease in pIC_{50} (8.08 ± 0.20) in ED- rings of NP *Ch* **Fig. 1A**. In MUA of P Ch, NCVR curve (R_{max} 44.09 ± 3.41%; pIC_{50} 6.05 ± 0.09) elicited in ED + rings was shifted to right with significant ($p<0.05$) decrease in R_{max} (25.37 ± 2.20%) and significant ($p<0.001$) increase pIC_{50} (7.76 ± 0.18) in ED-MUA rings **Fig. 1B**.

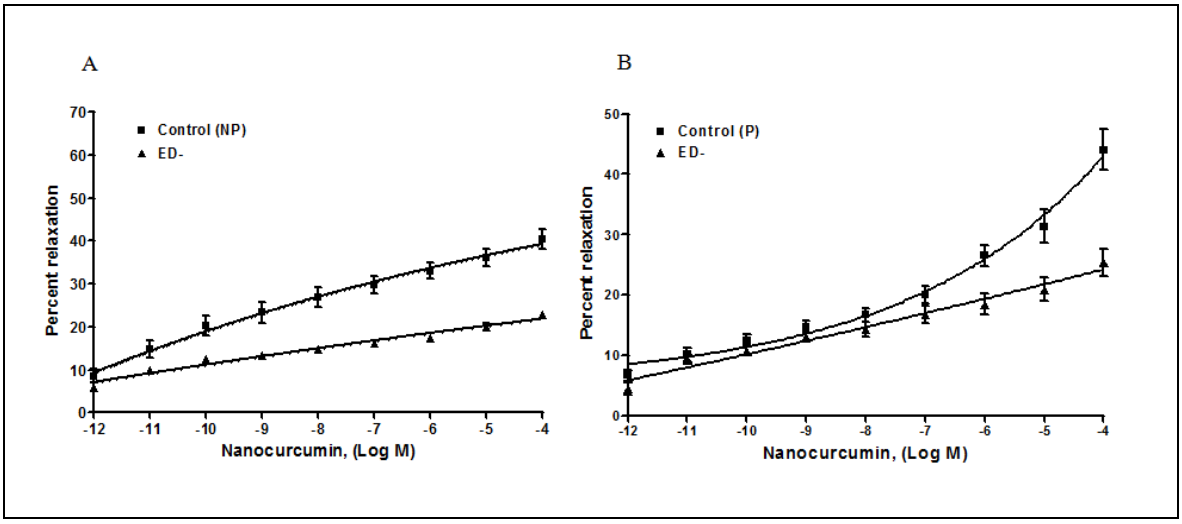

FIG. 1: NANO CURCUMIN (1PM-100 µM)-INDUCED CONCENTRATION RESPONSE CURVE ELICITED IN ED+/- MUA RING OF A) NP *Ch* AND B) P *Ch*

L-NAME, eNOS inhibitor and Indomethacin, a COX inhibitor and both attenuated nanocurcumin vasorelaxation in PE precontracted MUA rings **Table 1**. NCVR curve was shifted right with significant ($p<0.001$) decrease in R_{Bmax} (17.66 ± 0.45%) and pIC_{50} (7.02 ± 0.11) in presence of L-NAME, with significant ($p<0.05$) decrease in R_{Bmax} (28.42 ± 2.02%) and increase in pIC_{50} (9.38 ± 0.18)

in presence of Indomethacin. In presence of both L-NAME and Indomethacin, the NCVR curve was also shifted to the right with significant ($p<0.001$) decrease in R_{Bmax} (17.95 ± 1.43%) and pIC_{50} (7.04 ± 0.12) **Fig. 2A**. In MUA of P *Ch*, NCVR curve was shifted to right with significant ($p<0.05$) decrease in R_{Bmax} (27.34 ± 0.93%) and increase in pIC_{50} (6.75 ± 0.17) in presence of L-NAME, with non-significant decrease in R_{Bmax} (39.06 ± 1.80%) and significant ($p<0.001$) increase in pIC_{50} (10.81 ± 0.15) in presence of Indomethacin. In presence of L-NAME and Indomethacin, the NCVR curve was shifted to the right with significant ($p<0.001$) decrease in R_{Bmax} (24.50 ± 1.68%) and increase in pIC_{50} (9.28 ± 0.14) **Fig. 2B**.

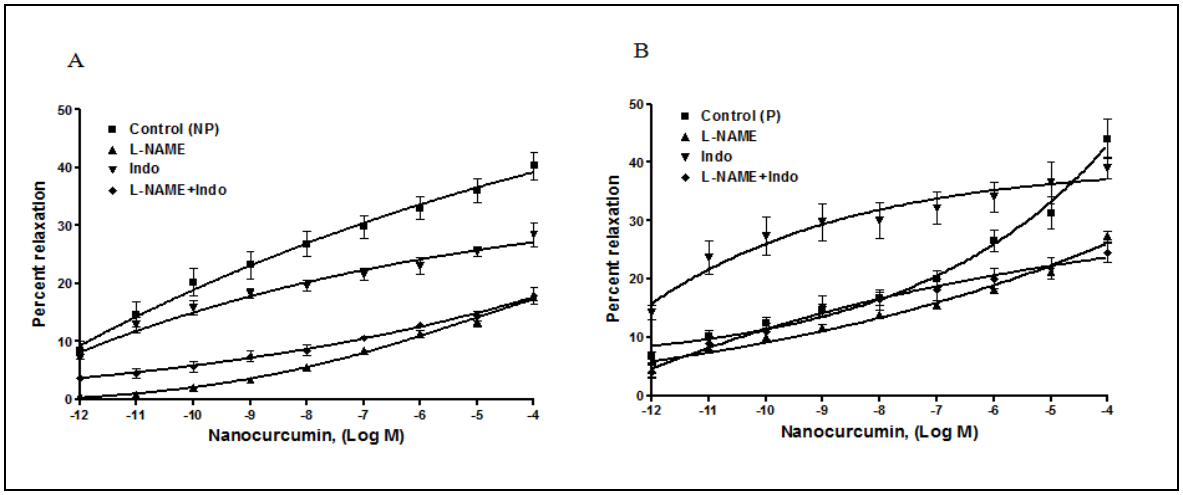

FIG. 2: NANOCURCUMIN (1PM-100 µM)-INDUCED CONCENTRATION RESPONSE CURVE ELICITED IN ABSENCE (CONTROL) OR IN PRESENCE OF L-NAME (10 µM) OR INDOMETHACIN (INDO, 10 µM) OR L-NAME AND INDOMETHACIN (L-NAME +INDO, 10 µM) IN MUA RING OF A) NP *Ch* AND B) P *Ch*

In presence of ODQ (sGC inhibitor, 10 µM), NCVR curve showed a non-significant decrease in R_{Bmax} (35.48 ± 1.29%) and a significant decrease ($p<0.001$) in pIC_{50} (6.79 ± 0.12) as compared to NP control **Fig. 3A**. In MUA of P *Ch*, NCVR curve was unaltered with a non-significant decrease in R_{Bmax} (50.54 ± 0.29) and significant ($p<0.001$) increase in pIC_{50} (7.85 ± 0.14) as compared to P control **Fig. 3B**.

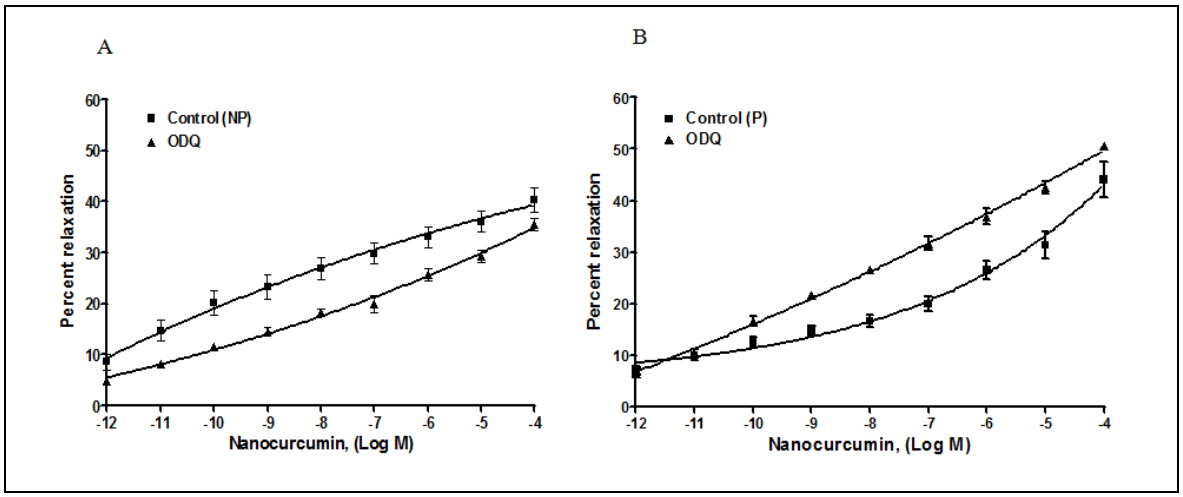

FIG. 3: NANOCURCUMIN (1PM-100 µM)-INDUCED CONCENTRATION RESPONSE CURVE ELICITED IN ABSENCE (CONTROL) OR IN PRESENCE OF ODQ (10 µM) IN MUA OF A) NP *Ch* AND B) P *Ch*

Gap junction uncouplers like Carbenoxolone/18β glycyrrhetinic acid did not alter NCVR significantly in MUA rings of both NP and P *Ch* **Table 1**. Carbenoxolone (10 µM), caused a non-significant decrease in R_{Bmax} (34.15 ± 1.30%) and significant ($p<0.001$) decrease pIC_{50} (7.86 ± 0.14) of NCVR curve. Similarly, 18β Glycyrrhetinic acid (10 µM) inhibited NCVR with significant ($p<0.05$)

increase in R_{Bmax} (51.91 ± 3.0 %) and decrease in pIC_{50} (8.13 ± 0.13) in MUA of NP *Ch* **Fig. 4A**. In MUA of P *Ch*, NCVR curve was shifted with a non-significant decrease in R_{Bmax} (40.21 ± 0.63%) and significant ($p<0.001$) increase in pIC_{50} (9.21 ± 0.15) in presence carbenoxolone. In the presence of 18 β-glycyrrhetinic acid NCVR curve showed a non-significant decrease in R_{Bmax} (41.41 ± 3.25%) and significant ($p<0.001$) increase in pIC_{50} (7.87 ± 0.16) **Fig. 4B**.

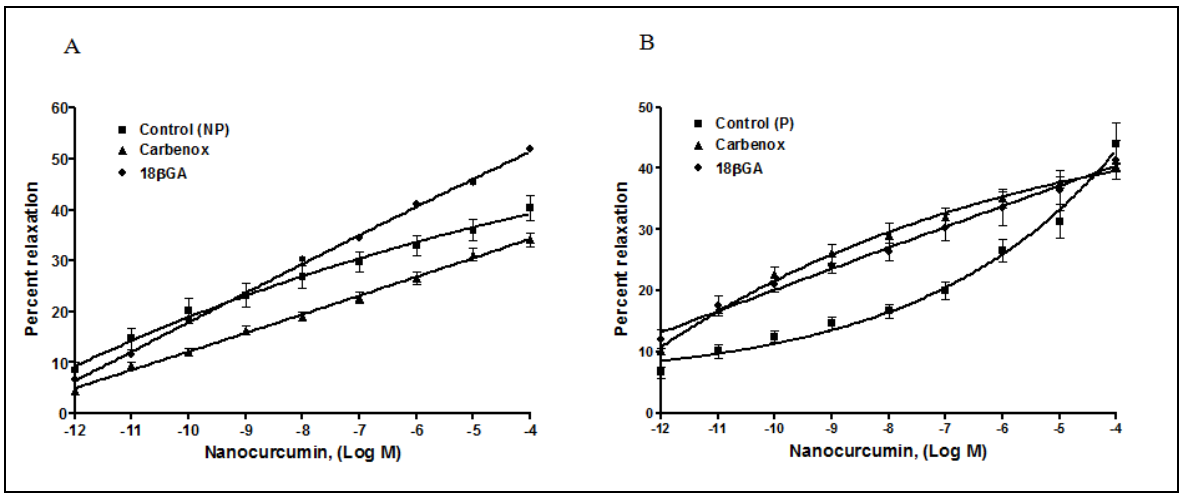

FIG. 4: NANOCURCUMIN (1PM-100 µM)-INDUCED CONCENTRATION RESPONSE CURVE ELICITED IN ABSENCE (CONTROL) OR PRESENCE OF CARBENOXOLONE (CARBENOX, 10 µM) OR 18β GLYCYRRHETINIC ACID (18β GA, 10 µM), IN MUA RING OF A) NP *Ch* AND B) P *Ch*

The major findings are i) The maximal vasorelaxation obtained from the NCVR curve elicited in PE- precontracted ED+ MUA rings were almost identical in P (44.09%) than NP *Ch* (40.36%). Endothelium removal decreased the maximal NCVR to 22.93% and 25.37% in MUA of NP and P *Ch*, respectively. In MUA rings of NP and P *Ch*, NCVR is mediated by an identical endothelium-dependent component. ii) L-NAME, Indomethacin, L-NAME + Indomethacin decreased the maximal NCVR to 17.66%, 28.42%, 17.95% in MUA ring of NP and 27.34%, 39.06%, 24.50% in MUA ring of P *Ch*, respectively. iii) In presence of ODQ, the maximal CVR was inhibited to 35.48% in NP but augmented to 50.54% in MUA ring of P *Ch*. iv) Carbenoxolone did not alter NCVR in both MUA of NP (34.15%) and P (40.21%) *Ch.* 18β glycyrrhetinic acid augmented NCVR to 51.91% in MUA of NP but did not attenuate in MUA of P (41.41%) *Ch.*

Cumulative addition of graded concentration of Nanocurcumin to the PE-precontracted MUA rings of NP or P *Ch* resulted in vasorelaxation response. Nanocurcumin-induced vasorelaxation response (NCVR) in ED+ MUA of NP (40.36%) was slightly increased in P (44.09%) *Ch*. Removal of endothelium did significantly decrease the R_{max} of NCVR curve to 22.93% and 25.37% in P *Ch* demonstrating that about 17% and 19% of NCVR is endothelium-dependent in MUA of NP and P *Ch*, respectively. This clearly demonstrates that vasorelaxation to nano-curcumin is mediated by endothelium-dependent and independent component in MUA of NP and P *Ch*. Curcumin –induced vasorelaxation has been reported in rat aorta [15], porcine coronary arteries [16], rabbit basilar arteries [17], rat mesenteric arteries [18], goat ruminal artery [19,] and uterine artery [20].

The information on the vasorelaxation effect of nano-curcumin in any arterial model is almost lacking. So, we have discussed several aspects of the mechanism of action of nano-curcumin vasorelaxation on the basis of its targets of action. L-NAME, Indomethacin, L-NAME + Indo-methacin decreased significantly the maximal NCVR to 17.66%, 28.42%, and 17.95% in MUA ring of NP *Ch*, respectively. Hence, 22%, 12% and 22% of NCVR are mediated by endothelium-dependent eNOS-NO and COX-PGI_2 pathways. In conclusion, Nanocurcumin activates predominantly the L-NAME-sensitive eNOS and secondarily Indomethacin COX-PGI_2. In MUA of P *Ch*, the R_{Bmax} obtained from the NCVR curve in the presence of L-NAME, and L-NAME + Indomethacin decreased significantly to 27.34% and 24.50%.

Indomethacin did not reduce the NCVR. These findings clearly show that endothelium-dependent and L-NAME sensitive eNOS is exclusively sensitive to Nanocurcumin in MUA ring of P *Ch.* In conclusion, Nanocurcumin activates exclusively L-NAME –sensitive eNOS and mediates endothelium-dependent vaso-relaxation involving eNOS-NO-cGMP pathways similar to the endothelial mechanism of vasorelaxation of curcumin observed in porcine coronary arterial rings and goat uterine artery [16, 20].

In the presence of ODQ, the maximal NCVR was non-significantly inhibited to 35.48% in NP and augmented to 50.54% in the MUA ring of P *Ch* suggesting that nano curcumin-induced vaso-relaxation did not activate directly sGC. In goat ruminal artery, the mechanism of vasorelaxation to curcumin *via* activation of sGC-cGMP pathways-with opening of K^+ ion channels [19] does not appear to involve in the mechanism of NCVR in MUA ring of *Ch*. On the other hand, our previous studies showed that nano-curcumin directly activates the K_V, KCa, Kir channels in NP Ch, and opens KC_a and K_V channels in P *Ch* to cause hyperpolarization in vascular smooth muscle membrane and vaso-relaxation in goat uterine artery [21].

In order to examine the effect of NC on MEGJ, NCVR was elicited in the presence of uncouplers of GJ like Carbenoxolone and 18β glycyrrhetinic acid. NCVR was not attenuated in MUA of NP and P *Ch* in presence of GJ uncouplers suggesting that NC has no modulatory effect at myoendothelial gap junction in MUA of Ch. on contrast the modulatory effect of Curcumin on gap junctions has been reported in astrocyte cells of SD rats [22] and crypt cells of Azoxymethane (AOM)-induced colon carcinogenesis in mice [23]. This result clearly demonstrates that nanoformulation of Curcumin does not activate MEGJ in goat uterine blood vessels as that of Curcumin.

TABLE 1: R_{max} AND PIC_{50} OF NANO CURCUMIN (1 PM-100 µM) IN ENDOTHELIUM INTACT (ED+) OR IN ENDOTHELIUM DENUDED (ED-) OR IN ABSENCE (R_{MAX}) OR IN PRESENCE (R_{BMAX}) OF L-NAME (10 µM) OR INDOMETHACIN (10 µM) OR L-NAME (10 µM) AND INDOMETHACIN (L-NAME + INDO, 10 µM) OR ODQ (10 µM) OR CARBENOXOLONE (10 MM) OR 18β GLYCYRRHETINIC ACID (18βGA, 10 µM) IN PE (10 µM)-PRECONTRACTED MUA RINGS OF NP AND P *Ch*

Treatment	N Value		R_{max}/ R_{Bmax} (%)		pIC_{50}	
	NP	P	NP	P	NP	P
Control (ED+)	10	10	40.36 ± 2.38	44.09 ± 3.41	8.83 ± 0.12	6.05 ± 0.09
ED-	6	6	22.93 ± 0.80[a]	25.37 ± 2.20[b]	8.08 ± 0.20[b]	7.76 ± 0.18[a]
L-NAME	6	6	17.66 ± 0.45[a]	27.34 ± 0.93[b]	7.02 ± 0.11[a]	6.75 ± 0.17[b]
Indomethacin	6	6	28.42 ± 2.02[b]	39.06 ± 1.80	9.38 ± 0.18[b]	10.81 ± 0.15[a]
L-NAME + Indo	6	6	17.95 ±1.43[a]	24.50 ± 1.68[a]	7.04 ± 0.12[a]	9.28 ± 0.14[a]
ODQ	6	6	35.48 ± 1.29	50.54 ± 0.29	6.96 ± 0.14[a]	7.85 ±0.14[a]
Carbenoxolone	6	6	34.15 ±1.30	40.21 ± 0.63	7.86 ± 0.14[a]	9.21 ± 0.15[a]
18βGA	6	6	51.91 ±3.0[b]	41.41 ± 3.25	8.13 ± 0.13[b]	7.87 ±0.16[a]

a ($p<0.001$), b ($p<0.05$) represents a level of significance between the rows within each column. The values are expressed as Mean ± SEM. N value = Total number of MUA rings used in the experiments

CONCLUSION: Nanocurcumin potently dilates the middle uterine artery of P *Ch* than that of NP *Ch*. Nanocurcumin selectively increases the NO turnover via activation of eNOS in MUA of P *Ch* without the involvement of sGC and myo-endothelial gap junctions.

It is possible that the NO thus produced by nano-curcumin in the endothelium diffused to vascular smooth muscles to activate K^+-channels to cause hyperpolarisation and vasorelaxation. These studies clearly support that nano curcumin exhibits a precise signaling target in the endothelium with better vasodilator effect than curcumin, which acts at multiple sites. Nanocurcumin has the potential to revolutionize the health industry, especially in the therapeutic management of hypertensive disorders in pregnancy, such as preeclampsia.

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CONFLICTS OF INTEREST: The authors declare that there are no conflicts of interest.

REFERENCES:

1. Antza C, Cifkova R and Kotsis V: Hypertensive complications of pregnancy: a clinical overview. Metabolism 2018; 86: 102-11.
2. Vanhoutte PM, Shimokawa H, Feletou M and Tang EH: Endothelial dysfunction and vascular disease-a 30th anniversary update. Acta Physiologica 2017; 219: 22-96.
3. Sorensen CM and Cupples WA: Myoendothelial communication in the renal vasculature and the impact of drugs used clinically to treat hypertension. Current Opinion in Pharmacology 2019; 45: 49-56.
4. Johnson ML, Redmer, DA, Reynolds LP and Grazul-Bilska AT: Gap junctional connexin messenger RNA expression in the ovine uterus and placenta: effects of estradiol-17β-treatment, early pregnancy stages and embryo origin. Domestic Animal Endo 2017; 58: 104-12.
5. Hitzerd E, Broekhuizen M, Neuman RI, Colafella KM, Merkus D, Schoenmakers S, Simons SH, Reiss IK and Danser AJ: Human placental vascular reactivity in health and disease: implications for the treatment of pre-eclampsia. Current Pharma Design 2019; 25: 505-27.
6. Stanić Z: Curcumin, a compound from natural sources, a true scientific challenge-a review. Plant Foods for Human Nutrition 2017; 72: 1-12.
7. Hay E, Lucariello A, Contieri M, Esposito T, De Luca A, Guerra G and Perna A: Therapeutic effects of turmeric in several diseases: an overview. Chemico-Biological Interactions 2019; 108729.
8. Campbell MS and Fleenor BS: The emerging role of curcumin for improving vascular dysfunction: a review. Critical Reviews in Food Scie and Nut 2017; 58: 2790-99.
9. Perrone D, Ardito F, Giannatempo G, Dioguardi M, Troiano G, Lo Russo L, De Lillo A, Laino L and Lo Muzio: Biological and therapeutic activities, and anticancer properties of curcumin. Experimental and Therapeutic Medicine 2015; 10: 1615-23.
10. Tsuiji K, Takeda T and Li B: Inhibitory effect of curcumin on uterine leiomyoma cell proliferation. Gynecological Endocrinology 2011; 27: 512-17.
11. Cheng KK, Yeung CF, Ho SW, Chow SF, Chow AH and Baum L: Highly stabilized curcumin nanoparticles tested in an *in-vitro* blood-brain barrier model and in Alzheimer's disease Tg2576 mice. The AAPS J 2013; 15: 324-36.
12. Suresh K and Nangia A: Curcumin: pharmaceutical solids as a platform to improve solubility and bioavailability. Crystal Engineering Communications 2018; 20: 3277-96.
13. Kalyane D, Raval N, Maheshwari R, Tambe V, Kalia K and Tekade RK: Employment of enhanced permeability and retention effect (EPR): nanoparticle-based precision tools for targeting of therapeutic and diagnostic agent in cancer. Materials Science and Engineering C 2019; 98: 1252-76.
14. Gera M, Sharma N, Ghosh M, Huynh DL, Lee SJ, Min T, Kwon T and Jeong DK: Nanoformulations of curcumin: an emerging paradigm for improved remedial application. Oncotarget 2017; 8: 66680-98.
15. Sasaki Y, Goto H, Tohda C, Hatanaka F, Shibahara N, Shimada Y, Terasawa K and Komatsu K: Effects of curcuma drugs on vasomotion in isolated rat aorta. Biological and Pharmaceutical Bulletin 2003; 26: 1135-43.
16. Xu PH, Long Y, Dai F and Liu ZL: The relaxant effect of curcumin on porcine coronary arterial ring segments. Vascular Pharmacology 2007; 47: 25-30.
17. Ahn CM, Park BG, Woo HB, Ham J, Shin WS and Lee S: Synthesis of sulfonyl curcumin mimics exerting a vasodilatation effect on the basilar artery of rabbits. Bioorga and Medicinal Chemistry Lett 2009; 19: 1481-83.
18. Zhang H, Liu H, Chen Y and Zhang Y: The Curcumin-induced vasorelaxation in rat superior mesenteric arteries. Annals of Vascular Surgery 2018; 48: 233-40.
19. Dash JR and Parija SC: Spasmolytic effect of curcumin on goat ruminal artery is endothelium independent and by activation of SGC. Research in Vete Sci 2013; 95: 588-93.
20. Jandhyam H and Parija SC: Curcumin vasorelaxation in uterine artery of goat (*Capra hircus*) is mediated by differential activation of nitric oxide, prostaglandin I2, soluble guanylyl cyclase, and gap junction communication. Pharmacognosy Magazine 2019; 15: 495-01.
21. Jandhyam HL and Parija SC: Curcumin and nanocurcumin differentially activate K^+ channels in uterine artery of non-pregnant and pregnant *Capra hircus*. Annals of Phytomedicine 2018; 7: 165-72.
22. Stridh MH, Correa F, Nodin C, Weber SG, Blomstrand F, Nilsson M and Sandberg M: Enhanced glutathione efflux from astrocytes in culture by low extracellular Ca^{2+} and curcumin. Neurochemical Research 2010; 35: 1231-38.
23. Lai CS, Wu JC, Yu SF, Badmaev V, Nagabhushanam K, Ho CT and Pan MH: Tetrahydrocurcumin is more effective than curcumin in preventing azoxy-methane-induced colon carcinogenesis. Molecular Nutrition and Food Research 2011; 55: 1819-28.

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