Antihypertensive activity of Diethyl-4, 4'-dihydroxy-8, 3'-neolign-7, 7'-dien-9, 9'-dionate through increase in intracellular cGMP level and blockade of calcium channels (VDCC) and opening of potassium channel and in vivo models (SHRs and L-NAME induced hypertension)

Arjun Singh¹², Debabrata Chanda³, Arvind Singh Negi⁴

¹ISF College of Pharmacy, Moga-142001, Punjab, India, ²CSIR-Central Institute of Medicinal and Aromatic Plants, Lucknow, India, ³Molecular Bioprospection, CSIR-CIMAP, India, ⁴Medicinal Chemistry, CSIR-CIMAP, India

In the present study, the antihypertensive and vasorelaxant potential of neolignan1 (Diethyl-4,4&⁶#697;-dihydroxy-8,3&⁶#697;-neolign-7,7&⁶#697;-dien-9,9&⁶#697;-dionate) produced concentration dependent relaxation with pD₂ 5.16 ± 0.05 and Eₘₐₓ 96.97% ± 1.12%; n=16 in rat aorta and rat mesenteric artery with Eₘₐₓ 93.09% ± 1.38% and pD₂ 5.392 ± 0.04; n=8. The neolignan1 relaxation is independent of endothelium and is sensitive to ODQ ([1H-[1, 2, 4] oxadiazolo [4, 3-a] quinoxalin-1-one; a blocker of soluble guanylyl cyclase (sGC) which synthesizes cGMP (cyclic guanosine monophosphate), Potassium depolarizing solution (KCl [60 mM]; to explore the role of potassium channels) and their specific blockers such as TEA (BKCa), 4-AP, BaCl₂ and Glibenclamide in rat mesenteric artery and nifedipine 1 µM (Blocking VDCC in rat aorta) was used. ELISA analysis of treated arterial tissues showed significant concentration-dependent increase in cGMP level in treated tissues compared to control (neolignan1 10, 30 µM) and a synergistic increase in cGMP level rises 26.66 fold compared to control when used in combination with sildenafil 10 µM; a known inducer of cGMP level by selectively blocking cGMP specific phosphodiesterase 5. Our present study reports for the first time that neolignan1 produce relaxation in isolated rat aorta through increase in intracellular cGMP level. The ODQ resistant relaxation of neolignan1 is mediated by blockade of voltage dependent L-type calcium channel (VDCC) as observed in the experiment with CaCl₂ and potassium channel (BKCa). Effect of neolignans on hemodynamic parameters in SHR and chronic L-NAME treated Wistar rats (50 mg/kg/day for 6 weeks) were evaluated through non-invasive and invasive blood pressure method. Vehicle control groups received tap water only. Hemodynamic parameters studied in in-vivo evaluation showed significant improvements in both SHRs (in control conditions, 173±3.00 mmHg and 143 ± 2.00 mmHg after neolignan1 treatment) and L-NAME models (In control condition, SBP 164.3±3.64 mmHg (n=6) and 138.7 ± 4.06 mmHg (Neolignan1 30 mg/kg) and 140.4±5.46 (Neolignan1 100 mg/kg) after six weeks of treatment) and was found to be well tolerated by Swiss albino mice in toxicity study. The present study concludes that neolignan1 exhibited antihypertensive potential in rats through rise in intracellular cGMP, blockade of VDCC and BKCa.