

Title	PHOSPHODIESTERASE 5 INHIBITORY ACTIVITY AND VASODILATION EFFECT OF CURCUMIN AND ITS ANALOGS ON RAT PULMONARY ARTERY
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ABSTRACT

Phosphodiesterase 5 (PDE5) inhibitors can be used for pulmonary artery hypertension treatment as they have vasodilator effect on pulmonary artery. We aimed to study curcumin and its analogues for PDE5 inhibitory activity and vasorelaxant action on rat pulmonary arteries. Three natural curcumins (1-3) and six synthetic analogues (4-9) were tested for PDE5 and PDE6 inhibitory activities using an enzymatic radioassay. Their vasodilator effects were examined in rat isolated pulmonary arteries and aorta using an organ bath technique. Curcumins showed mild PDE5 inhibitory activity ($IC_{50}=18\mu M$) while its analogues 7 and 9 showed higher activity ($IC_{50}=4\mu M$). The structure-activity relationship indicated the importance of methoxyl group at *meta*-position of curcumin to PDE5 inhibition effect. However, only 1, 3, and 4 had selectivity for PDE5 over PDE6. All analogues possessed concentration-dependent vasorelaxant effect in pulmonary arteries ($EC_{40}=29-90\mu M$, maximum response=60-90%), while in aorta only small responses to most of the compounds (1-8) were found (maximum response<40%). Endothelial removal of pulmonary artery reduced vasodilator responses to demethoxycurcumin (2) and some analogues (5, 8, 9). Curcumin analogues are potential lead compounds to develop efficacious and selective pulmonary antihypertensives by acting on PDE5 or other pulmonary endothelial targets.