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BETULINIC ACID AMELIORATES ENDOTHELIUM-DEPENDENT RELAXATION IN L-NAME-INDUCED HYPERTENSIVE RATS BY REDUCING OXIDATIVE STRESS

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Objective Modern pharmacological studies reveal that betulinic acid (BA), the key active constituent of traditional Chinese cardiovascular herbs Zizyphi Spinosi semen, up-regulated endothelial nitric oxide synthase (NOS) and down-regulated NADPH oxidase, and our previous study shows that BA ameliorated the impairment of endothelium-dependent relaxation (EDR) induced by H_2O_2 in rat aortas. Here, we hypothesised that BA may attenuate endothelial dysfunction in hypertensive rats via its modulation of the oxidative stress and vascular NO pathway.

Methods Male Sprague–Dawley rats were injected with N^{ω}-nitro-L-arginine methyl ester hydrochloride (L-NAME) (15 mg/kg/day, intraperitoneal) for four weeks to induce

hypertension. After treatment with L-NAME for two weeks, rats with mean blood pressure >120 mm Hg measured by tail-cuff method were considered hypertensive and then injected with BA (0.8, 4, 20 mg/kg/day, intraperitoneal) for the last two weeks. The effect of BA on the tension of rat thoracic aortic rings was measured in an organ bath system. The levels of nitric oxide (NO), reactive oxygen species (ROS), and the activity of superoxide dismutase (SOD) and NOS in aortas were assayed.

Results (1) BA (0.1 to 100 μM) evoked a concentration-dependent relaxation in endothelium-intact normal rat aortic rings (the E_{max} reached 74.06±6.18%, and EC_{50} was 1.67 μM), which was significantly attenuated by pretreatment with L-NAME (100 μM) or methylene blue (MB, 10 μM), but not by indomethacin (10 μM). (2) Pretreatment with EC_{50} concentration of BA enhanced the acetylcholine (ACh)-induced EDR, the E_{max} increased from 70.74±6.66% to 85.39±7.16% ($p<0.01$), which was also markedly reversed by both L-NAME and MB. (3) The blood pressure in hypertensive rats induced increased to 135.22±5.38 mm Hg ($p<0.01$ vs control group), which was markedly attenuated by high dose of BA (106.49±7.28 mm Hg). (4) The ACh-induced EDR in hypertensive rat aortic rings was impaired, and the E_{max} fell to 23.65±6.0% ($p<0.01$ vs control group), which was markedly improved by chronic treatment with BA (0.8, 4 and 20 mg/kg/d) for two weeks (the E_{max} reaching 31.53±4.41%, 36.60±9.16% and 46.47±6.87%). (5) The increase of ROS level and the decrease of NO level, SOD and eNOS activities in hypertensive rat aortas were markedly inhibited by BA.

Conclusion BA decreased blood pressure and improved ACh-induced EDR in L-NAME-induced hypertension rats, which may be mediated by reducing oxidative stress and retaining the bioavailability of NO.