The Natural Product Zerumbone Suppresses Pressure Overload-Induced Cardiac Dysfunction by Inhibiting Cardiac Hypertrophy and Fibrosis

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Citation: *European Cardiology Review* 2021;16:e70. **DOI:** https://doi.org/10.15420/ecr.2021.16.PO14

Objectives: We assessed the hypothesis that zerumbone (ZER) , a major active terpene found in endemic wild ginger species, suppresses cardiac hypertrophy and fibrosis *in vitro* and *in vivo*.

Materials and methods: The effects of ZER on phenylephrine (PE)-induced hypertrophic and on transforming growth factor beta (TGF-β)-induced fibrotic responses were examined in primary cultured cardiomyocytes and fibroblasts from neonatal rats. Transverse aortic constriction model mice (n=6–10) were randomly divided into two groups and orally administered with ZER 20 mg/kg or vehicle for 8 weeks. Cardiac function was evaluated by echocardiography. Changes in cardiomyocyte surface area and degree of fibrosis were observed by histological analysis (HE and WGA staining). The total mRNA levels of the genes associated with hypertrophy and fibrosis were measured by qRT-PCR. Akt phosphorylation and protein expression of α-SMA were assessed by western blotting.

Results: ZER significantly suppressed PE-induced increases in cell size, ANF and BNP gene expression, and Akt phosphorylation in cardiomyocytes. TGF-β-induced increases in collagen synthesis, mRNA levels of POSTN and α-SMA, and protein expression of α-SMA were lower in the ZER-treated cultured cardiac fibroblasts. Echocardiography results showed that left ventricular fractional shortening was increased and wall thickness was reduced in the ZER group compared with the vehicle group. Histological analysis showed that pressure overload-induced cardiac hypertrophy and cardiac fibrosis were inhibited in the ZER group compared with the vehicle group.

Conclusion: These results suggest that zerumbone ameliorates pressure overload-induced cardiac dysfunction, at least in part by suppressing both cardiac hypertrophy and fibrosis. ❑