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Isoquercetin Improves Atherosclerosis in ApoE$^{-/-}$ Mice via the TNF-α/p38MAPK/NF-κB/RBP4 Pathway

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SUMMARY*. The aim was to evaluate the effect and mechanism of isoquercetin on atherosclerosis (AS). Twenty ApoE$^{-/-}$ mice were randomly divided into a) a model treatment group (tanshinone A) and b) a control group (C57BL/6J mice) with 10 mice in each group. Serum was obtained from tumour necrosis factor (TNF)-α mice and an automatic biochemical analyser detected serum TG, TC, HDL-C, and LDL-C levels based on the ELISA assay. Additionally, morphological aortic tissue changes were observed with hematoxylin and eosin (HE) staining. Furthermore, tumour necrosis factor α (TNF-α), mitogen activated protein kinase (p38MAPK) nuclear factor-κB (p38MAPK NF-κB) and retinol binding protein-4 (RBP-4) were quantified with the WB assay, while the reverse transcriptase polymerase chain reaction (RT-PCR) was used to detect the aortic TNF-α, NF-κB and RBP4 gene expressions. Compared with the NC group, TG, TC, and LDL-C levels in the serum of model group increased significantly ($P < 0.05$) and HDL-C levels significantly decreased ($P < 0.05$). Large plaque formation was visible in the lumen of aortic AS, while TNF-α, p38MAPK, NF-κB and RBP4 proteins and TNF-α, NF-κB and RBP4 messenger ribonucleic acid (mRNA) levels increased significantly ($P < 0.05$). Compared with the model group, the levels of TG, TC and LDL-C in the isoquercetin group were significantly decreased ($P < 0.05$), the HDL-C levels increased significantly ($P < 0.05$), the aortic lumen of the AS plaque area decreased significantly, while the TNF-α, p38MAPK, NF-κB, RBP4 protein and corresponding mRNA levels were reduced significantly ($P < 0.05$). In conclusion, isoquercetin could regulate blood lipid and anti-AS effects. Its mechanism may participate in the regulation of the TNF-α/p38MAPK/NF-κB/RBP4 signalling pathway.

RESUMEN. El objetivo fue evaluar el efecto y el mecanismo de la isoquercetina sobre la aterosclerosis (AS). Veinte ratones ApoE$^{-/-}$ se dividieron aleatoriamente en a) un grupo de tratamiento modelo (tanshinona A) y b) un grupo de control (ratones C57BL/6J) con 10 ratones en cada grupo. Se obtuvo suero de ratones con factor de necrosis tumoral (TNF)-α y un analizador bioquímico automático detectó los niveles séricos de TG, TC, HDL-C y LDL-C con base en el ensayo ELISA. También se observaron cambios morfológicos en el tejido aórtico con tinción con hematoxilina y eosina (HE). Además, el factor de necrosis tumoral α (TNF-α), el factor nuclear de la proteína quinasa activada por mitógeno (p38MAPK)-κB (p38MAPK NF-κB) y la proteína de unión al retinol-4 (RBP-4) se cuantificaron con el ensayo WB, mientras que la reacción en cadena de la polimerasa de transcriptasa inversa (RT-PCR) se usó para detectar las expresiones génicas aórticas de TNF-α, NF-κB y RBP4. En comparación con el grupo NC, los niveles de TG, TC y LDL-C en el suero del grupo modelo aumentaron significativamente ($P < 0.05$) y los niveles de HDL-C disminuyeron significativamente ($P < 0.05$). Se observó una gran formación de placa en la luz de la EA aórtica, mientras que los niveles de TNF-α, p38MAPK, NF-κB y RBP4 y los niveles de ácido ribonucleico mensajero (ARNm) de TNF-α, NF-κB y RBP4 aumentaron significativamente ($P < 0.05$). En comparación con el grupo modelo, los niveles de TG, TC y LDL-C en el grupo isoquercetina disminuyeron significativamente ($P < 0.05$), los niveles de HDL-C aumentaron significativamente ($P < 0.05$), la luz aórtica del área de la placa AS disminuyó significativamente, mientras que la proteína TNF-α, p38MAPK, NF-κB, RBP4 y los niveles de ARNm correspondientes se redujeron significativamente ($P < 0.05$). En conclusión, la isoquercetina podría regular los lípidos en sangre y los efectos anti-AS. Su mecanismo puede participar en la regulación de la vía de señalización TNF-α/p38MAPK/NF-κB/ RBP4.

KEY WORDS: atherosclerosis, inflammation, isoquercetin, RBP4, TNF-α.

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