CYCLOSPORIN - A DEPENDENT EFFECT OF PLANTAGO MAJOR L. POLYPHENOLS ON LIVER MITOCHONDRIAL MEGAPORE

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ABSTRACT

The pathological opening of the mitochondrial permeability transition pore (mPTP) leads to cell death. This study investigated the effects of glucopyr-T and xylopyr-T polyphenolic compounds isolated from Plantago major L. on the mPTP of rat liver mitochondria in a cyclosporin A–dependent manner. The results indicate that these compounds are promising modulators of mPTP activity.

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According to literature data, the cyclosporin A (CsA)–sensitive mitochondrial permeability transition pore (mPTP) plays a crucial role in various physiological and pathological processes. An excessive accumulation of Ca^{2+} ions together with the action of different stress factors induces a transition of the mPTP from its normal physiological state to a pathologically open conformation. This leads to mitochondrial dysfunction, swelling of mitochondria, and disruption of the outer mitochondrial membrane. As a result, cytochrome c and other pro-apoptotic proteins localized in the mitochondrial intermembrane space are released into the cytosol. These events subsequently activate apoptotic and necrotic pathways, ultimately resulting in cell death. In recent years, increasing attention has been focused on the modulation of the mitochondrial permeability transition pore by biologically active compounds, particularly polyphenols.

Materials and Methods: Hexahydroxydiphenoyl-1-(O-β-D-glucopyranoside)-2-(O-4-D-galloyl-β-D-glucopyranoside) (glucopyr-T) and hexahydroxydiphenoyl-1-(O-2-O-galloyl-β-D-glucopyranoside)-1-(O-β-D-xylopyranoside) (xylopyr-T), isolated from Plantago major L., were investigated for their effects on the mitochondrial permeability transition pore (mPTP) of rat liver mitochondria in a cyclosporin A (CsA)–dependent manner. The study was

performed using outbred white rats weighing 180–200 g. Liver mitochondria were isolated by differential centrifugation. Mitochondria were incubated in a medium containing (mM): KCl 120, succinate 5, KH_2PO_4 1, Ca^{2+}–EGTA buffer 0.02, and Tris–HCl 20 (pH 7.2). The mitochondrial protein concentration was adjusted to 0.3–0.4 mg/mL. To evaluate CsA-dependent modulation of mPTP, cyclosporin A was used at its half-maximal inhibitory concentration (IC_{50}) of 0.23 μM.

Results: The addition of Ca^{2+} to the incubation medium induced the opening of the mitochondrial permeability transition pore (mPTP) in rat liver mitochondria, which was manifested by mitochondrial swelling. Cyclosporin A significantly inhibited Ca^{2+}-induced mPTP opening, confirming the CsA-sensitive nature of the pore. The polyphenolic compounds glucopyr-T and xylopyr-T isolated from Plantago major L. demonstrated a modulatory effect on mPTP activity. In the presence of cyclosporin A, both compounds attenuated mitochondrial swelling, indicating their involvement in the regulation of CsA-sensitive mPTP opening. The observed effects suggest that glucopyr-T and xylopyr-T contribute to the stabilization of mitochondrial membrane integrity under Ca^{2+}-induced stress conditions

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