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Molecular characterization of the protective mechanism of coumarin derivatives against oxidative stress in rat liver

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By

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بسم الله الرحمن الرحيم

﴿ قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيمُ ﴾

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ABSTRACT

Abeer Ibraheem Mogadem. Molecular characterization of the protective mechanism of coumarin derivatives against oxidative stress in rat liver. Department of Biochemistry, Faculty of Science, Ain Shams University.

Natural products, for a long time, have been recognized as an invaluable source for the most active components of medicines for preventing and treating many diseases including liver diseases. In recent years, herbal medicines derived from plant extracts have become a subject of interest because of their beneficial effects on human health. Among various phytochemicals, polyphenols have attracted much attention because of their broad range of biological activities related to medicinal uses. One such phytochemical is coumarin (1,2-benzopyrone), a phenolic compound derived from Cinnamon bark. The phenolic nature of the compound itself proves it to be a potent antioxidant. The present study aims to investigate the protective effects of two coumarin derivatives, umbelliferone and daphnetin, against carbon tetrachloride (CCl_4)-induced oxidative stress and liver damage in rats and elucidate the underlying mechanism. For control purposes, a side-by-side comparison with hesperidin, an antioxidant flavonoid known for its protective effect against CCl_4-induced hepatocyte injury, was done. Treatment of male Swiss albino rats with umbelliferone, daphnetin or hesperidin, along with CCl_4, significantly improved the CCl_4-

induced elevations in liver enzyme activities as well as lipid profile and kidney function parameters. In addition, the two compounds alleviated the increased level of lipid peroxidation and increased the level of total antioxidant activity. On the other hand, the investigated compounds were able to prevent the CCl_4-induced histopathological alterations of the liver tissues.

The molecular mechanism underlying the protective effect of these compounds was then investigated using western blot analysis, real-time quantitative PCR and enzyme activity assay. Similar to hesperidin, both umbelliferone and daphnetin, induced the nuclear translocation and activation of the nuclear factor erythroid 2 (NF-E2)-related factor 2 (Nrf2), thereby inducing the expression and activity of the cytoprotective heme oxygenase-1 (HO-1). These results suggest that umbelliferone and daphnetin have good potential as therapeutic agents via their ability to attenuate oxidative stress by activating Nrf2-mediated HO-1 induction.

Key words: Coumarin, umbelliferone, daphnetin, carbon tetrachloride, antioxidant, heme oxygenase-1 (HO-1), nuclear factor erythroid 2 (NF-E2)-related factor 2 (Nrf2).

CONTENTS

LIST OF ABBREVIATIONS

ADP	adenosine diphosphate
ADPS	N-ethyl-N-propyl-m-anisidine
Akt	serine/threonine kinase (Protein Kinase B; PKB)
ALT	alanine transaminase
AMP	adenosine monophosphate
AMV	avian myeloblastosis virus
ANOVA	one-way analysis of variance
ALP	alkaline phosphatase
ARE	antioxidant response element
AST	aspartate transaminase
ATP	adenosine triphosphate
BCA	bicinchoninic acid
BSE P	bile salt efflux pump
cAMP	cyclic adenosine monophosphate
cDNA	complementary deoxyribonucleic acid
cGMP	cyclic guanosine monophosphate
CNC	cytoskeleton binding protein Kelch-like erythroid
CYP	cytochrome P
DAPH	daphnetin
DEPC	diethylpyrocarbonate
DILI	drug-induced liver injury
DISC	death-inducing signaling complex
DNA	deoxyribonucleic acid
dNTP	deoxyribonucleotide
DTT	dithiothreitol