Modulation Of Resistance To Sorafenib In Human Hepatocellular Carcinoma Cell Line(s) Using Phytochemical(s)

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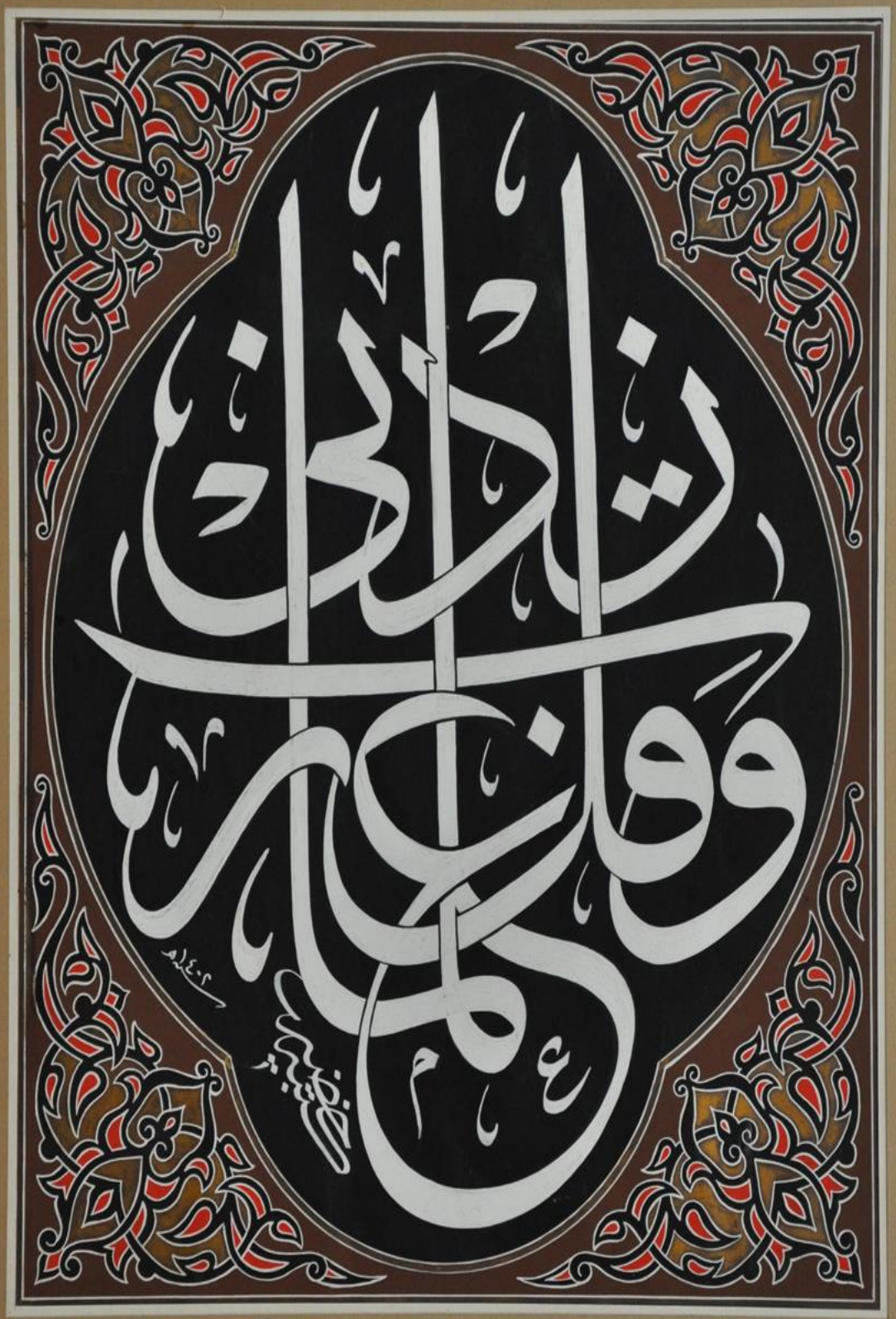

Dedication

This work is especially dedicated to the soul of my beloved grandfather, **Abd El-Sattar Alady**. *I am really indebted to you, your prayers have finally come true my dear grandfather.*

Mai Abd El-Mageed

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Abstract

Abstract

Sorafenib is the only chemotherapeutic agent currently approved for the treatment of unresectable hepatocellular carcinoma (HCC). However, poor response rates have been widely reported. Indole-3-carbinol (I3C) is a potential chemopreventive dietary phytochemical. The present study aimed to explore the potential chemomodulatory effects of I3C on sorafenib in HepG2 cells as well as the possible mechanisms underlying this modulation. HepG2 cells were treated with different concentrations of sorafenib and I3C. Concentration-survival curves were generated and the concentration of I3C which inhibited the growth of cells by 5% was selected for studying the modulatory effects exerted by I3C on sorafenib cytotoxicity. The effect of the combination on apoptosis, angiogenesis and invasiveness were investigated. Moreover, the involvement of NADPH oxidase-1 (NOX-1) enzyme was explored. Flowcytometric DNA-ploidy analysis was also carried. Indole-3-carbinol has been shown to enhance the cytotoxic activities of sorafenib in HepG2 cancer cells. This could be partially attributed to increased apoptosis by augmenting the activity of caspase-8 and -3 and decreasing the angiogenic potentials via decreasing the expression of p-ERK, HIF-1α and VEGF. The combination had a suppressive effect on epithelial-mesenchymal transition (EMT) by increasing the expression of E-cadherin and decreasing the expression of snail and clusterin. Increased NOX-1 expression was also observed which might indicate the involvement of reactive oxygen species (ROS) in I3C chemomodulatory effects. Additionally, the combination induced cell cycle arrest at the G_0/G_1 phase. It is worth mentioning that the combination had no effect neither on the level of p-Akt nor on the mRNA level of the EGFR. In conclusion, these findings provide evidence that I3C chemosensitizes HCC HepG2 cells to sorafenib anti-cancer activity.

Keywords: *sorafenib, indole-3-carbinol, hepatocellular carcinoma, apoptosis, angiogenesis, NOX-1.*

List of Contents

List of Abbreviations

AhR	Aryl hydrocarbon receptor
Akt	Protein kinase B
ANOVA	One way analysis of variance
Apaf-1	Apoptotic protease activating factor 1
ATCC	American Type Culture Collection
Bax	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma-2
Bcl-xL	B-cell lymphoma-extra large
CDK	Cyclin dependent kinase
CLDs	Chronic liver diseases
Ct	Cycle threshold
DFG	Asp-Phe-Gly
DIM	3,3'-diindolylmethane
DMSO	Dimethyl sulfoxide
dNTP	Deoxyribonucleotide
E-cadherin	Epithelial-cadherin
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
eIF4E	Eukaryotic translation initiation factor 4E
EMT	Epithelial-mesenchymal transition
ERK	Extracellular signal-regulated kinase
FAK	Focal adhesion kinase
FBS	Fetal bovine serum