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Polyphenols act synergistically with doxorubicin and etoposide in leukemia cell lines

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Background: The study aimed to assess the effects of polyphenol when used in combination with doxorubicin and etoposide, and determine whether polyphenols sensitized leukemia cells, causing cell-cycle arrest, inhibition of cell proliferation and induction of apoptosis. The rationale being that in some solid tumors, polyphenols have been shown to sensitize cells to apoptosis and/or cell-cycle arrest, potentially reducing doses, whilst maintaining efficacy.

Method: Quercetin, apigenin, emodin, rhein, cis-stilbene were investigated alone and in combination with etoposide and doxorubicin in two lymphoid (Jurkat and CCRF-CEM) and two myeloid (THP-1 and KG-1a) leukemia cells lines. Measurements were made of ATP levels (CellTiter-Glo®assay), cell-cycle progression (propidium iodide (PI) staining and flow cytometry) and apoptosis (NucView-caspase-3 assay and Hoechst 33342/PI staining). The effects of these combinations on the apoptotic pathway (caspases-3, -8 and -9 Glo®luminescent assays), glutathione levels (GSH-Glo™-glutathione assay and cell tracker™ green-5-chloromethylfluorescein-diacetate-glutathione staining) and DNA damage (Alexa Fluor® 647 Mouse anti-H2AX staining) were also determined.

Results: Doxorubicin and etoposide in combination with polyphenols synergistically reduced ATP levels, induced apoptosis and increased S- and/or G2/M-phase cell-cycle arrest in lymphoid leukemia cell lines. In the myeloid cell lines, doxorubicin and etoposide displayed differential effects. Doxorubicin had a synergistic or additive effect when combined with quercetin, apigenin, emodin and cis-stilbene, but had an antagonistic effect when combined with rhein. Combination treatment caused a synergistic down regulation of glutathione (GSH) levels and increased DNA damage, driving apoptosis via caspase 8 and 9 activation. However, in myeloid cells were an antagonist effect this was associated with an up-regulation of GSH levels, a reduction in DNA damage and apoptosis.

Conclusion: Doxorubicin and etoposide activity can be enhanced by polyphenols, particularly in lymphoid leukemia cells, although effects were strongly dependent on type of cell line, with some interactions were antagonistic in myeloid cell lines.

Biography

Amani Mahbub has completed MSc in Biomedical Basis of Disease in 2010 and PhD in Anti-Cancer Potential of Polyphenols in Treatment of Leukemia in 2015 at the Sheffield Hallam University of Biomedical Research Centre – Cancer Research, Sheffield, UK. She has been interested in investigating the biological effects of a number of nutraceutical compounds such as polyphenols alone and in combination with chemotherapies on the induction of apoptosis, reduced cell proliferation and signalling pathways that involved in the pathogenesis of leukaemias. She also has four published papers in the *Journal of Pathology* (2012), the *Journal of Anti-cancer Agents in Medicinal Chemistry* (2013) and recently two in Nature (2015), and two more papers under publications. In addition, she was awarded, the Alastair Currie prize for the best poster presentation at the Pathological Society of Great Britain & Ireland Conference in 2012, Sheffield, UK; and Best Poster Prize at 4th International Conference on Blood Malignancies & Treatment, 2016 in Dubai, UAE. Currently, she is working at Umm Al-Qura University in Laboratory Medicine of Applied Medical Sciences College – Pathology Department, Makkah, KSA.

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