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Glutathione is key to the synergistic enhancement of doxorubicin and etoposide by polyphenols in leukaemia cell lines.

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Abstract (600 word limits)

Recently published in Nature: Cell Death and Discovery, Mahbub et al 2015 have demonstrated that polyphenols can synergistically enhance the action of the topoisomerase II inhibitors: doxorubicin and etoposide in leukaemia cells. A reduction of glutathione (GSH) was strongly associated with sensitising cells to the pro-apoptotic effects of polyphenols when used in combination with doxorubicin or etoposide. Importantly, when polyphenols and topoisomerase II inhibitors were combined, it was possible to induce a synergistic decrease in cell proliferation (measured as ATP levels), cell-cycle arrest and induction of apoptosis in leukaemia cell lines (Mahbub et al, 2015). Five polyphenols that had been previously shown to induce apoptosis in leukaemia cells (quercetin, apigenin, emodin, rhein and cis-stilbene) (Mahbub et al, 2013) were combined with doxorubicin or etoposide in two lymphoid (CCRFCEM and Jurkat) and two myeloid (THP-1 and KG1a) cell lines. These cell lines were selected as they had been identified as the most sensitive and most resistant to polyphenol-induced apoptosis; (Mahbub et al, 2013) in addition, two non-tumour control haemopoietic stem cells (HSCs) (CD133+ and CD34+) were investigated. In the two lymphoid cell lines, it was shown that all studied polyphenols when used in combination with each topoisomerase II inhibitor caused a synergistic or additive decrease in cell proliferation, G2M or S phase cell-cycle arrest and apoptosis (Mahbub et al, 2015). This was associated with a synergistic/additive reduction of GSH levels, increased caspase 3, 8 and 9 activity, and DNA damage (Mahbub et al, 2015). In the non-tumour control HCS cells the polyphenols had a protective effect; following combination treatment with the topoisomerase II inhibitors there was an increase in cell proliferation and a decrease in apoptosis (Mahbub et al, 2015). In myeloid cell lines there was a more differential effect: when quercetin and apigenin were used in combination with each topoisomerase II inhibitor, there was a synergistic/additive decrease in cell proliferation, cell accumulation in G2M and S phase of the cell cycle and an increase in apoptosis (Mahbub et al, 2015). This was associated with decreased GSH levels, increased caspase 3, 8 and 9 activity, and DNA damage (Mahbub et al, 2015). However, when emodin, rhein and to a lesser extent cis-stilbene, were used in combination with each topoisomerase II inhibitor, there was an antagonistic increase in ATP, an inhibition of apoptosis and no cell-cycle arrest (Mahbub et al, 2015). This was associated with an elevation of GSH levels and reduction of caspase 3, 8 and 9 activities, and little or no DNA damage (Mahbub et al, 2015). Examination of basal GSH levels showed that the levels in the lymphoid leukaemia cell lines were significantly lower than those of the non-tumour control HSCs and myeloid cell lines. This could explain why the lymphoid cell lines are more susceptible to polyphenol/topoisomerase II inhibitor treatment compared with the myeloid cell lines. The identification of GSH as a key player in the induction of apoptosis was first

highlighted by Franco and Cidlowski in 2009 (Franco et al, 2009). Initially, GSH depletion was considered as a by-product of ROS production during mitochondrial permeability during apoptosis via the intrinsic route; (Franco et al, 2009) however, it is now clear that although mitochondrial ROS formation is crucial for apoptosome formation; (Sato et al, 2004) reduced GSH is necessary for normal cells to undergo apoptosis, independently of ROS (Franco et al, 2007). This led to the suggestion that polyphenol-mediated decrease in intrinsic GSH or efflux can sensitise lymphoid cancer cell lines to topoisomerase II inhibitors, which results in the synergistic and additive induction of apoptosis. The results of Mahbub et al (2015), raise the possibility of a similar effect in myeloid malignancies treated with topoisomerase II inhibitors, in that dietary polyphenols may prevent etoposide/doxorubicin-induced antitumour activity. The mechanism of action of polyphenolmediated antagonism of topoisomerase II inhibitors is unclear. However, it is known that GSH is contra-indicated for other chemotherapy agents, such as for cisplatin, where GSH supplementation inhibits the action of cisplatin. However, GSH-mediated depletion appears unrelated to cisplatin insensitivity in myeloid leukaemia cell Lines (Amran et al, 2005). This is, however, in contrast to most other tumour models, suggesting that alternate multi-drug resistance mechanisms may be a feature of myeloid leukaemia cell lines. Similarly, recent work has shown that antioxidants can increase the metastasis of melanoma in mice, (Le Gal et al, 2015) which raises the possibility that in some cancer types, polyphenols other antioxidants could be detrimental. Thus, it is fundamental to tailor any treatment, be it with novel antitumour agents such as polyphenols or standard chemotherapy, to the specific cancer types and investigate any possible treatment interactions.

Biography (200 word limit)

Amani Mahbub, Saudi have completed MSc of Biomedical Basis of Disease in 2010 and PhD of 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 is 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 have 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). In addition, she was awarded three prizes: (1) The Alastair Currie prize for the best poster and presentation at the Pathological Society of Great Britain & Ireland Conference in 2012, Sheffield, UK; (2) Best poster prize for research entitled: Polyphenols Act Synergistically with Doxorubicin and Etoposide in leukaemia cell lines at the 4th International Conference on Blood Malignancies and Treatment: 18th -19th April (2016), Dubai –UAE; (3) Best poster award for research entitled: Polyphenols Act Synergistically with Doxorubicin and Etoposide in Leukaemia cell lines at the 14th World Cancer and Anti-Cancer Therapy Convention and that held in Nov 21-23, 2016 in Dubai, UAE. Currently, She is working as Assistant Professor in Pathology and the Vice Head of Laboratory Medicine Department in Faculty Applied of Medical Sciences– Umm Al-Qura University, Makkah, KSA.

References

➢ Mahbub AA et al. Nature - Cell Death Discov 2015.
➢ Mahbub AA et al. Anticancer Agents Med Chem 2013; 13: 1601–1613.

➢ Franco R et al. Cell Death Differ 2009; 16: 1303–1314.
➢ Sato T et al. J Immunol 2004; 173: 285–296.
➢ Franco R et al. J Biol Chem 2007; 282: 30452–30465.
➢ Amrán D et al. Biochim Biophys Acta 2005; 1743: 269–279. (Amran et al, 2005)
➢ Le Gal K et al. Sci Transl Med 2015; 7: 308.

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