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The Anti-Cancer Potential of Polyphenols in the Treatment of Leukemia

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Leukaemia is a complex disease affecting all blood cell lineages. It affects millions of people worldwide each year and mortality rates are high, despite considerable improvements in treatment. Thus, new therapies for leukemia are urgently needed to improve leukemia patients' health and survival. Since polyphenols exert pro-apoptotic effects in solid tumours, our study investigated the effects of polyphenols in Hematological malignancies. Methods: The effects of eight polyphenols (quercetin, chrysin, apigenin, emodin, aloe-emodin, rhein, cis-stilbene, and trans-stilbene) was studied on cellular proliferation, the induction of apoptosis and cell cycle progression in four lymphoid (JURKAT, MOLT-3, CCRF-CEM and U937) and four myeloid (HL-60, THP-1, K562 and KG-1a) leukaemia cells lines, together with normal haematopoietic control cells (CD34+ HSC and CD133+ HSC) from cord blood. Further to this, an investigation was made of the effects of the most promising polyphenols used in combination with five standard chemotherapeutic agents (etoposide, doxorubicin, methotrexate, 6mercaptopurine, and 5-fluorouracil). For this polyphenol and chemotherapy combination work, four leukemia cells lines were used: the two most sensitive (JURKAT and CCRFM-CEM) and two most resistant (KG1a and THP-1) to polyphenol treatment. Subsequently, an investigation was undertaken to identify potential mechanisms of action of these polyphenols when used alone and in combination with chemotherapeutics. The extrinsic and intrinsic apoptotic pathways were investigated together with effects on glutathione levels and DNA damage. Results: Emodin, quercetin, and cis-stilbene were the most effective polyphenols at decreasing cell viability and inducing apoptosis. Lymphoid cell lines were normally more sensitive to polyphenol treatment compared to myeloid cell lines; however, those myeloid (KG-1a and K562) cell lines which were most polyphenol resistant; were however affected by emodin and quercetin at micromolar treatment doses. Non-tumour cells were less sensitive to all polyphenols compared to the leukemia cells. Mechanistically, most polyphenols alone depleted glutathione (GSH) levels associated with a direct activation in caspase 8 and caspase 9 in leukemia cell lines at 24 h. Polyphenols also had differential capacities to induce DNA damage in the leukemia cell lines. Polyphenols acted synergistically in lymphoid cell lines and differently in myeloid cell lines producing either synergistic, additive, competitive antagonistic or antagonistic effects; when they were combined with topoisomerase inhibitor agents (etoposide and doxorubicin). In contrast, they worked antagonistically with anti-metabolites agents (methotrexate and 6-mercaptopurine) in both lymphoid and myeloid leukaemia cell lines. Mechanistically the synergistic induction of apoptosis observed following the combination of polyphenols with chemotherapeutic agents was caused by the direct activation of intrinsic or/ and extrinsic apoptotic pathway through the up-regulation of caspase 8 or caspase 9 within the lymphoid and myeloid leukaemia cell line. Furthermore, it has been shown the synergistic effects observed when polyphenols and chemotherapy agents were combined was correlated with down regulation of GSH levels and an induction of DNA damage which drove apoptosis. Alternatively, where there was an antagonist effect, there was an upregulation of GSH levels, a reduction in DNA damage and the level of apoptosis. Conclusions: These findings demonstrate that polyphenols induce apoptosis and arrest cell cycle in leukemia cell lines which could translate to anti-cancer activities in leukemia, although the effects were dependant on polyphenol type and origin of the cell line investigated. Importantly, the differential sensitivity of emodin, quercetin, and cis-stilbene between leukemia and normal cells suggests that polyphenols are potential therapeutic agents for leukemia. Furthermore, this study concluded that the efficacy of standard chemotherapeutic agents was differentially modulated by polyphenols, producing either synergistic, additive or competitive antagonistic/antagonistic effects, which was dependent on the type of polyphenol, chemotherapy agent and cell line. Interestingly the study showed that synergistic or antagonistic effects observed following the combination treatments were strongly dependent on the modulation of glutathione levels in association with the formation of γ-H2AX nuclear foci and DNA damage in leukemia cell lines.

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