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Bergamottin, natural furanocoumarin in grape fruit juice, chemosensitize tumors for chemotherapeutic agents and induces apoptosis through inhibition of STAT3 signaling pathways

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Background: Signal transducers and activator of transcription 3 (STAT3) activity is related to the cell growth, survival, proliferation, metastasis, and angiogenesis of various cancer cells, and that determined inhibitory effect in several studies.

Objective: It was investigated whether bergamottin (BGM) exerts its anticancer effect through modulation of STAT3 activation pathway in multiple myeloma (MM).

Methods: The effect of BGM on STAT3 activation, associated protein kinases, STAT3-regulated gene products, cellular proliferation, and apoptosis was examined.

Results: It was found that BGM in grape fruit juice had inhibitory effect on STAT3 in MM cells. The suppression was mediated through the inhibition of phosphorylation of c-Src, Janus-activated kinase 1 (JAK1), and Janus-activated kinase 2 (JAK2). Pervanadate reversed the BGM induced down-regulation of STAT3 activation, suggesting the involvement of a protein tyrosine phosphatase (PTP). Furthermore, BGM induced the expression of the tyrosine phosphatase SHP-1, and gene silencing of the SHP-1 by small interfering RNA, abolished the ability of BGM to inhibit STAT3 activation, suggesting a critical role for SHP-1 in the action of BGM. BGM has down regulated the expression of STAT3-regulated gene products such as COX-2, VEGF, Cyclin D1, Survivin, IAP-1, Bcl-2, and Bcl-xl. This correlated with an increase in apoptosis as indicated by an increase in the sub-G1 arrest and caspase-3 induced PARP cleavage. Also, this agent significantly potentiated the apoptotic effects of bortezomib and thalidomide in MM cells.

Conclusion: Obtained results suggest that BGM is a novel blocker of STAT3 activation that may have a potential in chemoprevention of MM cells and other cancers.

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