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Anticancer effects of lipid encapsulated Bilberry GRP94 protein and prosurvival autophagy, the Achilles heel on a novel pre-clinical model for imaging cancer-associated dormancy.

Introduction: The interplay between tumour cell intrinsic and extrinsic factors is critical in determining the outcome of cancer therapy. Recent studies indicate that pre-clinical and in vivo models of dormant cancer cells have been successfully utilized to delineate the mechanisms underlying dormancy. However, the lack of animal models of dormant cancer cells is a major limitation. We aimed to identify and develop clinically relevant novel strategies to suppress or prevent the emergence of metastasis.

Methods: Rapidly accumulating laboratory and clinical research evidence indicates that anthocyanins have anticancer activity and more intriguing, the evaluation of bilberry anthocyanins as chemo-preventive agents is progressing. These applications are collectively due to the anthocyanins up-regulating tumour suppressor genes, inducing apoptosis in cancer cells, repairing and protecting genomic DNA integrity, which is important in reducing age-associated oxidative stress, as well as improving neuronal and cognitive brain function. Bilberry genomic DNA integrity, which is important in reducing age-associated oxidative stress, as well as improving neuronal and cognitive brain function.

Results: A concentration of 0.006 mg/50 mL of Bilberry NNS was used to study the apoptotic/cytotoxic effects on K562 cancer cells. Flow cytometric fluorescent quantification of the uptake of Propidium Iodide in a special cell viability formulation into dead K562 cells was used to determine the effects of Bilberry on the viability of K562 cells. The concentrations of Bilberry that showed the highest levels of percentage inhibition, relative to the control populations, were biphasic, showing 60–70% inhibition between 0.018–1.14 mg/ml (n=6) and 60% inhibition at 80 mg/ml. The lowest % inhibition (30%) occurred at 40 mg/ml. The LD50 was determined to be 0.01–0.04 mg/ml of Bilberry per 10% of cell culture exposure. At 48 hr. incubation, the highest % inhibition was only 27%, suggesting a long-term apoptotic event being involved. These levels, which showed direct cytotoxic effects, were 10 times lower than what is required for the Bilberry that is not encapsulated. The 10 fold increase in bioavailability with the Bilberry NNS and its water solubility show the feasibility of using Bilberry NNS in cancer patient clinical trials.

Conclusions: The evaluation of Bilberry in pre-clinical and in vivo models of dormant cancer cells has been successfully utilized to delineate the mechanisms underlying dormancy. However, the lack of animal models of dormant cancer cells is a major limitation. We aimed to identify and develop clinically relevant novel strategies to suppress or prevent the emergence of metastasis.