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Flavonol-enriched fraction from *Vaccinium macrocarpon* fruit inhibits matrix metalloproteinase-2, matrix metalloproteinase-9 and urokinase-type plasminogen activator expression in human prostate cancer cells *in vitro*

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ABSTRACT:

Background: Prostate cancer, amongst other cancer types has a genetic and environmental component, which can contribute to prostate cancer development and progression. *Vaccinum macrocarpon* (American cranberry) is a botanical that contains several phytochemicals which have been suggested to play a role in preventing cardiovascular disease, cancer, and urinary tract infections as well as in the maintenance of oral health.

Context and purpose of this study: This investigation evaluated the effects of a flavonol-enriched fraction (FL) from the American cranberry (*Vaccinium macrocarpon*) containing quercetin and myricetin glycosides on matrix metalloproteinase (MMP) and urokinase-type plasminogen activator (uPA) activities and their associated regulatory proteins in DU145 human prostate cancer cells *in vitro.*

Results: A flavonol-enriched fraction (FL) was prepared from *Vaccinium macrocarpon* berries and the effect of this fraction on prostate cancer cell behaviour was assessed using biochemical and molecular approaches including cytotoxicity assays and Western blot analysis to determine protein expression. Cranberry FL decreased cellular viability of DU145 cells at a concentration of 25 ug/ml by 20% after 6 hours of treatment. Further investigations determined that associated with this cytotoxicity, cranberry FL decreases matrix metalloproteinase (MMP) (specifically MMP-2 and MMP-9) activity and urokinase plasminogen activator (uPA) activity through effects on specific temporal MMP regulators and uPA regulators and by affecting either the phosphorylation status and/or expression of specific MAP kinase, PI-3 kinase, NF-kB and AP-1 pathway associated proteins.

Conclusion: This study demonstrates, for the first time, the ability of *Vaccinium macrocarpon* flavonols to modulate cellular pathways associated with migration, invasion, and proliferation, suggesting that cranberry (*Vaccinium macrocarpon*) is a viable candidate for further research as a natural product that may protect against certain cancers.

Key Words: *Vaccinium macrocarpon* , matrix metalloproteinases, urokinase, anti-cancer activity