



### Susceptibility of leukemia cells to synergistic treatment with vitamin C and select flavonoids

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Ascorbic acid is a well-known antioxidant that has been used worldwide as a dietary supplement. However, in recent years it has given promising results as an anticancer agent, especially when administered intravenously in high doses.<sup>1,2</sup> Another potent antioxidant group that has been studied are the flavonoids. These have shown anti-inflammatory and anti-proliferative properties in some cancer cells. We demonstrate the synergy between selected flavonoids and ascorbic acid, especially with curcumin and myricetin, in inducing cell death in selected leukemia cell lines. It was further confirmed that these combinations showed little toxicity to healthy primary human *peripheral blood mononuclear cells* (PBMCs).

Studies have shown a significant loss in ten eleven translocation (TET2) enzymes in leukemia cells leading to loss in 5-hydroxymethylcytosine (5hmc levels). Increasing the level of 5hmc would help to restore TET2 levels, which promotes DNA demethylation, differentiation, and subsequent cell death by activating tumour suppressing genes. Research has shown that ascorbic acid helps to promote this. In light of this, combination treatment of ascorbic acid with select flavonoids was tested identify if 5hmc levels were further increased. This turned out not to be the case.<sup>3,4</sup>

Using tethered bilayer lipid membranes in conjunction with electrical impedance spectroscopy, cell death via membrane disruption as a result of these compounds was discounted. Instead it was identified that these combinations are inducing cell death via an apoptotic pathway. To identify the relevant pathway, we present data on *reactive oxygen species* (ROS) production following combination treatment, as well as determining any mitochondrial membrane potential changes. It is hoped that a better understanding of these mechanisms would help develop effective, low-cost combination therapy for the treatment of leukemias in resource-poor countries.

#### References

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