May apple inspires new anti-tumour compounds that trigger preferential death of cancer cells

Mayapples (*Podophyllum peltatum)* are woodland plants, typically growing across most of the eastern United States and southeastern Canada. All the parts of the plant are poisonous even the leaves and the root. Mayapple contains podophyllotoxin which is highly toxic if consumed internally, thus it can only be used externally as a topical medicine. Podophyllotoxin is used on the skin for the treatment of external warts, caused by some types of the human papillomavirus (HPV). It is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system. Modification of podophyllotoxin chemical structure leads to semisynthetic derivatives such as etoposide and teniposide. These derivatives are less toxic than podophyllotoxin so they can be administered internally. Currently, they are used either alone or in combination with other therapies as anti-tumour agents for the treatment of a variety of malignancies including lung cancer, lymphoma and leukaemia. Unfortunately, there are still some drawbacks associated with these agents such as the metabolic inactivation of one thermodynamically unstable ring in their chemical structure. This metabolic inactivation is called (epimerisation) and it renders these compounds inactive as anticancer agents after their administration.

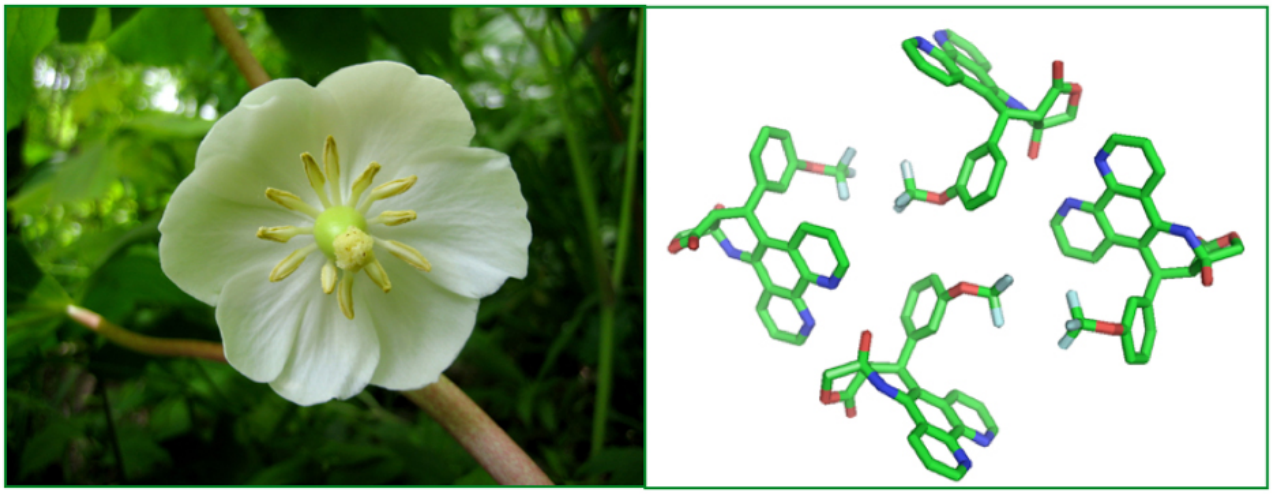

Fig. 1. Podophyllotoxin analogues with novel chemical features imparting more stability and selectivity as anticancer agents.

In this study we introduced a structural modification in the podophyllotoxin-like derivatives, so that this metabolic inactivation (epimerization) is precluded. In chemistry words, we changed the labile (*trans*) ring into the more thermodynamically stable (*cis*) ring and yet retained a potent anticancer activity. We managed to confirm the configuration of our compounds using various spectroscopic techniques as well as X-ray crystal structure studies. Our compounds were tested in vitro against

two types of human cancer types (breast-MCF-7) and (prostate-22Rv1) and obtained very promising activity profiles. We also studied the effect of our compounds at the subcellular level using confocal microscopy from which we have obtained strong evidence that our compounds show greater selectivity for cancer cells than the healthy ones. We also used computer models to explain the correlation between the chemical structure and the observed biological activity.

In conclusion, we have prepared for the first time (*cis*) podophyllotoxin analogues that are able to evade the unwanted epimerisation feature of the currently used podophyllotoxin derivatives (*trans*). Our study also showed that these compounds have strong preferential toxic effects on cancer cells rather than normal ones. We believe these findings lay a foundation for the development of better therapies capable of combating cancer.

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Publication

Novel cis-selective and non-epimerisable C3 hydroxy azapodophyllotoxins targeting microtubules in cancer cells.
Kandil S, Wymant JM, Kariuki BM, Jones AT, McGuigan C, Westwell AD.
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