EPA-4 3β-methoxy-Withaferin A lacks anticancer potency

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Withaferin A (Wi-A), a key withanolide compound that was first isolated and characterized from the roots of Ashwagandha (Withania somnifera), a tropical herb of great medicinal value. We have earlier shown that leaves of Ashwagandha also possess Wi-A and exhibit cytotoxicity to a variety of cancer cell lines. Molecular analysis revealed activation of p53 tumor-suppressor and oxidative stress pathways in cancer cells (1-3). Methylation of several organic heterocyclic compounds has been shown to augment stability and hence their therapeutic potency (4). In view of this information, we aimed to characterize anticancer potency of methoxy-Withaferin A (mWi-A; substituted by a ß-methoxy group at position 3). Molecular docking and bioinformatics analyses of the predicted protein targets revealed stronger binding of that Wi-A as compared to mWi-A (5). Consistent with this, whereas Wi-A caused strong growth arrest/apoptosis and inhibited migration, methoxy mWi-A failed in inducing such effects even at 5 fold higher doses. We further found that Wi-A caused reduction in the level of several proteins associated with invasion and metastases, mWi-A remained ineffective. Taken together, the present study demonstrated that the cytotoxic potential of natural withanolides is tightly controlled by their structure. Small modification such as 3β-methylation of Withaferin A exerts major impact on its therapeutic potency.

References

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