**PhD thesis title:** **Molecular insights and therapeutic potential of natural compounds**

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## ABSTRACT

The high cost of drugs and the speed of growing drug resistance has made modern medicine unaffordable to people in economically impoverished and developing countries. However, traditional home remedies are often cheaper and have fewer side effects but are not always accepted because of a lack of scientific understanding. Therefore, the goal of this thesis was to investigate the molecular mechanisms of compounds found in natural sources using computational simulations supplemented with experimental evidence. Withanolides derived from the Ashwagandha plant and compounds from the honeybee propolis are the main focus of this thesis. Firstly, these natural compounds were investigated against cancer-related targets. Withaferin-A (Wi-A) and Withanone (Wi-N) from Ashwagandha and Caffeic Acid Phenethyl Ester (CAPE) from honeybee propolis were found to be potent against DNA methyltransferases. The studies suggested that Withanolides might also be potent against Phosphodiesterase-4D (PDE4D) related cancers. Furthermore, the antiviral properties of the natural compounds were studied. Withanolides such as Withanoise-IV, Withanoside-V and Withanone and honeybee propolis-related compounds such as CAPE, individually and in combination were effective against Severe Acute Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) *in silico* and *in vitro* experiments. Additionally, natural products were explored to investigate their ability to overcome cancer resistance by inhibiting efflux proteins such as ATP-binding cassette subfamily G member 2 (ABCG2). The study suggested that Stock1n-87939 (3-(5,11-dioxoisoindolo[2,1-a]quinazolin-6(5H,6aH,11H)-yl)-N-(1H-indol-4yl)propenamide) could be a potent ABCG2 inhibitor. Ashwagandha and honeybee propolis compounds have been shown to have neuroprotective effects in the literature. However, no experimental evidence was present on whether they could penetrate the Blood Brain Barrier (BBB). Hence, steered molecular dynamics simulation and the umbrella sampling approach were used to study the passive diffusion of the natural compounds through BBB. It was found that only CAPE, but not the Withanolides (Wi-A and Wi-N), was found to be permeable through BBB and hence could be used as potential neurotherapeutics.

Overall, the thesis presents compelling evidence supporting the potential of natural products as a valuable source for drug discovery. The implications of these findings could pave the way for the development of safer and more effective drugs.