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Pomegranate phytochemical-loaded nanocarriers as therapeutic anti-cancer agents: an *in-silico* study

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Melanoma, an aggressive skin cancer arising from abnormal melanocytes, is often triggered by UV exposure, showing high heterogeneity and poor prognosis due to rapid metastasis. Synthetic BRAF inhibitors such as Vemurafenib, Dabrafenib, and Encorafenib are approved drugs used to treat metastatic melanoma, which causes adverse side effects. Pomegranate (*Punica granatum L.*) is a natural source offering potent antioxidant, anti-inflammatory, and anti-cancer effects. Its diverse polyphenol content provides stronger free radical scavenging activity, thus mitigating itself as a potential natural anti-cancer therapeutic. Recent research studies have shown that these polyphenols possess strong anti-cancer activity through a variety of mechanisms. An *in-silico* study can provide insights about these different mechanisms and about structural features required to improve inhibitory activities. In this computational study, sixteen major phytochemicals: Ellagic Acid (EA), Ellagic Acid Glucoside, Ellagic Acid 4-*O*-xylopiranisode (EAX), Citric acid, 1,3,6,-Tri-*O*-Galloyl-D-Glucose, *D*-(+)- Catechin (DC), Gallic Acid, Galloyl-6-*O*-Diglucoside, Phellatin, Phlorozin, Quercitrin, Vanillic Acid, Cyanidin-3,5-*O*-Diglucoside, Delphinidin-3-*O*-Glucoside, Pelargonidin -3,5-*O*-Diglucoside, Delphinidin-3,5-*O*-Diglucoside were subjected to optimization using DFT with B3LYP method and 6-31G basis set and subsequently to molecular docking against the BRAF-V600E protein, which was modeled using SWISS-MODEL. Docking studies were performed using AutoDock 4, where eight phytochemicals showed commendable results with low binding energies where EA (-8.39 kcal/mol), EAX (-8.26 kcal/mol) and DC (-8.13 kcal/mol) had the lowest. The selected phytochemicals were individually evaluated with chitosan and ovalbumin-based nanoparticle systems, demonstrating promising results in performance and compatibility. However, based on the releasing capability of chitosan, it showed better efficacy. Further, Molecular Dynamic (MD) simulations were conducted to evaluate the stability in physiological conditions. Toxicology studies using ADMET Lab 2.0 revealed that several phytochemicals had favorable safety profiles, while others remained within acceptable limits. Overall, Chitosan was proven *in-silico* to be a viable nanoparticle drug system with all eligible phytochemicals further being proved through analysis of MD trajectories.

Keywords:
Chitosan, Docking, Melanoma, Pomegranate