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Natural antiviral drugs as novel hepatitis b virus polymerase-inhibitors: Cell culture and molecular docking study

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Hepatitis B virus (HBV) causes chronic liver diseases, including fulminant liver failure, cirrhosis and hepatocellular carcinoma, affecting about two billion of world population. Despite high anti-HBV efficacies, the nucleoside analogs (e.g., lamivudine) lead to the emergence of drug-resistance, interferons (e.g., IFN-α causes adverse side-effects. Comparatively, various natural or plant products have shown similar or even better efficacy. Hence, new antiviral strategies must focus not only on synthetic molecules but also on potential natural compounds. In this report, we have combined the *in vitro* cell culture and *in silico* molecular docking methods to assess the novel anti-HBV activity and delineate the inhibitory mechanism of selected plant-derived pure compounds of different classes. Of the tested (2.5-50 µg/ml) twelve non-cytotoxic compounds, ten (10 µg/ml) were found to maximally inhibit HBsAg production at day 5. Compared to quercetin (73%), baccatin III (71%), psoralen (67%), embelin (65%), menisdaurin (64%) and azadirachtin (62%) that showed high inhibition of HBeAg synthesis, lupeol (52%), rutin (47%), β-sitosterol (43%) and hesperidin (41%) had moderate efficacies against HBV replication. Further assessment of quercetin in combination with the highly active compounds, enhanced its anti-HBV activity up to 10%. Being the most important drug target, a 3D structure of HBV polymerase (Pol) was modeled and docked with the active compounds, including lamivudine as standard. Docking of lamivudine indicated strong interaction with the modeled HBV Pol active-site residues that formed stable complex (ΔG=-5.2 kcal/mol). Similarly, all the docked antiviral compounds formed very stable complexes with HBV Pol (ΔG=-6.1 to -9.3 kcal/mol). Taken together, our data suggest the anti-HBV potential of the tested natural compounds as novel viral Pol-inhibitors.

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