Advances in a nanoformulation of calcium phosphate and natural compounds (BC-ACP NPs) for colorectal cancer treatment: antitumor effect and toxicity

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Abstract
Amorphous calcium phosphate nanoparticles (ACP NPs) exhibit excellent biocompatibility and biodegradability properties. ACP NPs were functionalized with two coumarin compounds (esculetin and euphorbetin) extracted from Euphorbia lathyris seeds (BC-ACP NPs) showing high loading capacity (0.03% and 0.34% (w/w) for esculetin and euphorbetin, respectively) and adsorption efficiency (2.6% and 33.5%, respectively). BC-ACP NPs, no toxic to human blood cells, showed a more selective cytotoxicity against colorectal cancer (CRC) cells (T-84 cells) (IC50, 71.42 µg/ml) compared to non-tumor (CCD18) cells (IC50, 420.77 µg/ml). Both, the inhibition of carbonic anhydrase and autophagic cell death appeared to be involved in their action mechanism. Interestingly, in vivo treatment with BC-ACPs NPs using two different models of CRC induction showed a significant reduction in tumor volume (62%). A poor invasion of normal tissue were also observed. New experiments are being carried out to determine the lack of toxicity of nanoparticles as well as the characteristics of their biodistribution. These results show a promising pathway to design innovative and more efficient therapies against CRC based on biomimetic calcium phosphate NPs loaded with natural products.

References

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Figures

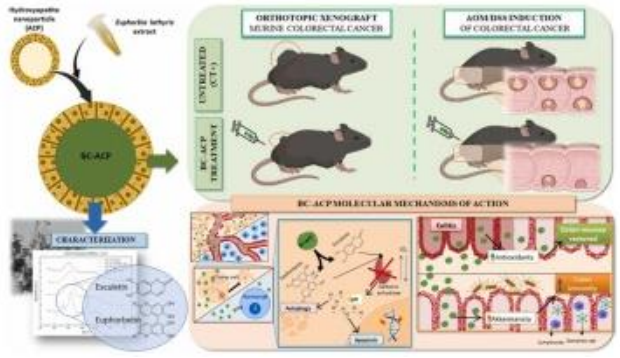

Figure 1. Schematic representation of the model of antitumor activity of BC-ACP according to the results obtained. (A) EPR phenomenon and selective accumulation of BC-ACP in cancer tissues (orange) with respect to normal tissues (blue). (B) Increased endocytosis in cancer cells with respect to normal cells. (C) Effect of BC-ACP in the colonic mucosa, consisting of antioxidant effect of esculetin and euphorbetin that reverts inflammation in the colonic mucosa and (D) increases Akkermansia colonization and colonic immunity. (E) Euphorbetin and esculetin present in BC-ACP nanoparticles inhibit carbonic anhydrase in tumors, decreasing intracellular pH and leading to cell death, mainly by autophagy but also by apoptotic pathways