Arecoline and the 30-100 kDa fraction of areca nut extract differentially regulate mTOR and respectively induce apoptosis and autophagy-A pilot study model

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Abstract

Areca nut (AN) is recognized as a human carcinogen; however, few studies of the cytotoxic effects of AN ingredients on cells have been reported. In Taiwan, AN, lime and inflorescence of Piper betle are the common components of betel quid (BQ). We recently noticed that extract of AN (ANE), but not those of lime and inflorescence of Piper betle, induces rounding cell morphology and nuclear shrinkage in different types of carcinoma cells. In this study, the rounding cell activity was first traced to the partially purified >/=10 kDa fraction (ANE >/= 10 K) and subsequently to the 30-100 kDa fraction (ANE 30-100 K). ANE and ANE >/=10 K stimulated nuclear shrinkage ($P < 0.001$ in both cases) and the clearance of the cytoplasm. ANE, ANE >/= 10 K, and ANE 30-100 K induced the cleavage of LC3-I ($P < 0.05$, 0.01, and 0.05, respectively) and the emergence of autophagic vacuoles (AVs) and acidic vesicles. On the other hand, arecoline (Are, the major alkaloid of AN) triggered caspase-3 activation, peri-nuclear chromatin condensation, and micronucleation. Meanwhile, ANE 30-100 K, but not Are, inhibited the phosphorylation of the mammalian target of rapamycin (mTOR)-Ser(2448). In conclusion, this study demonstrates that different AN ingredients exerting differential impact on mTOR-Ser(2448) phosphorylation are capable of triggering apoptosis and autophagy.