**ROS-independent activity of the novel artemisinin WHN-11 towards growth inhibition and cellular dysfunction in triple-negative breast cancer (TNBC) cells**

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**Introduction:** Novel artemisinins are synthesized for improved bioavailability, therapeutic efficacy,target specificity and reduced side effects. We investigated the selective inhibition of a panel of novel artemisinins against triple-negative breast cancer (TNBC) cells, an aggressive subtype of breast diseases with the poorest prognosis.

**Methodology:** Cell viability assays (MTT and SRB), western blots, immunoprecipitation, qPCR, confocal microscopy, and flow cytometry were conducted to investigate the mechanism of action of the novel artemisinins.

**Results:** Among the novel artemisinins, the hit compound WHN-11 exhibited cytotoxicity against cancer cells and cancer stem-cell activities at low micromolar concentrations. In HCC1937 cells, WHN-11 inhibited cell survival independent of excessive reactive oxygen species (ROS) production, promoting apoptosis through the activation of caspase cleavage and suppression of B-cell lymphoma extra-large (Bcl-xL), an anti-apoptotic protein. WHN-11-treated cells exhibited mitochondrial depolarization and cytoplasmic ATP depletion, a consequence of the opening of the mitochondrial permeability transition pore (mPTP) at low calcium ion circulation. Replacing cell growth media with galactose instead of glucose, considerably increased the susceptibility of HCC1937 cells to the cytotoxic effect of WHN-11, further suggesting a compromised mitochondrial function. Consistent with these, WHN-11 treatment increased mitochondrial fission. Treatment with WHN-11 increased the formation of autophagosomes, acidic vesicular organelles and lipid dropletsand increased the dissociation of Bcl2-Beclin1 complexes. We observed an inhibition of the autophagic flux, and induction of proteotoxic stress by increased Hsp70 mRNA expression and proteasome-independent accumulation of ubiquitinated proteins.

**Discussion and Conclusion:** This study suggests that the novel artemisinin WHN-11 showed activity against TNBC via multiplemechanisms that were independent of ROS formation.

**References:**

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