J Infect Dis Ther 2018, Volume 6
DOI: 10.4172/2332-0877-C3-045

Artemisinin derivatives and synthetic trioxane trigger apoptotic cell death in asexual stages of *Plasmodium*

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Statement of problem: Although over the last fifteen years, the prevalence of malaria became reduced by over half but developing resistance against artemisinin derivatives and its combinations, which are the only ray of hope to treat resistant malaria set back the control efforts and the key hindrance to achieve the goal of malaria elimination till 2030. In spite these artemisinins are precious antimalarials, their action mechanism is yet to be fully understood. Reactive oxygen species (ROS) produces by cleavage of endoperoxide bridge of artemisinin derivatives are known to be its antimalarial efficacy. Since ROS could induce apoptosis, here we had explored the effect of artemisinin derivatives on the apoptotic machinery of the malaria parasite, Plasmodium falciparum, and its survival.

Methodology: The effect of α/β arteether, artesunate and a synthetic 1,2,4 trioxanes was studied on the apoptotic machinery of asexual blood stages of *Plasmodium falciparum* 3D7. We have evaluated the hallmark marker of the apoptotic pathway; disturbance in mitochondrial membrane potential, caspase activation and in situ DNA fragmentation.

Findings: Results have shown that cleavage of peroxide bridge of artemisinin derivatives and 1,2,4 trioxane generate reactive oxygen species which depolarize mitochondrial membrane potential and make it permeable which further followed by downstream events of apoptotic cell death like activation of the caspase-like enzyme and DNA fragmentation.

Conclusion and significance: The results suggested that artemisinin derivatives and synthetic trioxane induce apoptosis in the erythrocytic stage of malaria parasite: *Plasmodium falciparum*. Since Plasmodium has metacaspase at the place of caspases, which are found in human, it could be exploited as the new therapeutic target for malaria.

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