Contribution ID: **248** Type: **not specified**

Solving the Old Problem of Anti-schistosomal Drug Resistance: A Role for Praziquantel and Polyphenols?

Thursday, 21 November 2024 09:30 (30 minutes)

Schistosomiasis is a devastating parasitic disease caused by the Schistosoma species. It affects over 260 million people worldwide, with the highest morbidity and mortality rates in sub-Saharan Africa. Despite its significant impact on public health, Schistosomiasis remains one of the neglected tropical diseases. Praziquantel (PZQ) is currently the only drug that treats all schistosomiasis infections due to its availability, cost-effectiveness, and minimal side effects. However, recent studies showed the emergence of PZQ-resistant strains due to drug pressure. Exposure of the schistosome parasite to extreme conditions during its developmental stage triggers the expression of heat shock and universal stress proteins. The universal stress G4LZI3 protein has been identified as a potential target for developing new anti-schistosomals. Protein structure is integral to drug design and comprehension of various biological systems and pathways. Hence, X-ray crystallography was employed for the structural determination of this protein, while bioinformatics was used to identify potential polyphenolic compounds with additive 'druggable' ROS-scavenging potential to ameliorate anti-schistosomal drug resistance against PZQ.
More so, glycolytic proteins have emerged as possible drug targets and vaccine candidates for treating schistosomiasis. Since proteins do not function alone, disrupting essential protein-protein interactions using small molecule inhibitors has become a more promising approach to resolving drug resistance in diseases. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and Triosephosphate isomerase (TPI) are glycolytic proteins with crucial cooperative role in generating energy for the worm's motility and survival. Therefore, disrupting this critical GAPDH˜TPI protein complex should decrease the worms' energy levels, thus creating an unfavourable environment for the parasite to thrive. Raman and UV-vis spectroscopy, coupled with Microscale Thermophoresis were used to investigate this postulated interaction. Virtual screening, molecular docking and molecular dynamics simulation were employed to identify inhibitors against this protein-protein interaction. In vitro screening of these compounds on various stages of the schistosome worms will validate the druggability of these compounds.

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Session Classification: Plenary

Track Classification: AfLS