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Repositioning of synthetic emetine analogues as potential anti-malarial drugs and use of molecular modelling tools to aid in drug discovery

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Statement of the Problem: Drug resistance has emerged towards all antimalarials in use including the artemisinin-based combination therapies. There is a pressing need for novel anti-malarial treatments, but long development timelines cripple the process of drug discovery.

Methodology: An alternative to de novo drug design is offered by drug repositioning to help reduce the long timescale involved in bringing a drug to market. A huge investment of time and resources are needed for high throughput screening and in-silico virtual screening provides an inexpensive alternative to filter through large libraries of compounds.

Findings: Natural products have been a reliable source of anti-malarial treatments. Emetine dihydrochloride, an anti-amoebic compound, a plant-derived alkaloid has been identified on a reposition screen as a potent inhibitor of the multi-drug resistant strain K1 of *Plasmodium falciparum* (IC_{50}: 47nM) and shows ideal pharmacokinetic matching and synergy with atovaquone. The use of emetine has been prevented by its emetic and cardio-toxic effects. However, synthetic analogues of emetine hydrochloride have been claimed to be less cardio-toxic than the parent compound. Using *in-silico* modelling methods, synthetic emetine analogues were found to have the potential for retaining the anti-malarial activity. The results were verified experimentally. Emetine and its analogues were found to have gametocidal activity, multi-modal mechanism of action and showed no cross-resistance in multi-drug resistant strains. Virtual screening of FDA approved library of drugs was carried out to identify synergies and propose anti-malarial combination therapy between these drugs and synthetic emetine analogues.

Conclusion & Significance: Current void in the antimalarial drug market and spread of drug resistance strengthens the case of further investigation into powerful and affordable compounds such as emetine and its synthetic analogues for repositioned use as valuable antimalarial candidates.

Biography

Priyanka Panwar has completed her degree in Medicine and practiced for over two years in India. She is currently pursuing her PhD in Biomedicine in the UK. Her project is on anti-malarial drug discovery through repositioning. Over the course of this project, she has acquired expertise in parasitology and molecular modelling.

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