Commentary
Volume 11:3, 2022

Journal of Malaria Control and Elimination

ISSN: 2470-6965 Open Access

Antiplasmodial Cyclodecapeptides from Tyrothricin Share Target with Chloroquine

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Introduction

Malaria is one of the most prevalent diseases that can be found in tropical regions; it is estimated to cause 228 million new infections and 738,000 deaths globally during the first year (2020) of the COVID-19 pandemic, with sub-Saharan Africa accounting for nearly 95 percent of the burden and deaths from the disease. The number of fatalities in one year is more than quadruple that of the COVID-19 epidemic in Africa during a two-year period. The obligatory intracellular parasite *Plasmodium falciparum*, a unicellular protozoan, is responsible for the majority of malaria cases. As a result, malaria caused by *P. falciparum* continues to be a public health issue, particularly in underdeveloped nations [1-5].

Description

The sixth Millennium Development Goal (MDG) includes the target 6.C, "to have halted by 2015 and begun to reverse the incidence of malaria and other serious illnesses," as one of its objectives. Seven years later, the main obstacle to controlling malaria and a significant public health issue in poor and third-world nations continues to be the parasites' resistance to antimalarial medications. For instance, because to an increase in CQ resistant (CQR) *P. falciparum*, chloroquine (CQ), which was formerly the first line antimalarial medicine due to its low cost, low incidence of adverse effects and good effectiveness, has since been discontinued. It is urgent to create new medications with novel targets for *P. falciparum* due to the looming prospect of resistance by these parasites to artemisinin, the main active ingredient in modern antimalarial treatments (artemisinin combination therapies, or ACTs).

The changed erythrocyte membrane following infection by the malaria parasite is exploited as a target in efforts to create novel antimalarial medications. The anionic phosphatidylserine (PS) is transferred from the inner leaflet to the outer leaflet of the bilayer, changing the membrane's lipid asymmetry and the infected erythrocyte tends to be similarly anionic to bacterial cells, among other changes that take place in the infected erythrocyte plasma membrane (IEPM).

These erythrocyte membrane alterations raise the possibility that membrane-active substances, such as cationic antimicrobial peptides (AMPs) and membrane-active antibiotics, may exhibit selective activity towards both the infected erythrocyte membrane and the parasitophorous vacuole membrane that is derived from the host cell. Due to AMPs' beneficial qualities, particularly those that are taken into account for their usage as novel antimicrobials, they have in fact been examined as a potential source of future antimalarial medications. Despite coming from varied sources, the structural features of AMP families enable the fine-tuning of their physicochemical properties to enhance their antibacterial activities through structure-activity relationship research. It is possible to improve AMP structure and activity by taking into account how several factors, including size, charge, amphipathicity/hydrophobicity, supramolecular organisation and conformational flexibility, affect interactions with microbial targets.

Tyrothricin contains three cyclodecapeptides, each of which reacted differently with the three distinct *P. falciparum* strains. Because the cyclodecapeptides must first detect and pass the infected erythrocytic membrane before acting on the intraerythrocytic parasite, it is important to take these differences into account. As predicted, GS exhibited a resistance index of close to one and statistically comparable IC50 values against the three strains and it works only on the infected erythrocytic membrane. Therefore, it can be assumed that the three strains produce an infected erythrocyte with a similar lipid content that will be recognised by GS and will interact with the three cyclodecapeptides initially.

It is alarming that we found resistance in *P. falciparum*'s erythrocytic stage to the three cyclodecapeptides produced from tyrothricin, especially if membranes and lipids are the intended target. For this kind of target-dependent modification and resistance, a significant alteration in lipid composition would be required. The activity of TpcC with L-Trp3-D-Trp4 and Trp7 in its structure cannot be explained by membrane contact or a sequence-specific target. Following the SAR suggested by Rautenbach TpcC was less effective against the CQS 3D7 strain, which may be related to the poorer target interaction indicated above. However, the CQI D10 and CQR Dd2 strains showed the most effective activity. TpcC activity is shown to have an impact on chromatin shape by the SR-SIM study. Trp is known to interact with DNA and TpcC has three Trp residues. Additionally, TrcC containing two Trp residues caused condensation of the Bacillus subtilis nucleoid, demonstrating that these peptides may interact with DNA, according to Wenzel.

Conclusion

In this investigation, we once more discovered that TrcA and its two analogues, TpcC and PhcA, had strong antimalarial activity that was predominantly non-lytic and sequence specific. The findings support earlier research showing that GS was considerably outperformed by natural Trc equivalents in terms of antiplasmodial efficacy. In this investigation, we discovered that, for *P. falciparum* strains other than 3D7, Rautenbach's hypothesised size and hydrophobicity dependent SAR for the Trcs did not hold true.

Conflict of Interest

None.

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Received: 02 May, 2022, Manuscript No. mcce-22-68244; **Editor assigned:** 03 May, 2022, PreQC No. P-68244; **Reviewed:** 09 May, 2022, QC No. Q-68244; **Revised:** 18 May, 2022, Manuscript No. R-68244; **Published:** 25 May, 2022, DOI: 10.37421/2470-6965.2022.11.183

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How to cite this article: Ding, Derong. "Antiplasmodial Cyclodecapeptides from Tyrothricin Share Target with Chloroquine." Malar Contr Elimination 11(2022):183.