Unveiling Hidden Gems: Harnessing Plant Data for Antiplasmodial Drug Discovery

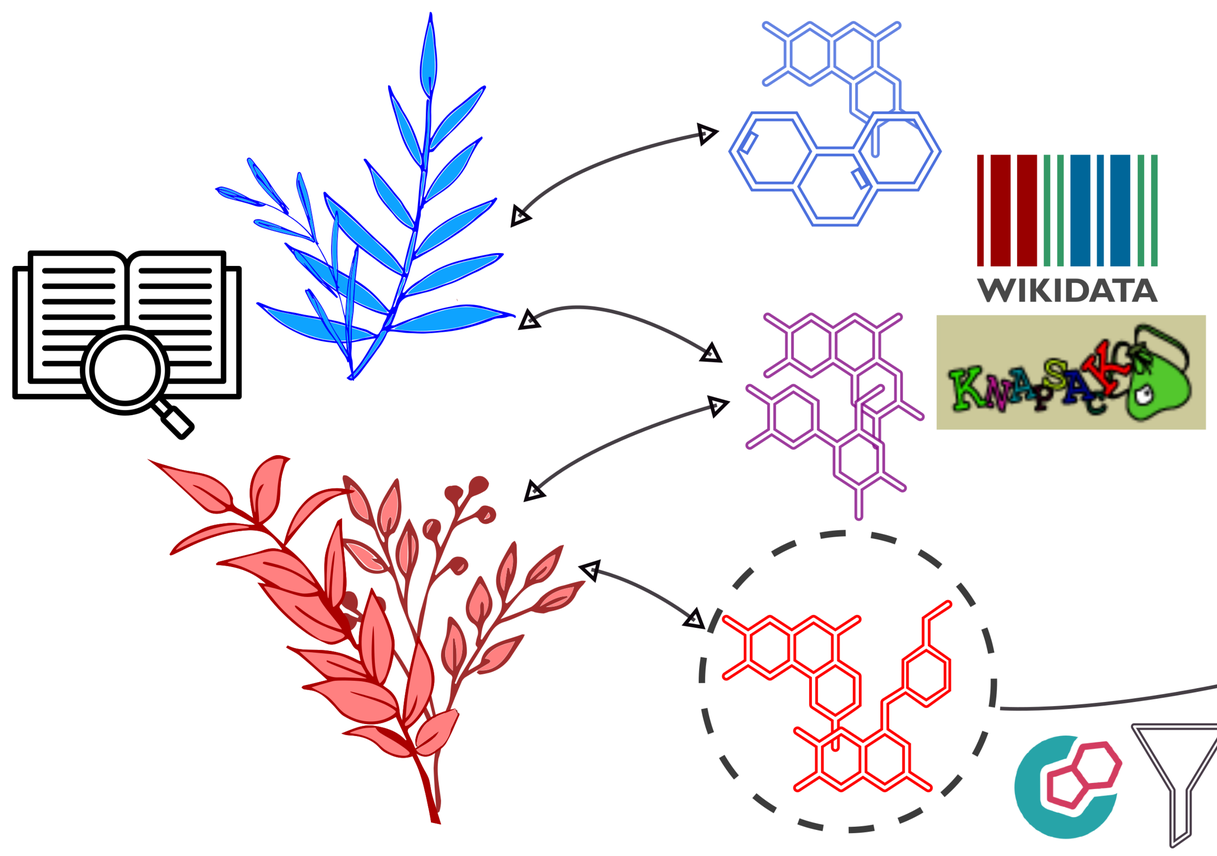
Adam Richard-Bollans[1,*] - Conal Aitken[1,2] - Eliot Jan-Smith[1] - Edward Straw[1] - Colin W. Wright[3] - Melanie-Jayne R. Howes[1,4]

[1]Royal Botanic Gardens, Kew, United Kingdom [2]University of St Andrews, United Kingdom
[3]University of Bradford, United Kingdom [4]Institute of Pharmaceutical Science, King's College London, United Kingdom
[*]a.richard-bollans@kew.org

Introduction

The conventional pipeline to find new antiplasmodial (antimalarial) compounds in plants is a resource-intensive process of plant selection, extraction of plant material, bioassay-guided fractionation, and compound isolation. This process generates large amounts of data regarding the activity of plant species and associated phytochemicals. We collected data on plant antiplasmodial activity and compound occurrences in Apocynaceae, Loganiaceae and Rubiaceae species with the aim of:

- Identifying overlooked compounds with high potential as novel antiplasmodials
- Demonstrating an efficient approach to advance selection of potential antiplasmodial compounds, without the immediate need to perform bioassay-guided fractionation



- Plant species are classified as active or inactive based on bioassay literature
- Known presences of compounds in these species are determined through WikiData and KNApSAcK
- Compounds found only in active species are initially selected
- Compounds that have already been tested or fail drug-likeness rules are removed
- Final set of compounds are prioritised via MAIP, which aims to predict blood stage malaria inhibition of compounds

Results

Of the compounds compiled from WikiData [1] and KNApSAcK [2], 1055 were identified as only occurring in active species, and 999 of these are not reported in bioassays against *Plasmodium* parasites in ChEMBL [3]. After pyrrolizidine alkaloids (associated with hepatotoxicity), non-orally bioavailable peptides and compounds that fail drug-likeness descriptors [4,5] were removed, 699 compounds remained and were ranked based on their MAIP score [6] with the top 50 compounds being selected for further investigation.

From these 50 candidates, 16 were found to have been previously investigated in antiplasmodial assays in the literature though not reported in ChEMBL. These compounds are shown to be particularly active against *Plasmodium* parasites, with a mean IC50 value of 4.4µM in *in vitro* tests compared to 13.7µM for tested compounds in all species in the study.

The remaining 34 candidate compounds are active leads which we aim to isolate from plant material and test.

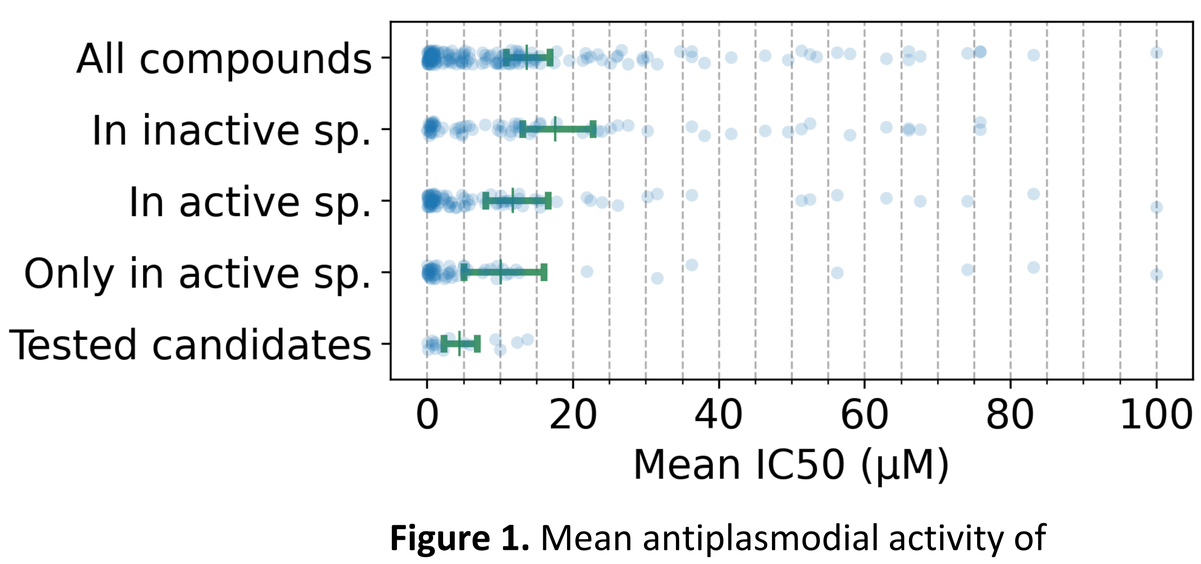


Figure 1. Mean antiplasmodial activity of phytochemicals from selected plant groups.

Conclusion

We have developed an approach that consolidates existing data and research to highlight potentially overlooked antiplasmodial compounds. The preliminary evidence indicates this to be a successful approach that can be further refined, for example, by narrowing the scope to specific *Plasmodium* strains, incorporating plant part information or extending the search to other plant families.

Acknowledgements

The first author would like to thank the **Bentham-Moxon Trust** for their financial support.

References

1. Denny Vrandečić and Markus Krötzsch, 'Wikidata: A Free Collaborative Knowledgebase', Communications of the ACM 57, no. 10 (2014): 78–85.
2. Farit Mochamad Afendi et al., 'KNApSAcK Family Databases: Integrated Metabolite–Plant Species Databases for Multifaceted Plant Research', Plant and Cell Physiology 53, no. 2 (2012).
3. David Mendez et al., 'ChEMBL: Towards Direct Deposition of Bioassay Data', Nucleic Acids Research 47, no. D1 (2019): 930–40.
4. Christopher A Lipinski et al., 'Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings', Advanced Drug Delivery Reviews 23, no. 1–3 (1997): 3–25.
5. Daniel F. Veber et al., 'Molecular Properties That Influence the Oral Bioavailability of Drug Candidates', Journal of Medicinal Chemistry 45, no. 12 (2002): 2615–23.
6. Nicolas Bosc et al., 'MAIP: A Web Service for Predicting Blood-stage Malaria Inhibitors', Journal of Cheminformatics 13, no. 1 (2021): 1–14.