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IN-VITRO ANTIMALARIA ACTIVITY EVALUATION OF EUGENOL'S TRANSFORMATION PRODUCTS AGAINST *PLASMODIUM FALCIFARUM* STRAIN 3D7 USING TRAGER AND JENSEN METHOD

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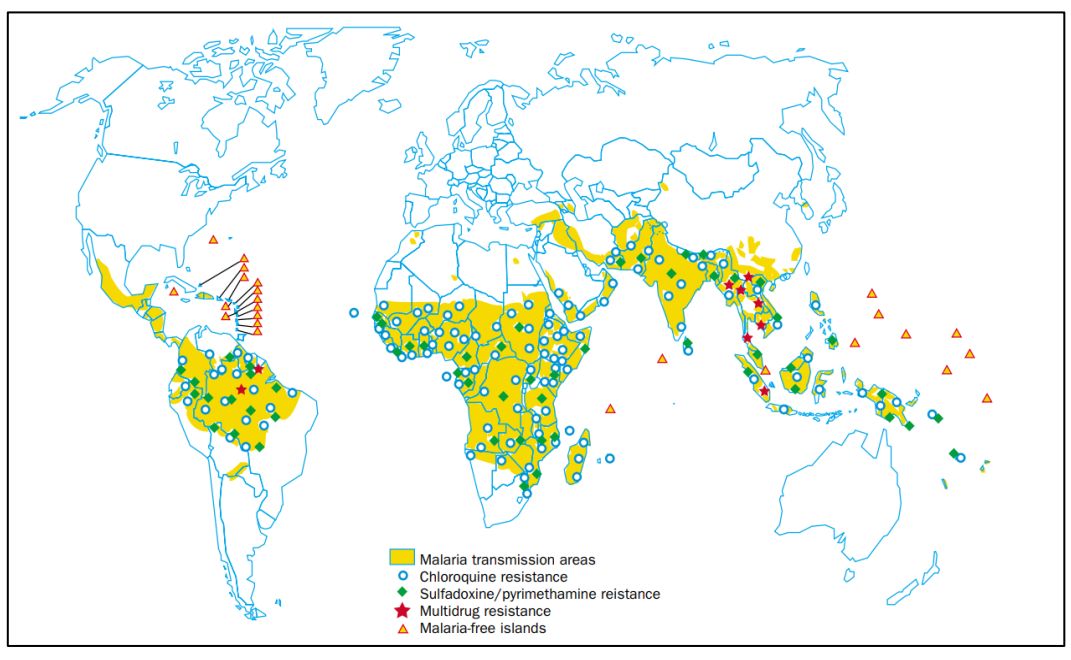
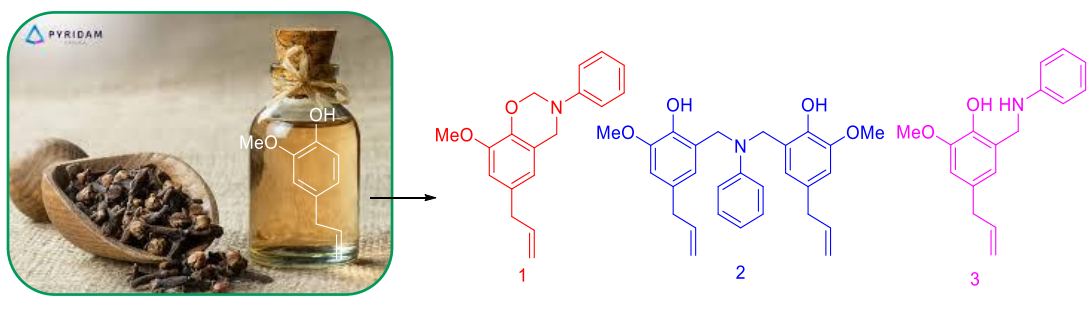
Background

Endemic malaria occurs in tropical areas with quite significant levels of morbidity and mortality. First line therapy using chloroquine and ACT (Artemisinin Based Combination) have reported resistance, therefore new drugs need to be developed.

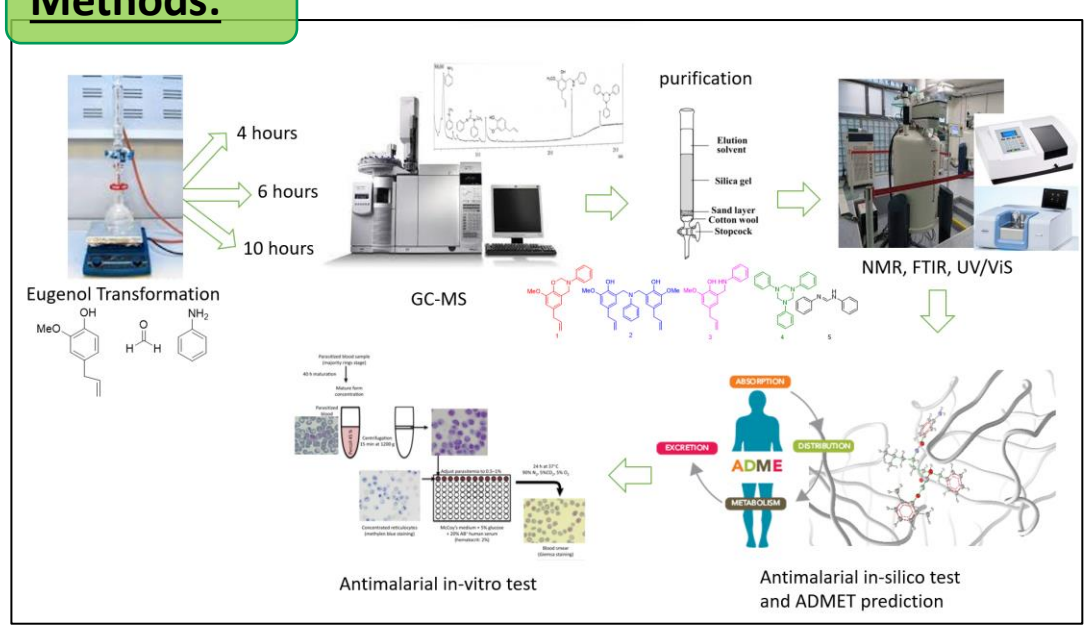


Aims:

This research aimed to find a potent antimalarial drug candidate which was derived from eugenol transformation.

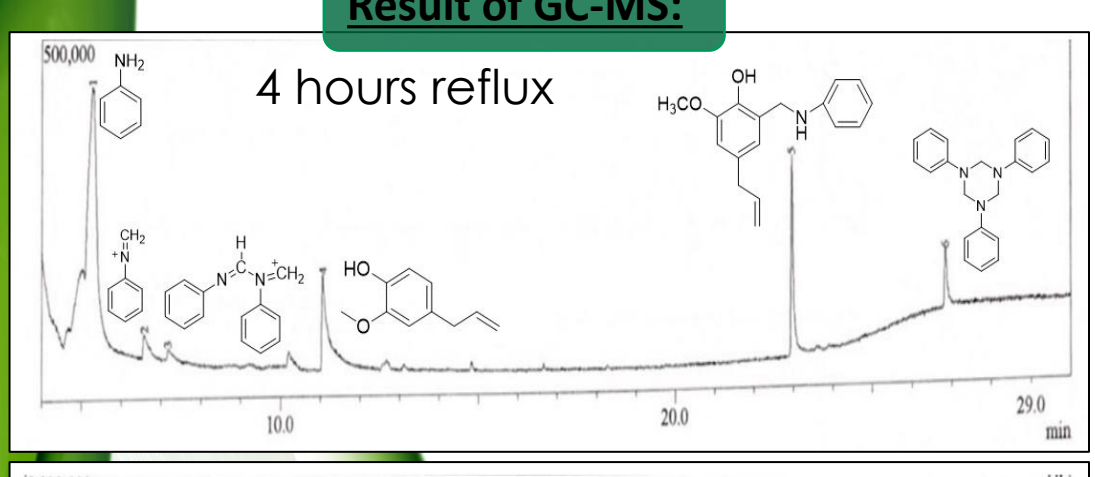


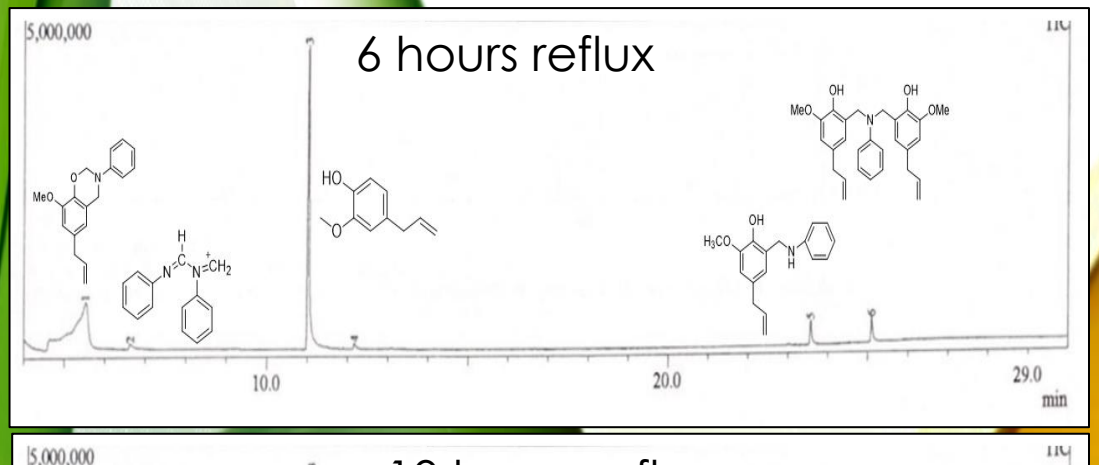
Methods:

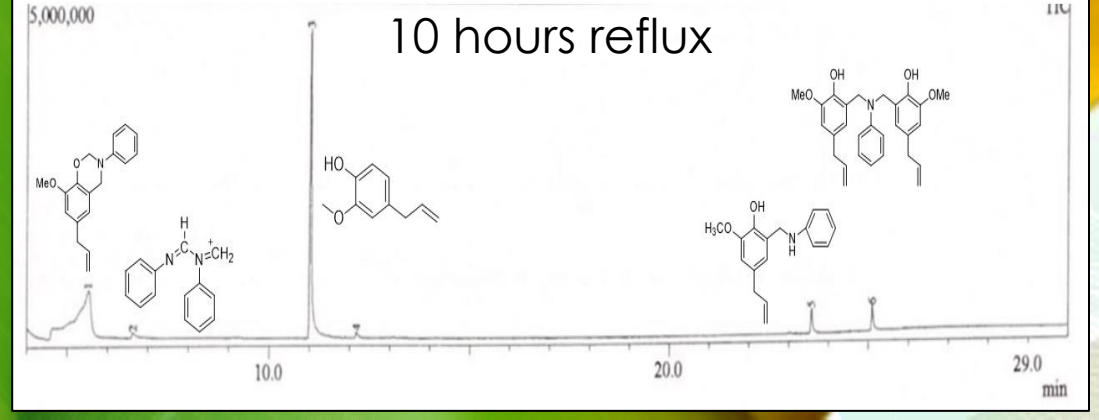


Transformation of eugenol was performed through the Mannich reaction with the starting materials formaldehyde and aniline yielded iminium salts and followed by treating with eugenol. The reflux process runs for 4, 6, and 10 hours, after which we perform product screening using GC-MS. The purification process utilizes column chromatography with a stationary phase silica gel 60 and mobile phase hexane:ethyl acetate (10:1).The structures of the compounds were confirmed by FTIR and ^{1}H-NMR. spectrometer UV/Vis and the The compounds were subjected to *in-silico* study for ADMET screening by pkCSM application. We also conducted molecular docking evaluation to aspartic protease receptor (PDB ID: 1LEE) using MVD software. *in-vitro* antimalarial test with the Trager and Jensen method.

Result of GC-MS:







Result of *in-silico* test

It showed that the compounds were had potential as antimalarial agent, better than the native ligand and the standard reference drug, chloroquine. And also having good result in terms of ADMET screening

Table 1. The Result of Molecular Docking Study on Aspartic Protease

Compound	MoldockScore (Kcal/mol)	H-Bond	Steric Interction
1	-90.63 ± 2.59	-	Asp 34 Tyr 77
2	-127.98 ± 1.37	Gly 36	Asp 214 Gly 216
3	-90.54± 0.69	Asp 214	Thr 217
4	-99.44± 0.98	-	Tyr 77 Gly 216
5	-77.92± 0.24	-	Tyr 77 Leu 131
Chloroquin	-96.56± 0.58	-	Asp 34 Gly 36 Tyr 77 Asp 214

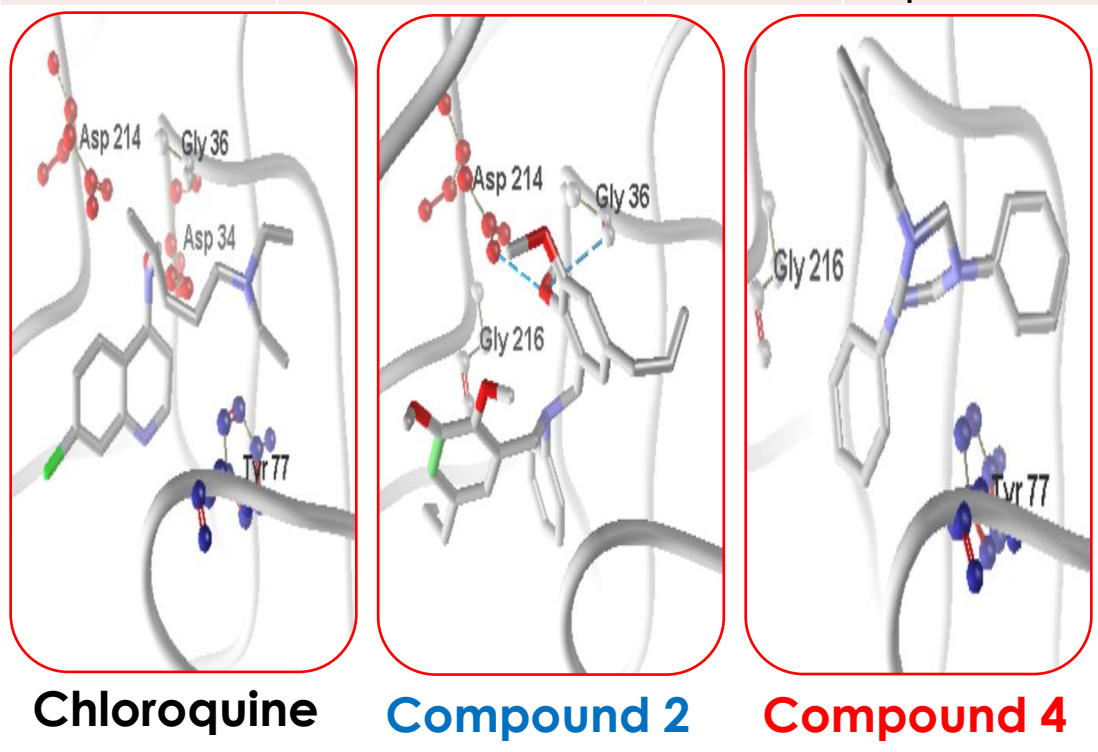


Table 2. The Result of Pharmacokinetics Prediction

Compound	GIT abs.	Dist. Log BBB	Meth.	Excretion log ml/min/kg
1	98.14	0.523	No	0.318
2	92.26	-0.519	Yes	0.586
3	89.42	0.055	No	0.409
4	97.87	0.916	No	0.147
5	90.02	0.122	No	0.395
Chloroquine	90.21	-2.872	No	0.022

Result of *in-vitro* test

The IC_{50} of the products were < 10 µM which is categorized as good activity, especially compounds **2** and **4**. Both compounds have IC_{50} < 1 µM which is categorized as excellent activity.

Table 3. The Result of *In-vitro* Antimalarial Test

Compound	IC50 (µM)
1	9.30 ± 0.57
2	0.02 ± 0.01
3	9.42 ± 0.24
4	0.16 ± 0.03
5	2.77 ± 0.89
Chloroquine	0.33 ± 0.43

Conclusion :

The transformation products of eugenol can be developed furthermore as antimalarial agents. The further research is focused on cytotoxic assays involving normal hepatic and kidney cell lines

Reference :

Indrayanto G, Putra GS, Suhud F (2021) Validation of in-vitro bioassay methods: Application in herbal drug research. Profiles Drug Subst Excip Relat Methodol 46 (6): 273–307.

Putra GS, Yuniarta TA, Syahrani A, Rudyanto M (2016) Synthesis, molecular docking study and brine shrimp lethality test of benzoxazine and aminomethyl derivatives from eugenol. Int J Pharm Res Rev 5(4): 1–11