Bioprospecting for antimalarials from medicinal plants

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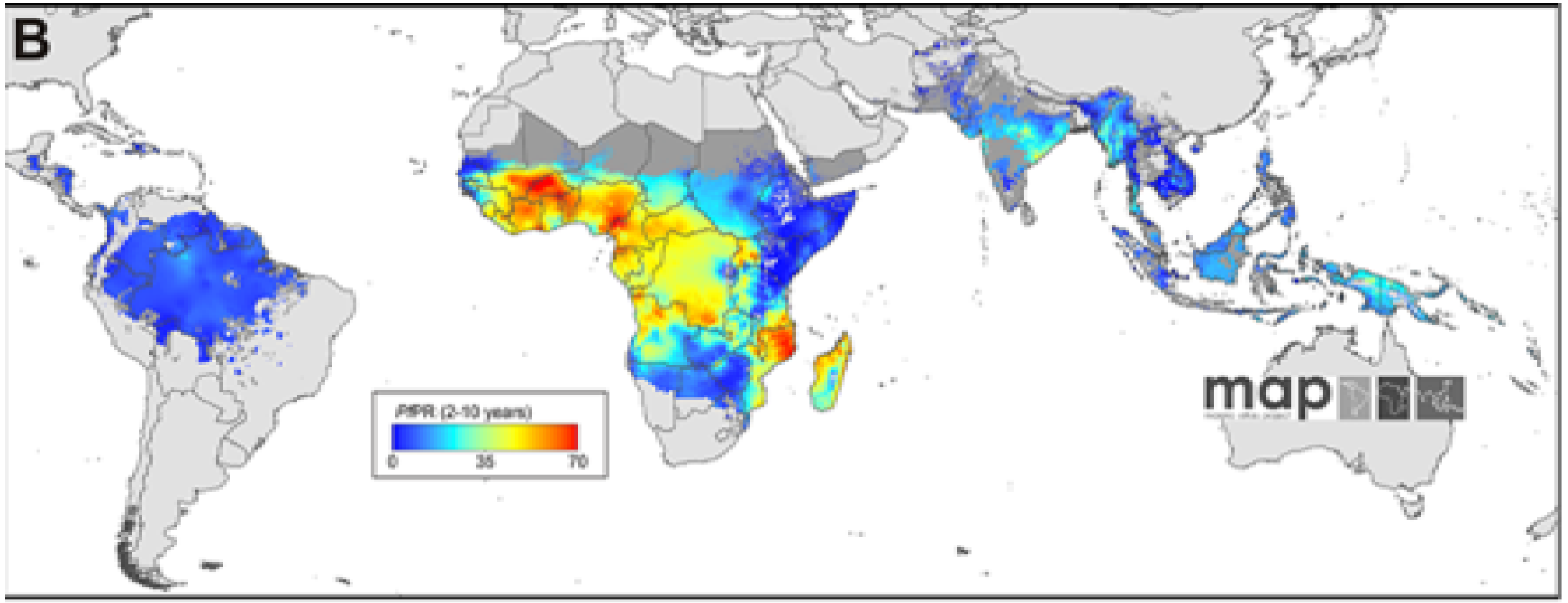
Why bioprospect for antimalarials

- Malaria is one of the most devastating diseases of the developing world
- Kills 1–3 million people annually, mostly affecting the children and pregnant women [1]
- In every 30 seconds, a child dies of malaria
- In Uganda, malaria accounts 30–50% of outpatient visits
- 35% of hospital admissions
- 9–14% of hospital deaths [2]

1. WHO, 2012; 2. Yeka et al. 2012

Malaria distribution- affect many tropical and subtropical regions of the world[3]



3. Gething et al., 2010

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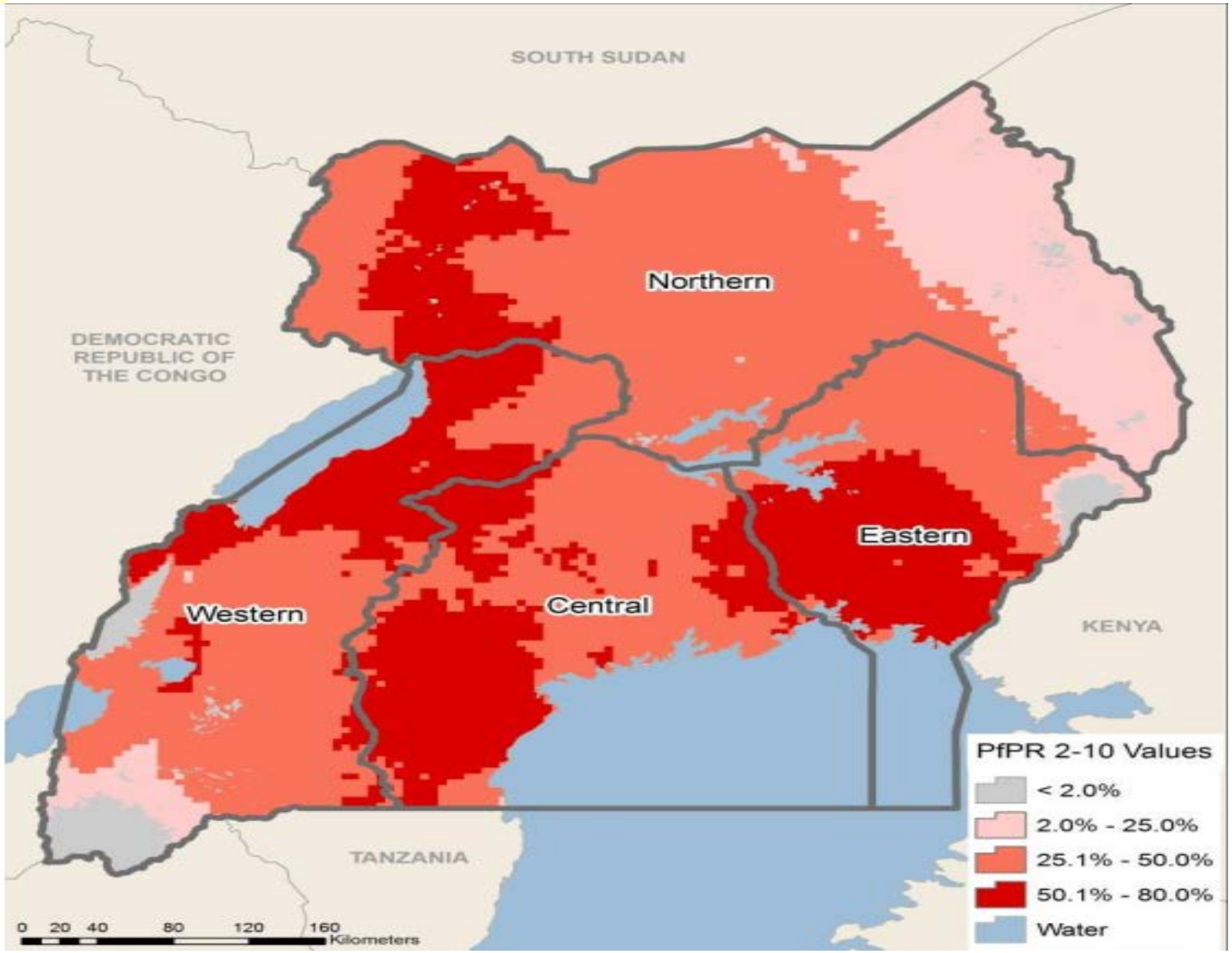
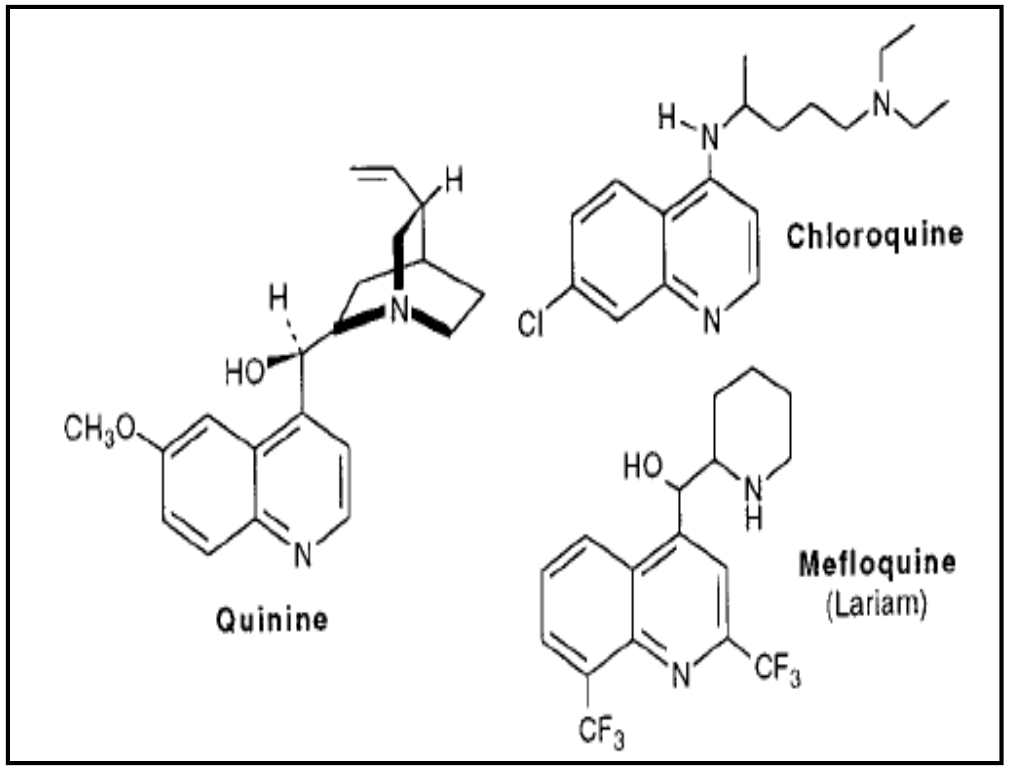
Malaria Endemicity in Uganda, 2010



Plants as sources of anti-malarials

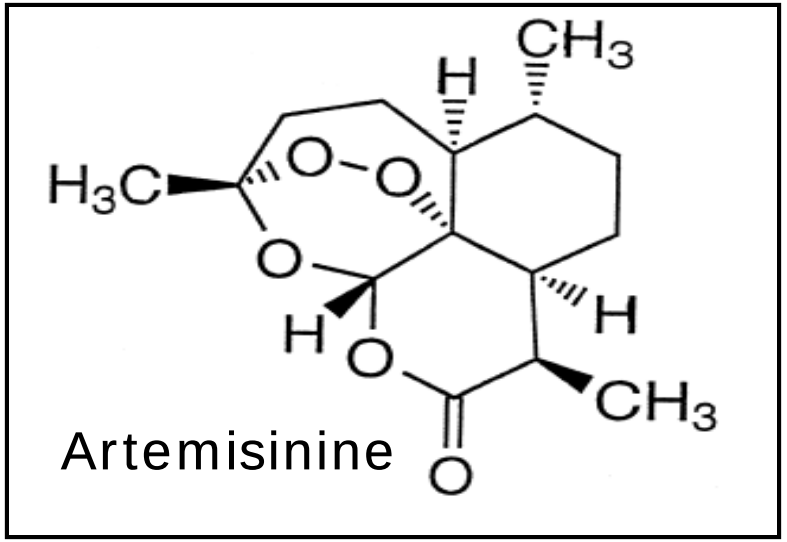
- Ant malarial compounds have been isolated from plants & developed into drugs e.g.

- Quinine isolated from Cinchona bark in 1820[7]

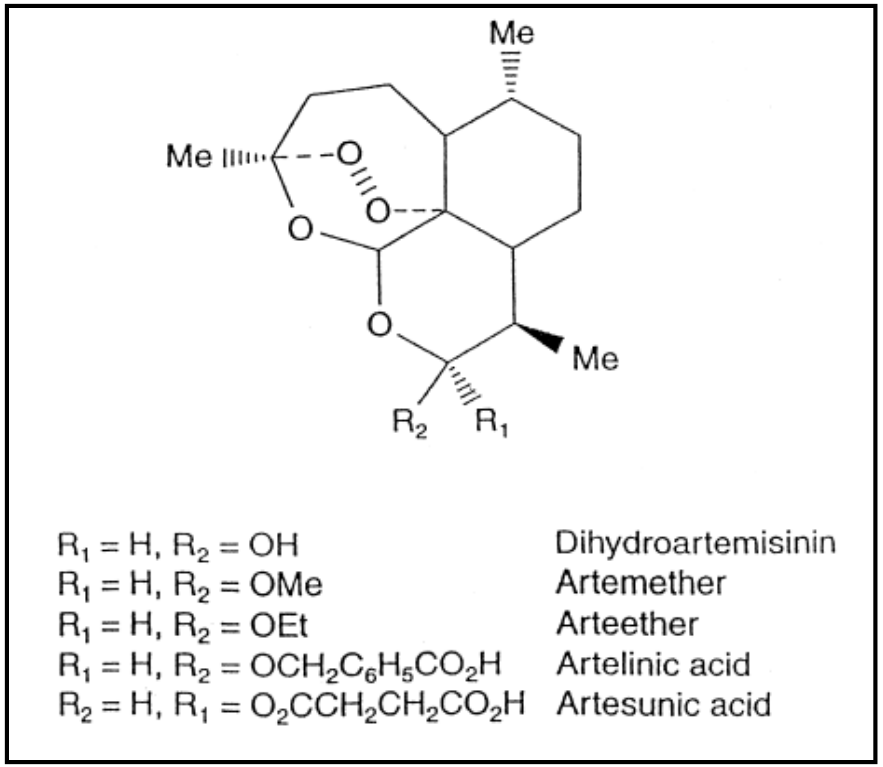


7. Seeman et al; 2001; 8. Murambiwa et al;2011

- Artemisinine isolated from *Artemisia annua*



Artemisinin Derivatives



9. Meshnick et al., 1996

Standardised herbal medicines for treatment of malaria

- **The use of many validated anti-malarial phytomedicines formulated from traditional medicines have been reported in recent years[10]**

- **Their use lifts the burden of drug pressure for development of resistance**
- **Act as alternatives where there is unavailability of the recommended anti-malarial**

Government approved

- ***Argemone mexicana* (Mali),**
- ***Artemisia annua (China)***
- ***Cinchona bark***

10. Willcox, 2011

Malaria treatment

- **WHO recommends artemisinin-based combination therapy (ACT), as the first-line treatment for malaria.**
- **Artemisinin-lumenfatrine (Coartem)**
- **Non artemisinin combinations like- atovaquone–proguanil (Malarone™)**
- **Sulphadoxine–pyrimethamine (Fansidar™).**
- **It is believed that combining two medicines with different mechanisms of action lowers the probability that a resistant parasite will emerge .**

Prevention: Malaria vaccine

- There are control measures such as vector control, insecticide-treated bed-nets and anti malarial therapy.

- A vaccine esp to infants and pregnant mothers would greatly contribute on the malaria prevention. Unfortunately, there is no vaccine available yet.

- The most advanced malaria vaccine candidate coded as “RTS, S,” has reached phase III clinical trials[10,11]

- GSK has applied for approval of RTS, S vaccine from the European medicine Agency .(www.reuters.com:July 24 ,2014)

10. Casares et al., 2010; 11. Moorthy et al., 2013); 12. Aide et al., 2011.

Challenges of malaria treatment

- In Uganda, a proper treatment of malaria can be estimated at 10-15 USD & not affordable to most people

- Parasite resistance to the cheap and available antimalarials (Chloroquine, mefloquine)

- Recently resistance to artemisinins has been reported[13]
- The need to search for more antimalarials is of utmost importance

13. WHO, 2012

The problem?

- **Though plants are being used in medicine, Most of them are not documented.**
- **Efficacy, safety and active compounds in some of the plants are not known**
- **This limits their wider use, standardization and development into drugs/medicines**

OBJECTIVES

- **Document the indigenous knowledge on the use of the medicinal plants- Creating a basis for phytochemical investigation**

- **Extract and screen for antiplasmodial activity**

- **Isolate & characterize the active compounds which can be lead compounds to discovery of new drugs.**
- **Markers for herbal preparations**

Materials and methods:

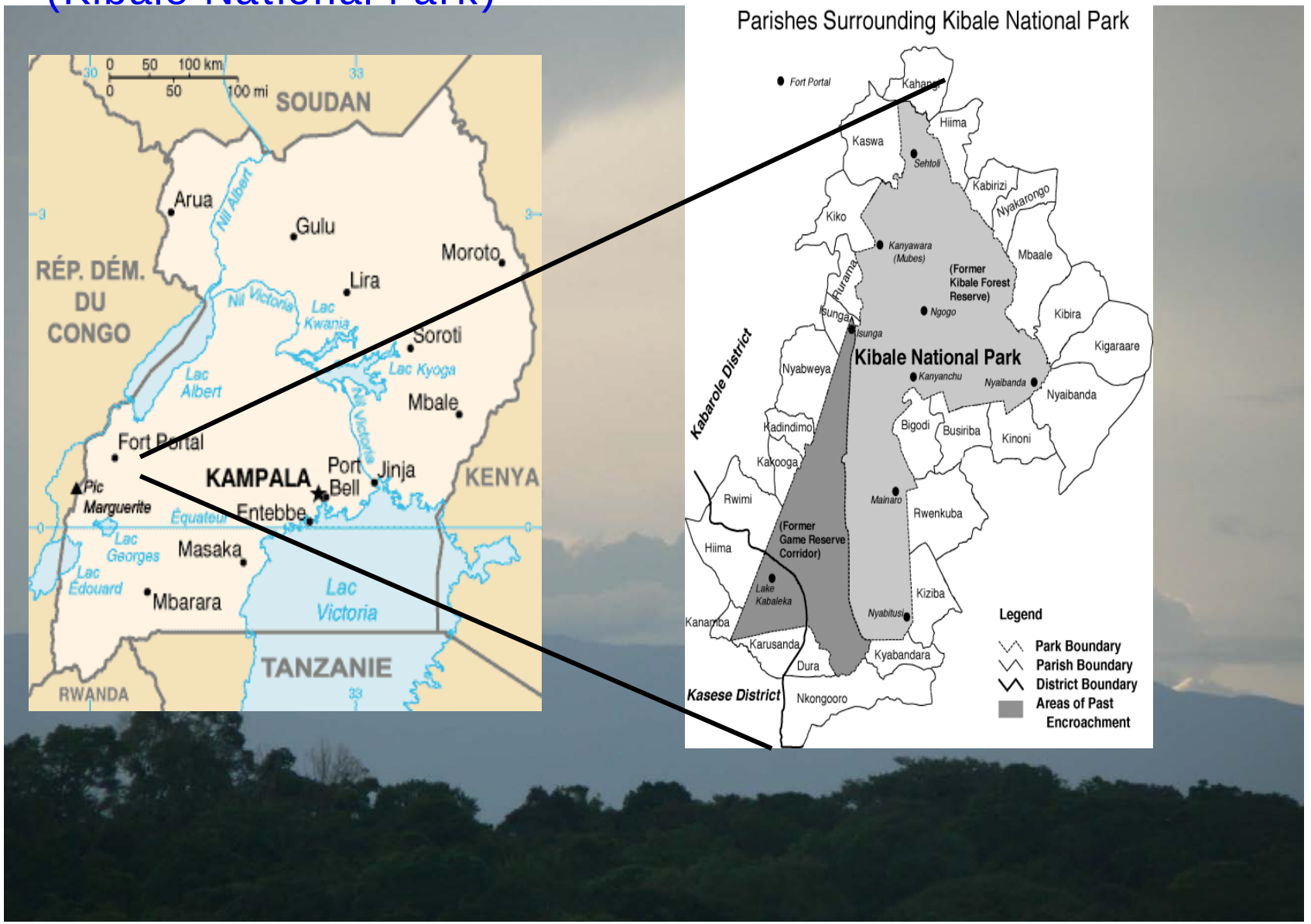
Ethnobotanical survey[15]

- **Efficacy – Antiplasmodial activity**

- determination the chemical structures; chromatopgraphic and spectroscopic means.

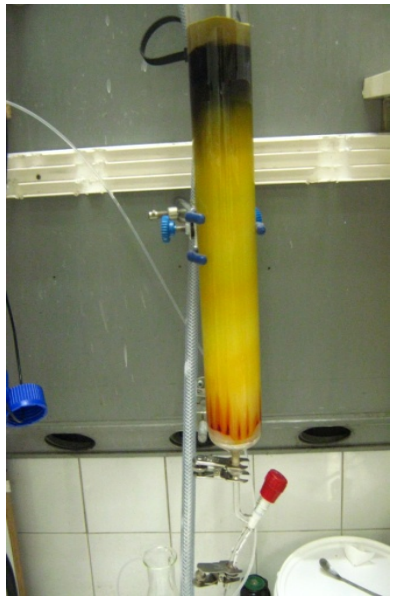
15. Tabuti, 2008

Materials and methods: Ethnobotanical survey: study site (Kibale National Park)

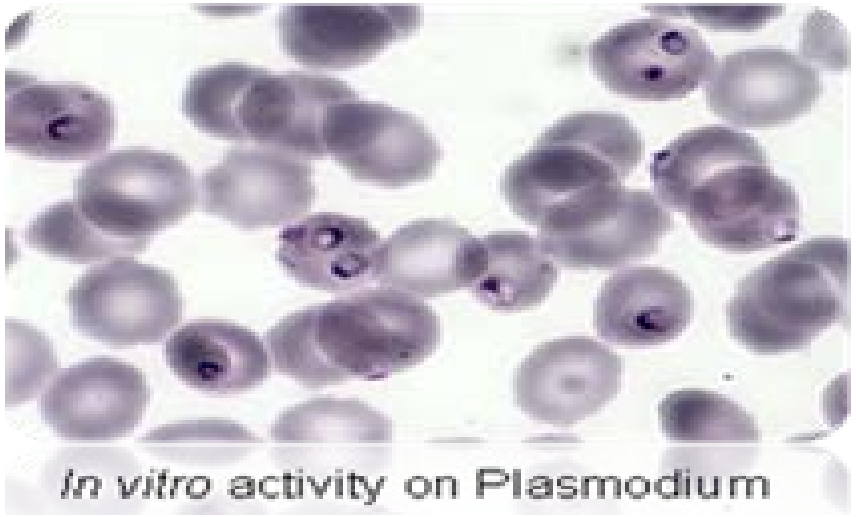


Isolation and Purification

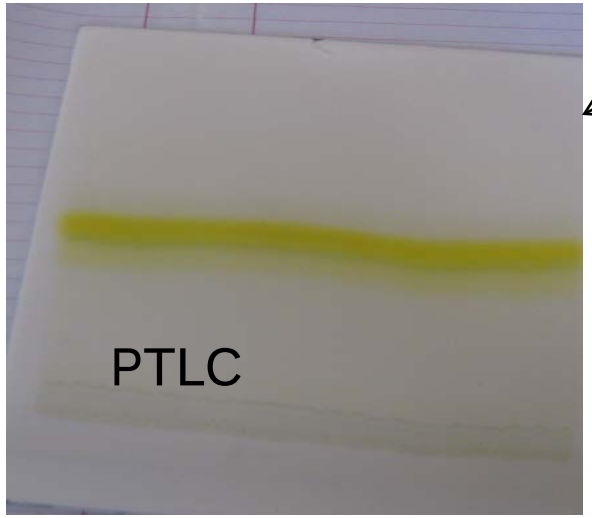
14, 15



fractions



Active fractions



Prep HPLC

SFC

Cytotoxicity

Pure compounds

14. Smilkstein et al., 2004; 15. Desjardins et al., 1979

Materials and Methods

- **1D and 2D-NMR spectra recorded on Bruker 300-600 MHz spectrometer**

- ^{1}HNMR & ^{13}CNMR
- DEPT- CH_2, CH_3,CH
- HSQC- **C-H** ↓
- COSY- **H-H** ↑
- HMBC-**H—C—C—C-**

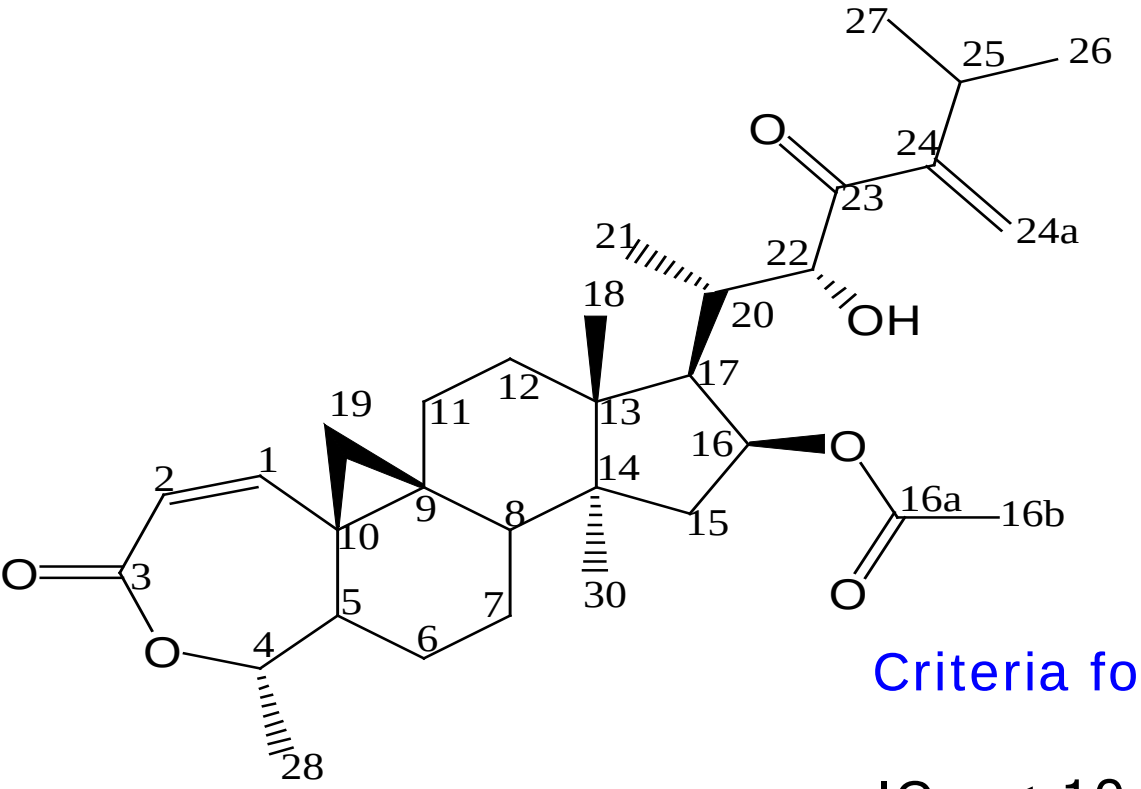
Results and discussions: Ethnobotanical survey

- **Data Organized in table form: Plant name, local name, diseases treated, plant part ; mode of preparation and administration;**

- **131 plant species belonging to 121 genera and 55 families were documented to treat several illnesses.**

Medicinal plants	Disease
Vernonia amygdalina (Kibirizi, omululuza, Olubirizi)	Malaria
Albizia coriaria (Omusisa, Mugavu, Omusita)	Cough
*Neoboutonia macrocalyx (*Ekihora, Omweganza*)*	malaria

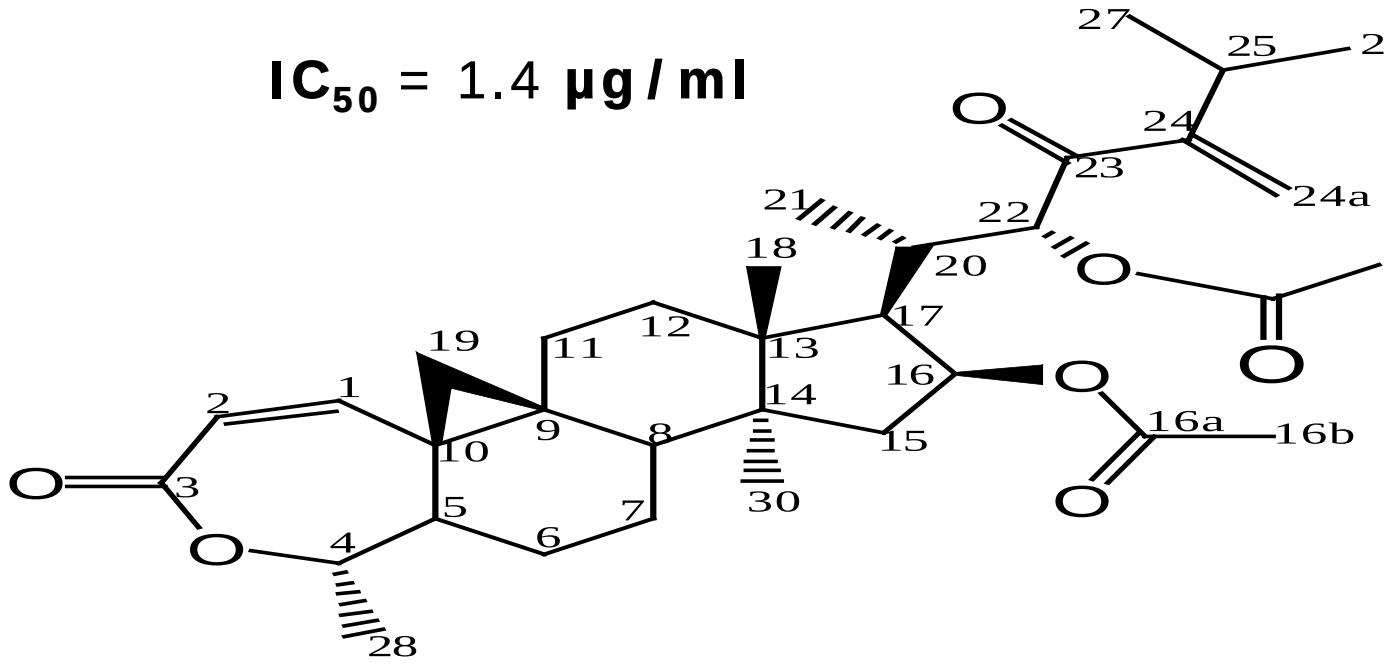
1. Neomacrolactone



IC_{50} = 1.1 µg/ml

2. 22α -acetoxyneomacrolactone

IC_{50} = 1.4 µg/ml



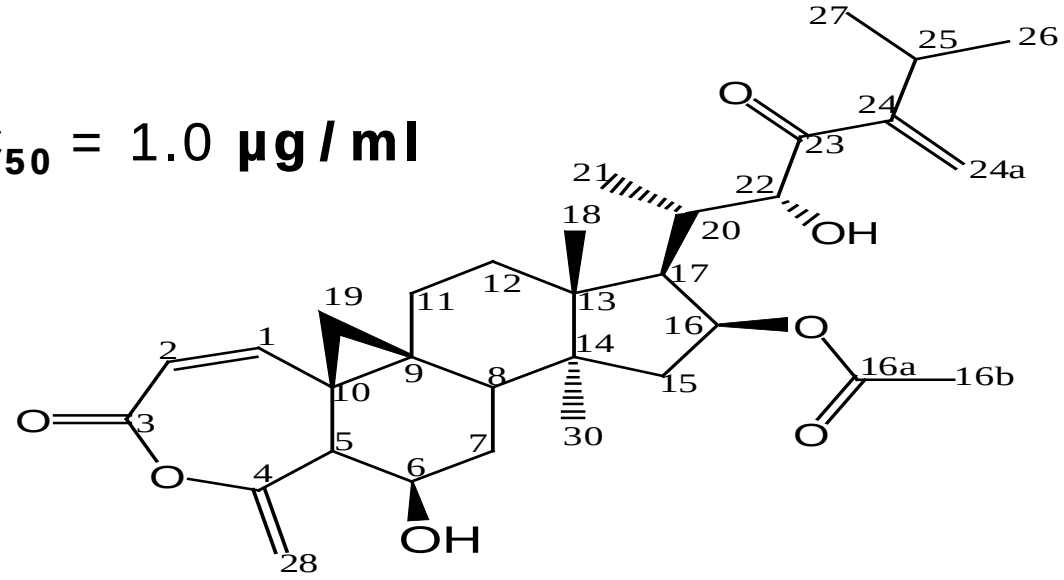
Criteria for in vitro anti plasmodial activity

IC_{50} < 10 µg/mL, good activity;
IC_{50} of 10-50 µg/mL, moderate activity; IC_{50} of 50-100 µg/mL, low activity;
IC_{50} > 100 µg/mL, inactive[17]

17. Batista (1989)

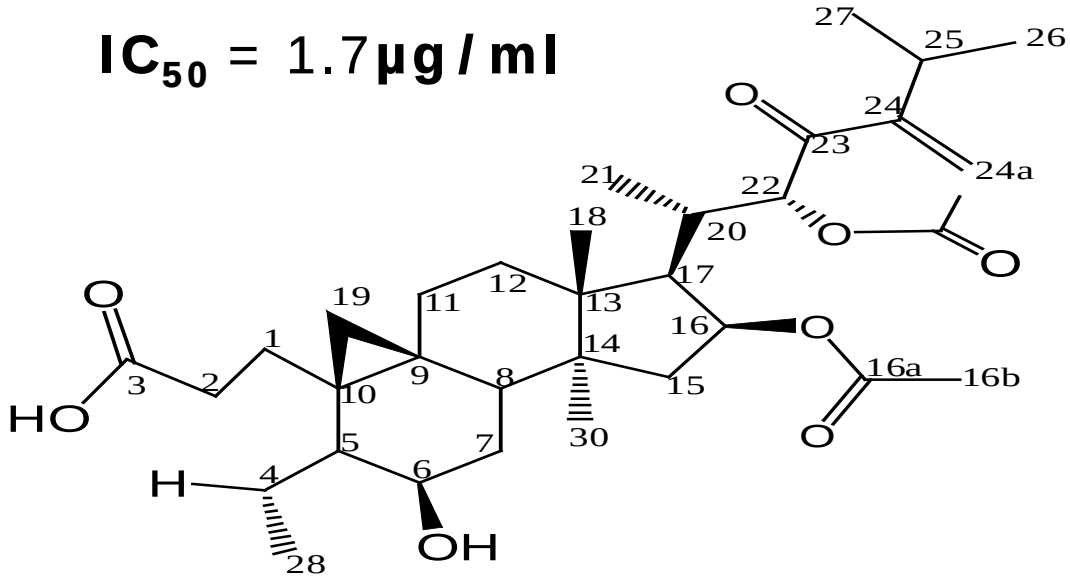
7. Neonthrene

IC_{50} = 1.0 µg/ml

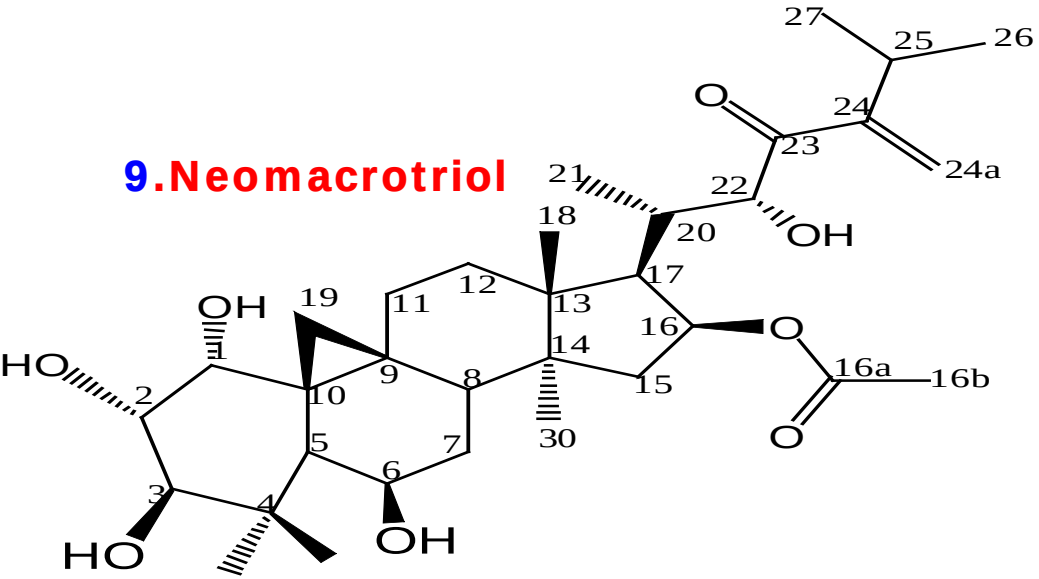


8. Neomacroin

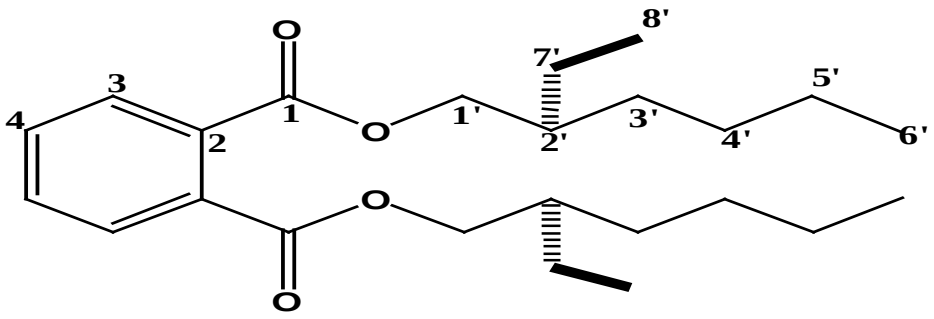
IC_{50} = 1.7µg/ml



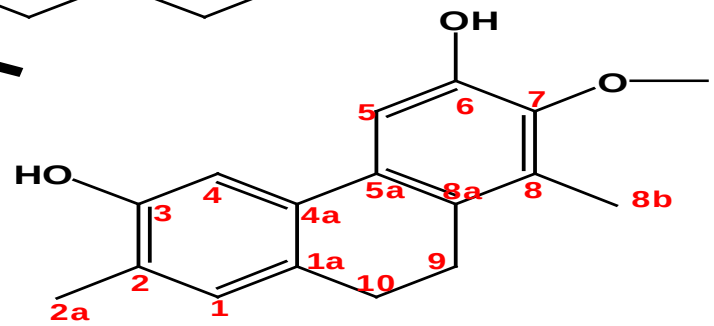
9.Neomacrotriol



10.Di-(2'-ethylhexyl) phthalate



11.7-methoxy-2, 8-dimethyl-9, 10-dihydrophenantherene-3, 6 diol



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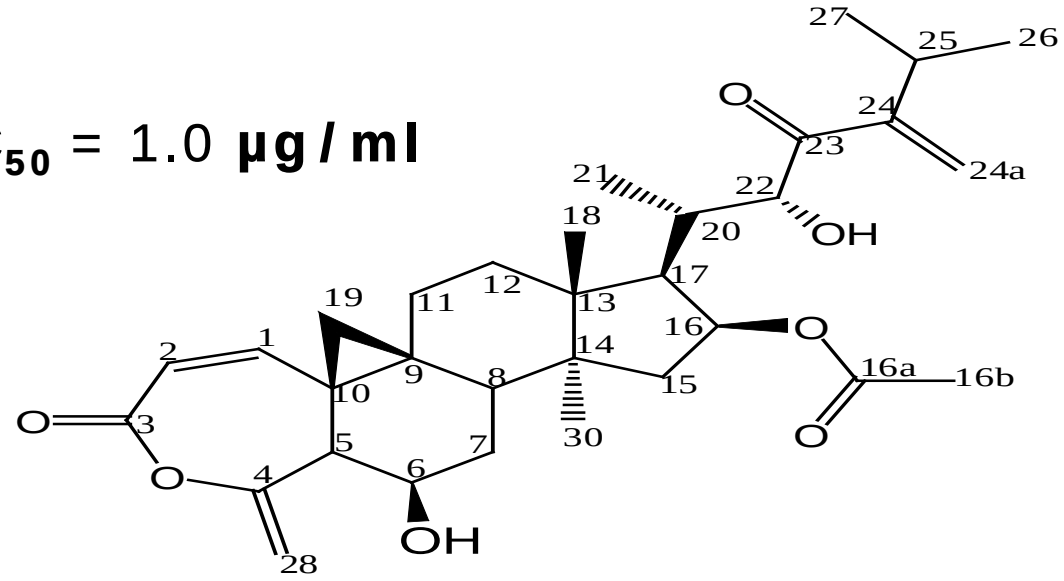

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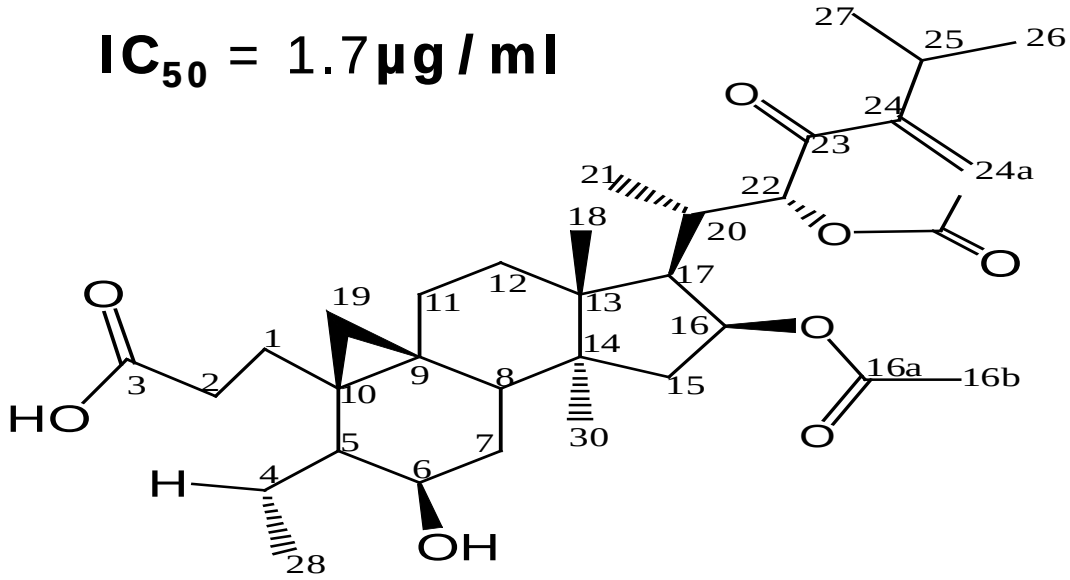

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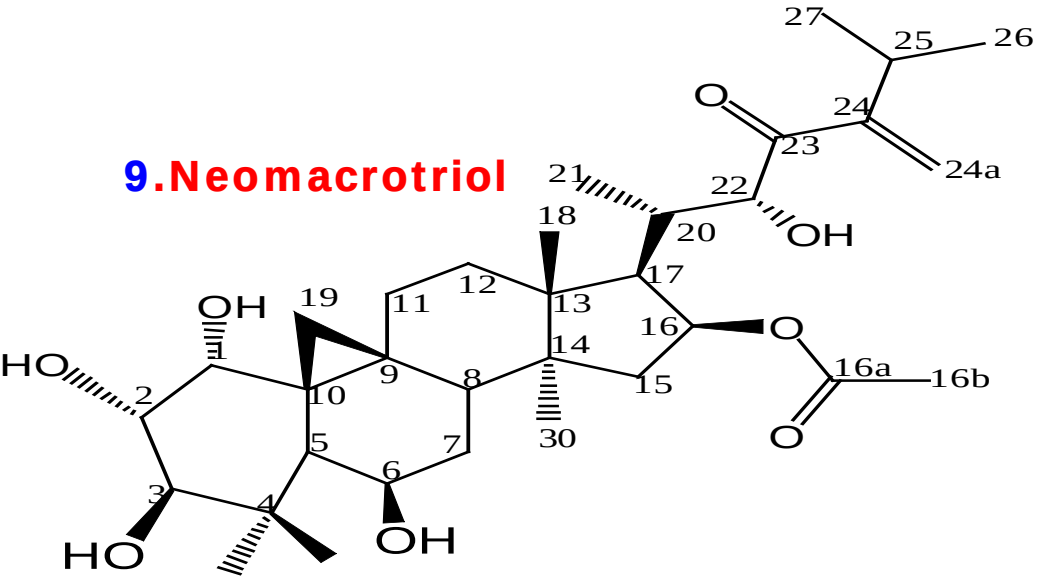

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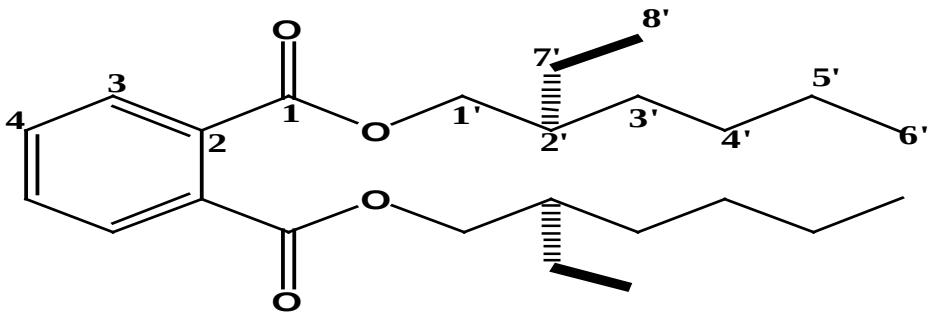

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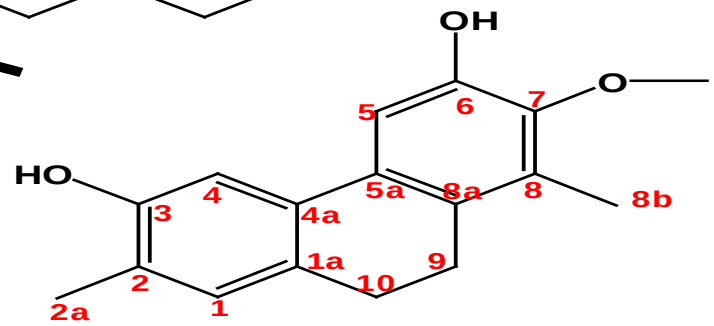

Conclusion and recommendations

- Traditional medicinal plants contribute significantly in the treatment of several diseases esp malaria in this area – need for conservation sensitisation- (medicinal plant gardens)
- These new compounds could serve as leads to the development of new drugs for malaria; need to look at their synergy with available antimalarial.
- Compounds –marker in formulation of a herbal preparation from this plant
- The identification of antimalarial chemicals from *N. Neoboutonia* suggests that these compounds may play a role in the medicinal properties of this plant and therefore its use as a medicinal plant is supported.

Acknowledgement

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SIG Science Initiative Group Institute for Advanced Study

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Thank you