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Tafenoquine As An Anti-Malarial In Treatment Of Babesiosis : A Systemic Review

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ABSTRACT :

Tafenoquine is a synthetic anti-malarial drug with significant potential in the treatment of both malaria and human babesiosis. Malaria, predominantly caused by Plasmodium falciparum and Plasmodium vivax, continues to pose a major global health burden, exacerbated by the emergence of drug-resistant strains that limit the effectiveness of conventional therapies. Babesiosis, a tick-borne disease caused by Babesia species, presents clinical manifestations similar to malaria and is increasingly prevalent. Tafenoquine, approved by the FDA in 2018, has shown efficacy in preventing relapses of Plasmodium vivax malaria and in treating Babesia microti infections, particularly in immunocompromised patients who are resistant to standard treatments. Its long half-life (14–21 days) and unique mechanisms of action, including the generation of reactive oxygen species (ROS) and inhibition of heme polymerization, make it a valuable therapeutic agent. This review highlights the structural characteristics, synthesis processes, pharmacodynamics, and therapeutic applications of tafenoquine, emphasizing its role in addressing the challenges associated with malaria and babesiosis.

Keywords: Tafenoquine, Plasmodium Vivax, Plasmodium Falciparum, Malaria, Babesiosis, Tick borne disease.

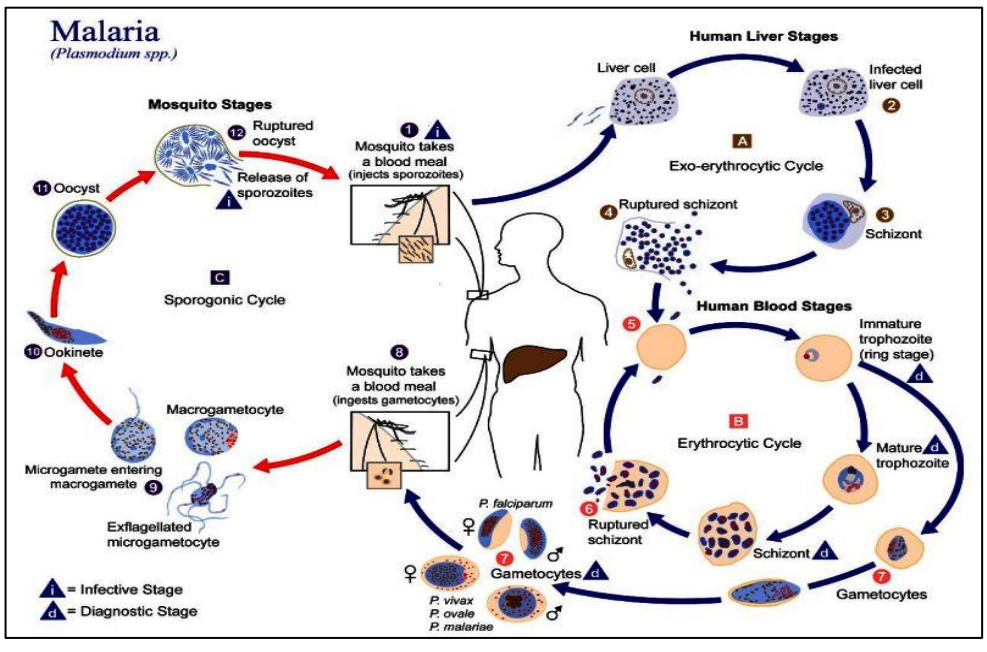
1. Introduction:-

1.1 Malaria:

Malaria is a serious disease spread by mosquitoes, causing around 627,000 deaths worldwide in 2020. Over the years, many medicines, like quinine, chloroquine, mefloquine, primaquine, and artemisinin-based therapies, have been created to treat it. However, using these drugs a lot has caused the malaria parasite to become resistant, meaning the medicines don't work as well anymore, and some can have harmful side effects. To address this, a new drug called tafenoquine has been developed to combat malaria more effectively.[1-6]

Malaria in humans is mainly caused by two species of parasites: Plasmodium falciparum and Plasmodium vivax. Although there has been a 37% reduction in malaria cases worldwide, there were still around 214 million new cases and 438,000 deaths in 2015. Africa was hit the hardest, accounting for 88% of these cases, while Southeast Asia had about 10% of the global malaria case.[7-9]

Fig 1:- Mechanism Action of Malaria



1.2 Babesiosis:-

Human babesiosis is a growing disease spread by ticks, caused by parasites that infect red blood cells. While there are hundreds of Babesia species, only a few infect humans, including Babesia microti, Babesia duncani, Babesia divergens, and a few other related species. These parasites can cause symptoms similar to malaria, and the disease is more common in areas where ticks are widespread.(3) Babesia species are parasites that infect red blood cells in animals. They are spread to mammals, including humans, through tick bites. The types of ticks that spread Babesia parasites depend on the region and the specific parasite. In the life cycle of Babesia, humans are usually infected by accident, with most cases caused by tick bites.[8-10]

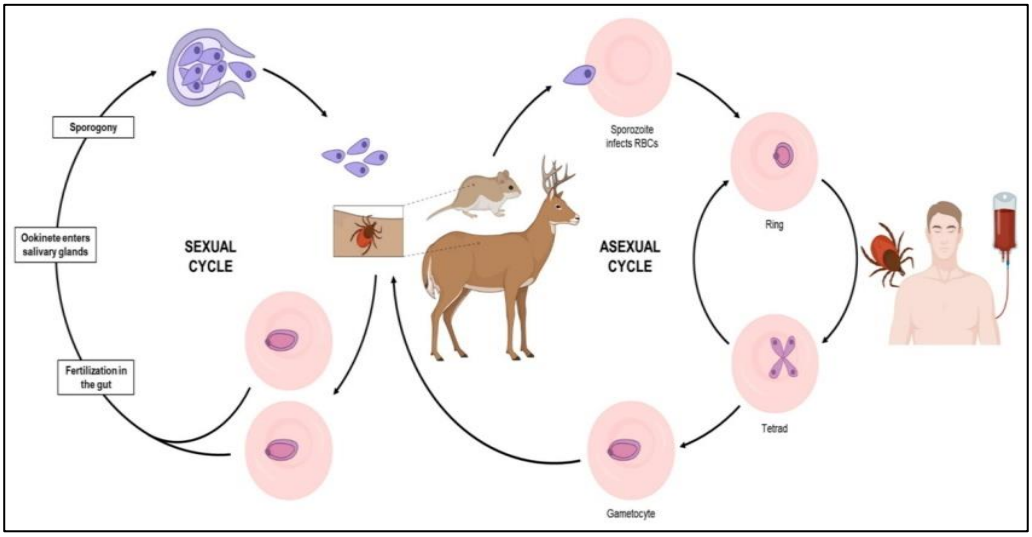


Fig 2:- Mechanism Action of Babesiosis[30]

2. Tafenoquine:-

Tafenoquine is a drug similar to primaquine, used to prevent malaria. It was approved by the US FDA in 2018 for two main purposes: to prevent malaria for up to 6 months and to stop the return of Plasmodium vivax malaria (a type of malaria). Because tafenoquine stays in the body for a long time (about 14–17 days), just one dose per week is enough to protect against malaria.[11-15]

Tafenoquine has been shown to effectively eliminate Babesia microti parasites in three different studies involving hamsters or mice, including mice with severely weakened immune systems (SCID mice). This suggests that tafenoquine could be useful for treating babesiosis; especially in patients with weak immune systems who may need months of treatment to fully recover. These patients include those who have been treated with rituximab.[16-19]

To understand the potential benefits of Tafenoquine, doctors treated an immune compromised patient who had multiple relapses of Babesia microti infection. The infection had become at least partially resistant to two other drugs, azithromycin and atovaquone. The patient was then given tafenoquine for six weeks, which they tolerated well. Over the following 19 months, after finishing the tafenoquine treatment, the patient stayed healthy and did not have any more relapses.[20-23]

2.1 Structure and Properties of Tafenoquine:-

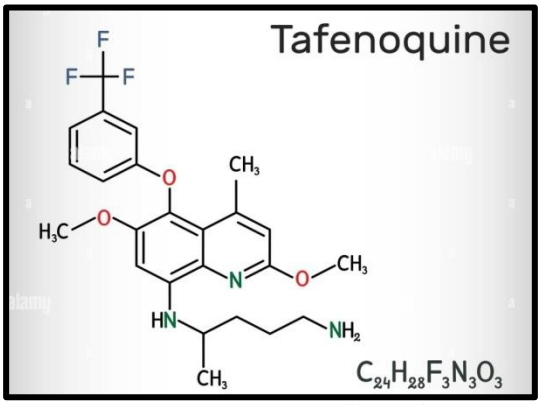


Fig 3 :- Chemical structure of the Tafenoquine

IUPAC Name:- 4-N-[2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinolin-8-yl]pentane-1,4-diamine.[25]
Molecular Formula:- C24H28F3N3O3.C4H6O4
Molecular Weight:- 463.49 g/mol.[26]

Dose:- 400 mg/day for 3 days.[27]
Category:- Anti Malarial Drug.
Other Name:- Etaquine**.**
Melting Point:- 217–219°C.[28]
Boiling Point:- 566-568°C. [29]
Density:- 1.44 g/cm^3.
Solubility:- Soluble in Water, Methanol and Ethanol.
Storage:-
1. Store at 20-25°C (68-77°F).
2. Protect from light.
3. Keep away from moisture.
4. Store in a tight container.

Half Life:-
1 Terminal half Life: 14-21 days.
2 Elimination half Life: 10-14 days.
Brand Name:- Krintafel and Arakoda.[25]
Indication:-
1. Treatment and prevention of plasmodium vivax malaria.
2. Radical cure of plasmodium vivax malaria.[30]

3. Mechanism of Action:-

Tafenoquine (TQ) works by converting into an active form in the body, helped by an enzyme called CYP2D6. The exact way it kills malaria parasites isn't fully understood, but studies suggest that it produces toxic molecules called reactive oxygen species (ROS). These molecules, like hydrogen peroxide, are harmful to the parasite.
In the parasite's red blood cell and liver stages, Tafenoquine metabolites interact with parasite enzymes that are more active during these stages. These interactions cause the production of ROS, which damage the parasite's cells, ultimately killing it.
Additionally, Tafenoquine blocks an important process in the parasite's red blood cell stage—heme polymerization. Normally, the parasite uses this process to neutralize toxic heme, a by product of its digestion of hemoglobin in red blood cells. By blocking heme polymerization, Tafenoquine makes the blood environment toxic for the parasite, which further helps kill it.[24]

4. Synthesis of Tafenoquine:-

Scheme 1:-

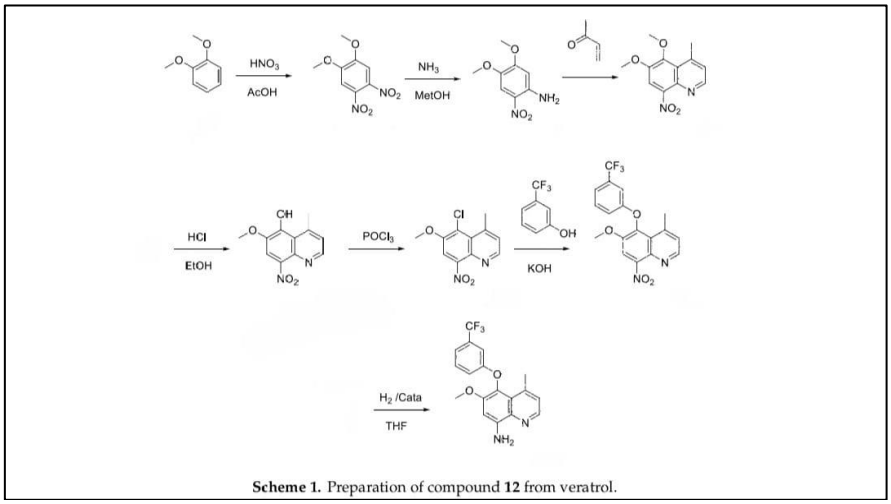


Fig 5:- Synthesis method of tafenoquine 1

Steps involved in Synthesis:-

1. **Starting Material:** The synthesis begins with veratrol (compound 5).
2. **Nitration:** Veratrol undergoes nitration to introduce nitro groups at the 4 and 5 positions, creating a dinitrated veratrol derivative.
3. **Selective Reduction:** One of the nitro groups is selectively reduced by treatment with ammonia in methanol, resulting in a compound with an amine group in one of the positions.
4. **Skraup Reaction:** The quinoline ring system (compound 8) is constructed using a Skraup reaction with methyl vinyl ketone. This reaction cyclizes the structure, forming a quinoline ring with functional groups in the desired positions.

5. **Selective Demthylation:** The methoxy group at the 5 position is selectively demethylated to produce a hydroxyl group, allowing for subsequent functionalization.
6. **Conversion to Chloroquinoline:** The hydroxyquinoline is converted into a chloroquinoline (compound 10) by treatment with phosphorus oxychloride, replacing the hydroxyl group with chlorine.
7. **Introduction of Trifluoromethylphenoxy Group:** The 5-chloroquinoline reacts with 3-hydroxybenzotrifluoride, introducing the desired trifluoromethylphenoxy group at the 5 position.
8. **Final Reduction:** The nitro group at the 8 position is reduced to form an amine group, yielding the key intermediate, compound 12(Tafenoquine), with an overall yield of 7%.[25]

5. Evaluation Parameters of Tafenoquine:-

Solubility:-

Tafenoquine exhibits varying solubility depending on the solvent, temperature, and pH. In water, its solubility is 0.4 mg/mL at 25°C and increases to 0.6 mg/mL at 37°C, both at pH 7.4. Its solubility changes with pH, ranging from 0.1 mg/mL at pH 1.2 to 0.4 mg/mL at pH 7.4. Temperature also plays a significant role, with water solubility increasing from 0.4 mg/mL at 25°C to 0.7 mg/mL at 40°C. In ethanol, tafenoquine is more soluble, with 50 mg/mL at 25°C and reaching 100 mg/mL at 60°C. Solubility is influenced by ethanol concentration, with the highest solubility of 70 mg/mL in 70% ethanol. In methanol, tafenoquine has an even higher solubility, starting at 70 mg/mL at 25°C and rising to 150 mg/mL at 60°C. Methanol concentration also affects solubility, with 70 mg/mL in pure methanol and decreasing as methanol concentration is reduced. Testing methods such as the shake-flask method, HPLC, and UV-Vis spectroscopy are used to assess these solubility profiles, which are critical for understanding the drug's formulation and bioavailability.

5.2 Stability:

Tafenoquine demonstrates stability under various conditions but requires specific precautions to maintain its integrity. Chemically, it is stable in aqueous solutions across pH 1-7 at 25°C, but it is sensitive to UV light and should be protected from direct sunlight. It remains thermally stable up to 60°C but decomposes at temperatures above 200°C. Tafenoquine is stable in the presence of oxidizing agents. Physically, it exhibits polymorphism, which can influence its solubility and bioavailability, and it is hygroscopic, meaning it absorbs moisture, so it must be stored in dry conditions. Biologically, tafenoquine is primarily metabolized by the enzyme CYP 2D6 and remains stable in human plasma at 37°C and pH 7.4, with 99.5% of the drug bound to plasma proteins. For optimal storage, tafenoquine should be kept at 20-25°C (68-77°F), with humidity levels below 60%, in a tight, light-resistant container to protect it from sunlight. Tablets have a shelf life of 2-3 years, while suspensions are stable for 1-2 years from the manufacture date. Its major degradation product is N-desmethyltafenoquine, along with minor metabolites. These stability profiles are crucial for ensuring the drug's efficacy and safety during its shelf life.

5.3 Melting point:-

Tafenoquine has a melting point range of 215-220°C (419-428°F) and begins to decompose at a temperature of 230-235°C (446-455°F). Differential Scanning Calorimetry (DSC) analysis reveals an onset temperature of 213.5°C (416.3°F), a peak temperature of 217.3°C (423.1°F), and an Endset temperature of 221.2°C (430.0°F). Thermogravimetric Analysis (TGA) indicates weight loss of 5% at 200°C (392°F) and 10% at 220°C (428°F). The drug also exhibits polymorphism, with Polymorph I melting between 215-218°C (419-424°F) and Polymorph II between 220-223°C (428-433°F). These thermal properties are essential for understanding the stability and formulation of tafenoquine.

Boiling Point:-

Tafenoquine does not have a distinct boiling point as it decomposes before boiling. Decomposition occurs at a temperature range of 230-235°C (446-455°F) under atmospheric pressure. The drug undergoes sublimation at 180-200°C (356-392°F) when exposed to reduced pressure. Its vapour pressure is extremely low, measured at 1.31 × 10^-7 Pa at 20°C and 1.51 × 10^-6 Pa at 50°C. Tafenoquine demonstrates thermal stability up to 200°C (392°F), with decomposition starting above 230°C (446°F), making these properties critical for handling and storage considerations.

5.6 Reactivity:-

Tafenoquine exhibits stable chemical reactivity under various conditions. It is hydrolytically stable in aqueous solutions across a pH range of 1-7 at 25°C and maintains stability up to 60°C, although decomposition occurs above 200°C. The drug is sensitive to UV light, requiring protection from direct sunlight, and remains stable in the presence of oxidizing agents. It is generally compatible with water, alcohols like ethanol and methanol, and most organic solvents such as acetone and dichloromethane. However, Tafenoquine should not be mixed with strong acids, strong bases, or reducing agents due to potential incompatibilities. Degradation pathways include hydrolytic degradation forming N-desmethyltafenoquine, as well as Photodegradation and thermal degradation producing unknown products. Tafenoquine demonstrates excellent stability in biological fluids, including plasma, blood, and gastric fluid, under physiological conditions (37°C, pH 1.2-7.4). [32]

6. Brand Products of Tafenoquine:-

6.1 Krintafel 150mgTablet:-

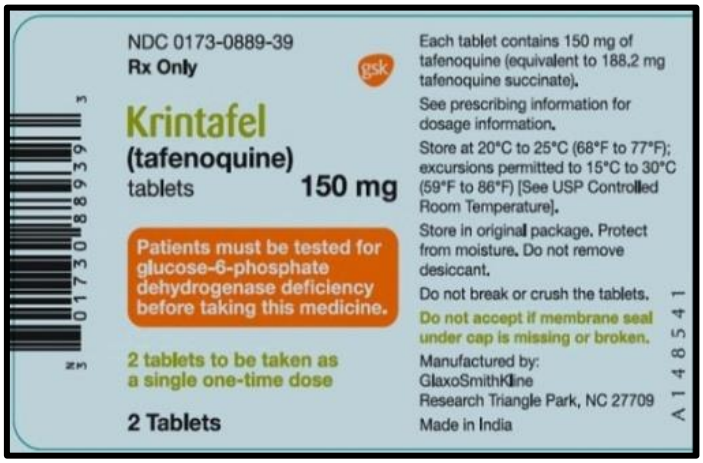


Fig 7:- Krintafel 150 mg Tablet

- **Medical Name:** -Krintafel.
- **API**:-Tafenoquine.
- **Dosage Form**: -150mg.
- **Storage:** -Store at room temperature 20^0C to 25^0C.
- **Manufactured by**: -GSK.[33]

6.2 Arakoda 1 00mg Tablet:-

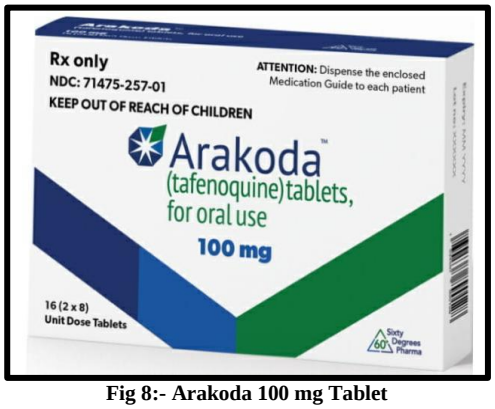


Fig 8:- Arakoda 100 mg Tablet

- **Medical Name:** -Arakoda.
- **API:** -Tafenoquine.
- **Dosage Form: -** 100mg.
- **Precaution:** -Keep out of reach of children.
- **Manufactured by**: -Sixty Degree Pharma.[34]

Conclusion:-

Tafenoquine, initially developed as an antimalarial agent, has shown significant potential in the treatment of Babesiosis, a parasitic infection transmitted by ticks. Its unique pharmacokinetic profile, including a long half-life and the ability to clear persistent infections, makes it a promising therapeutic option. This is particularly evident in immunocompromised patients and cases resistant to standard therapies such as azithromycin and atovaquone. Preclinical studies conducted in animal models and a clinical case report demonstrates its efficacy in eradicating Babesia microti and preventing relapse. These findings underscore the potential of tafenoquine to fill critical gaps in Babesiosis treatment. However, further clinical investigations are essential to establish its safety and efficacy in diverse patient populations.

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