Review Article

Innovation Strategies in 3D Drug Design: A Comprehensive Review of Azithromycin and Atovaquone for Babesiosis Disease

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ABSTRACT

Babesia parasites are the cause of the tick-borne disease babesiosis. It is usually transmitted through the bite of infected ticks, most often the black-legged tick (Ixodes scapularis). It mostly damages red blood cells. Additionally, babesiosis can be passed from mother to foetus during pregnancy or through blood transfusions. The common symptoms of babesiosis include fever, chills, fatigue and haemolytic anaemia. The drug used to treat babesiosis is azithromycin and atovaquone. The azithromycin is the antibiotic targets bacterial ribosome, while atovaquone is an anti-parasitic medicine acts on the electron transport chain of parasite like babesia. These two separate medications are used for different objectives. The combination of azithromycin and atovaquone typically aims to synergistically target multiple aspects of the infectious process. The 3-D drug designing is also known as molecular modelling, an important factor in determining the strength and selectivity of their protein-ligand interaction. It plays a critical role in the development and optimization of azithromycin and atovaquone for the treatment of babesiosis. This method helps in predicting their binding affinity, pharmacokinetics, effective and safety medication. The 3-D drug designing is used for several reasons such as structural insight, targeted optimization, virtual screening. The 3-D drug designing technique for azithromycin and atovaquone can facilitate more effective and durable treatment strategies. This article explains how you approach 3-D drug design.

Keywords: Babesia, azithromycin, atovaquone, molecular modeling, molecular dynamic stimulation, molecular docking, binding site prediction.

INTRODUCTION

The infectious disease babesiosis is brought on by parasites belonging to the genus *Babesia*. It mostly damages red blood cells and is spread by ticks, specifically members of the *Ixodes* genus, which is also responsible for spreading Lyme disease. The following is a synopsis of babesiosis's past. [1]

Figure 1: Babesia

HISTORY:

Discovery:

Babesia bovis, the causative agent of bovine babesiosis, and *Babesia canis*, the causative agent of *canine babesiosis*, were found by Romanian bacteriologist Victor Babeș in 1888, marking the first discovery of the genus Babesia.[1 6]

A splenectomized Yugoslavian farmer who had been bitten by an infected tick was the victim of the first known instance of babesiosis in humans, which was recorded in 1957. Later research revealed that the disease-causing organism was a protozoan parasite of the genus Babesia.[1 3]

Species Identification:

Several Babesia species have been found to cause illness in humans over time. *Babesia microti, Babesia divergens, Babesia duncani*, and *Babesia venatorum* (formerly known as Babesia EU1) are the most prevalent species.[1 3]

Numerous Babesia species have been linked to illness in both people and animals throughout the years. The most frequent species in the US that causes human babesiosis is *Babesia microti*, although *Babesia divergens* is more prevalent in Europe [1 6]

Distribution Geographically:

Babesiosis was initially discovered in Fever, chills, sweats, exhaustion, and muscle aches are typical symptoms. Initially thought to be indigenous to some parts of Europe, babesiosis has been documented in instances all over the world. The disease is more common in the Northeast and upper Midwest of the United States. [1 6 11]

Diagnosis and Treatment:

Blood smears are commonly examined under a microscope to look for signs of Babesia parasites within red blood cells. This is how babesiosis is diagnosed. Combinations of anti parasitic drugs such as atovaquone and azithromycin or

clindamycin and quinine are usually used in conjunction for treatment.[1,3,4]

Preventing tick bites is the main strategy for preventing babesiosis. This entails applying insect repellents, donning protective gear, checking thoroughly for ticks after being outside, and implementing tick control strategies in residential areas.[1 3 7]

Babesia parasites in red blood cells are usually found via microscopic analysis of blood smears for the diagnosis of babesiosis. Combinations of anti parasitic drugs, such as clindamycin and quinine or atovaquone and azithromycin, are frequently used as part of treatment.[3 6]

Research and Awareness:

Constant investigation endeavors to enhance our comprehension of the etiology, pathophysiology, diagnosis, and management of babesiosis. Public health initiatives also prioritize increasing knowledge about the illness and ways to prevent it[3 8]

The goal of ongoing research is to enhance our comprehension of babesiosis epidemiology, pathophysiology, diagnosis, and treatment. Efforts in the field of public health also centre on increasing knowledge about the illness and ways to prevent it from affecting the health of people and animals. [1 6 5]

TYPES:

Babesia-genus organisms are the source of the parasitic disease known as babesiosis. There are numerous *Babesia* species, each with a different geographic distribution, that can infect both humans and animals. Among the significant species are: [1 2 9]

Babesia microti:

The most frequent species in the US that causes babesiosis in humans is *Babesia microti*. The black-legged tick (*Ixodes scapularis*) and the western black-legged tick (*Ixodes pacificus*) are the main vectors of transmission. [1 10]

***Babesia divergens*:**

Mostly found in Europe, *Babesia divergens* causes babesiosis in people. It is spread by the castor bean tick, *Ixodes ricinus*. [2]

Babesia duncani:

Also referred to as the WA1-type *Babesia*, this species is carried by the same ticks that carry *B. microti* and is located on the west coast of the United States. [1]

Babesia bovis:

The bovine tick (*Rhipicephalus microplus*) is the primary vector of infection for this species, which mostly affects cattle. Although human infections are uncommon, it is possible for people to contract it. [3 11]

Babesia canine:

Canine babesiosis is caused by the species *Babesia canis*, which mainly affects dogs. The brown dog tick, or Rhipicephalus sanguineus, is the vector of transmission.[1]

***Babesia vogeli*:**

The brown dog tick (Rhipicephalus sanguineus) is the primary vector of *Babesia vogeli* infection, much like *B. canis.* In tropical and subtropical areas, it is frequently the cause of babesiosis in dogs. [3]

Babesia bigemina:

The cattle tick (*Rhipicephalus microplus)* is the primary vector of infection for this species, which mostly affects cattle. In tropical and subtropical areas, it is a major cause of bovine babesiosis. [2]

***Babesia venatorum**:*

This species, which is also present in Europe, can cause human babesiosis and is spread by the *Ixodes ricinus* castor bean tick. [2]

***Babesia gibsoni*:**

Mostly a parasite of dogs, *Babesia gibsoni* can also sporadically infect people, usually through tick bites or blood transfusions. [3]

Babesia bovis* and *babesia bigemina:

The two main species that cause bovine babesiosis in cattle are *Babesia bovis* and *Babesia bigemina.* They can infect people as well, though this is uncommon; usually through blood transfusions or tick bites. [2]

ADVANTAGES:

Cattle, dogs, and occasionally people are the main animals affected by babesiosis, which is caused by parasites of the genus *Babesia.* Even though the condition might be dangerous, babesiosis may provide the following benefits: [2 17]

Research in Biomedicine:

Babesiosis is used as a model system in several areas of parasitology, including as immunology, parasite-host interactions, vector biology, and medication development. Research on babesiosis aids in the development of novel diagnostic, therapeutic, and preventive techniques as well as a deeper comprehension of related parasite infections. [2]

Vaccine Development:

Research on Babesiosis has aided in the development of vaccines against related parasites as well as *Babesia* parasites. Research on *Babesia* provides insights that are useful in the development of vaccines against other parasites, which may have advantages for both people and animals. [17 18]

Knowledge of the immune system's reaction to a *Babesia* infection offers important insights into the host's defence systems against parasite infections. The creation of vaccinations and treatments for babesiosis and other infectious diseases can be influenced by this understanding.[17]

Drug Development:

Research on babesiosis aids in the hunt for novel medications and treatments that can be used to treat not just babesiosis but also other parasite illnesses. therapeutic development efforts are aided by the identification of therapeutic targets and the testing of possible treatments in animals afflicted with *Babesia.*[2 18]

Studying the life cycle and dynamics of *babesia* parasites, which are spread by ticks, helps us better understand tick ecology and diseases that are carried by ticks. With this information, strategies for managing tick populations and lowering the risk of tick-borne illnesses can be developed.[2 17]

DISADVANTAGES:

Of course! The following are a few drawbacks of babesiosis: [12]

Health Impact:

A variety of flu-like symptoms, such as fever, chills, exhaustion, and muscle pains, can be brought on by babesiosis. Severe cases can result in anaemia, organ failure, or even death, especially in elderly people, people with compromised immune systems, and people with other underlying medical issues. [1, 18]

Economic Burden:

Babesiosis treatment can result in high medical costs, including those for hospital stays, prescription drugs, diagnostic testing, and consultations with medical professionals. In addition, the illness and the long-term repercussions of the condition may result in a loss of productivity. [18 ,13]

Quality of Life:

Babesiosis symptoms, which include discomfort, pain, and exhaustion, can have a major negative influence on a person's quality of life. Severe cases might necessitate extended medical care and recovery, which would further interfere with everyday life tasks, employment, and interpersonal relationships .[1]

Risk of Transmission:

The main way that babesiosis is spread is by tick bites. Consequently, people who spend time outside in regions where infected ticks are common run the risk of being sick. In endemic areas, this risk may restrict outdoor jobs and leisure pursuits.[2, 18]

Co-Infections:

People living in areas where babesiosis is endemic run the risk of contracting additional tick-borne illnesses such anaplasmosis or Lyme disease. Co-infections can make diagnosis and treatment more difficult, which can have a more detrimental effect on health.[1, 2]

Difficulties with Diagnosis and Treatment:

It can be difficult to diagnose babesiosis, especially in areas where it is not widely known. Furthermore, certain anti parasitic drugs may be needed for treatment, and drug resistance might make it difficult to successfully manage the condition.[1 18]

IDEAL CHARACTERISTICS:

Human babesiosis is emerging tick –borne disease caused by intra erythrocytic protozoa.[14]

Babesiosis is primarily transmitted through blood transfusion and organ transplantation.

Babesia microti is a complex species that mainly infects small mammals and consist of five clades.

Where a splenectomised part – time farmer with fever and severe haemoglobinuria died ten days after symptoms first appeared.[15]

Nevertheless, transfusion transmission rarely results in babesiosis.

Red blood cells infected with protozoa of the genus *Babesia* cause the parasitic condition known as babesiosis. The optimal features of treating or controlling babesiosis would incorporate a number of crucial elements.

Early Diagnosis and Detection:

Timely treatment depends on the early diagnosis of babesiosis using reliable diagnostic procedures. Accurate diagnosis depends heavily on quick diagnostic procedures including polymerase chain reaction (PCR), serological assays, and blood smears.[2, 3]

Effective Treatment choices:

The best management for babesiosis entails timely removal of the parasite from the bloodstream using effective treatment choices. Anti parasitic drugs such azithromycin plus atovaquone, clindamycin plus quinine, or atovaquone-proguanil are frequently utilized. It is imperative to guarantee the accessibility and availability of these treatments. [2, 18]

Safety and Tolerability of therapy:

The optimal course of therapy should have few side effects and be both safe and well-tolerated by the patient. This is especially crucial for vulnerable groups, like the elderly and those with impaired immune systems.[3, 18]

Handling Complications:

Babesiosis can cause serious side effects, particularly in immune compromised people or people with underlying medical issues. Thus, the best course of treatment should involve monitoring for and managing possible side effects such organ failure, haemolytic anaemia, and co-infections with other pathogens like Lyme disease.[2, 3, 18]

Implementing preventive measures is essential to lowering the risk of babesiosis transmission. Insect repellents,

protective gear, avoiding tick-infested regions, checking for ticks after outdoor activities, and managing tick populations in endemic areas are some examples of these tactics.[18]

Public Health Education and Awareness:

Community involvement and disease prevention depend on public health initiatives that educate people about babesiosis, including its symptoms, transmission, and preventive actions.[3, 16]

Research and Development:

To gain a deeper understanding of the epidemiology, patho physiology, and management of babesiosis, ongoing research is required. This covers the creation of fresh vaccinations, medications, and diagnostic instruments.[2, 3]

Collaboration and Surveillance:

Effective surveillance, monitoring, and control of babesiosis outbreaks depend on collaboration between healthcare professionals, public health authorities, researchers, and communities. This entails exchanging data, materials, and best practices in order to tackle the illness in its entirety.[2 18]

CONSTITUENTS:

Babesia protozoa are the parasite infection that causes babesiosis. The components of babesiosis include several elements about the infection, how it spreads, clinical signs, diagnosis, therapy, and avoidance. The following are the main components of babesiosis:[1, 17]

Pathogen (*Bacillus* species):

The genus *Babesia* contains the parasites that cause babesiosis; human infections have been reported for a number of species, including *Babesia microti, Babesia divergens, Babesia duncani*, and others. [2]

Vector:

Ticks of *Ixodes*

The primary way that *babesia* parasites infect people is through the bite of an infected Ixodes tick, specifically *Ixodes ricinus* in Europe and *Ixodes scapularis* in North America.[1, 2]

Hosts in reservoirs:

Deer and mice are examples of both domestic and wild animals that act as reservoir hosts for *Babesia* parasites, helping to maintain the parasite's life cycle in Nature. [2 17]

Transmission route:

Babesia parasites are transmitted to humans by the feeding of infected ticks, which inject the parasites into the host's bloodstream.[1, 17]

Clinical Manifestations:

Babesiosis can cause a variety of clinical symptoms, including fever, chills, lethargy, sweats, myalgia, headache, nausea, and haemolytic anaemia. Severe cases can result in consequences such as organ failure and death, particularly in immune compromised patients.[17]

APPLICATION:

Protein that reacted with *B. gibsoni* – infected serum was selected and the applied to develop sero diagnostic methods, such as Enzyme linked immunosorbent assay and indirect combs test with the sera from dogs experimentally and naturally infected with *B. gibsoni* [17]

Recombinant Bg TRAP was difficult to express in large amounts in the Entamoeba Histolytica coli system.

DIAGNOSIS:

Person who is living on travelling while at risk of contracting *babesia microti* [1]

Where endemic babesiosis is present blood transfusion within six months and a high risk of babesiosis suspicion

SYMPTOMS:

High fever, tiredness, chills, sweating, headache, cough, loss of appetite, muscle or joint aches. [19]

SEVERE SYMPTOMS:

Pale skin (pallor)

Yellowish skin or eyes (jaundice)

Dark pee (urine)

Shortness of breath (dyspnea)

Nausea and vomiting

Neck stiffness

Abdominal pain [19]

CAUSES:

The protozoan parasites that cause malaria, toxoplasmosis and cryto sporidiosis are also found in the phylum apicumlexa, which includes the babesia species. Humans are infected by four clades of *babesia* species, the main species in each clade are

B.microti

B.duncani

B.divergens and

B. venatorum mostly closely related to the large *babesia* clade

Large *babesia* mostly infects ungulated but also includes K01 strain.[1]

MECHANISM OF ACTION:

uses

Used to treat babesiosis

Used as Anti malarial agent

It is act as blood schizonticides

It is also act as tissue schizonticides

Treatment of bacterial infection [20]

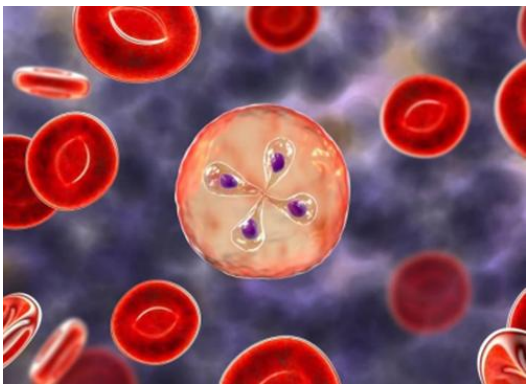


Figure 2: Virus attack on RBC

METHODOLOGY:

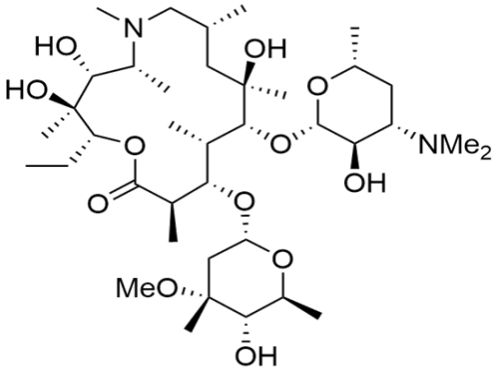
The 3-D structure of drug designing is an important factor in determine the strength and selectivity of their protein-ligand interaction.[22] Molecular docking, molecular modelling, and molecular dynamics simulations, binding site prediction and structure-activities relationship are some of the processes involved in 3D drug design.[23] Azithromycin is an antibiotic targets bacterial ribosome, while atovaquone is an anti parasitic medicine, acts on the electron transport chain of parasite like *babesia.* These two separate medications are used for different objectives. [22] The combination of azithromycin and atovaquone typically aim to synergistically target multiple aspects of the infectious process. For each of these substances, the following is an explanation of how you might approach 3D drug design:

Molecular modeling:

Utilize databases or molecular modelling software to obtain the three-dimensional structures of azithromycin and atovaquone. Optimize both molecules' geometries and make sure their conformations are stable by minimizing their energy. Here the first step is retrieving the 2D chemical structure of azithromycin and atovaquone from databases then convert into 3D by using software chem draw and chem sketch. [24]

It is used to study their three- dimensional structure, predict their interactions with target molecules (such as enzymes or receptors) and analyze their pharmacological properties. The molecular modelling for azithromycin can help in understanding its interaction with bacterial ribosome. Likewise, molecular modelling can help investigate the interactions between atovaquone and elements of the parasite's electron transport chain, like the cyto chrome bc1 complex. Through the process of mimicking atovaquone's binding to specific targets, scientists can learn more about the mechanism of action of atovaquone and figure out how to make it more effective against malaria. [25]

It can direct the creation of more effective and targeted medications to treat malaria and bacterial infections, respectively. Use a molecular visualization program like PyMOL, VMD, or Chimera to see the azithromycin's three-dimensional structure. This makes the spatial structure of the molecule easier to understand and makes results easier to communicate.[25]



Azithromycin

Figure 3:

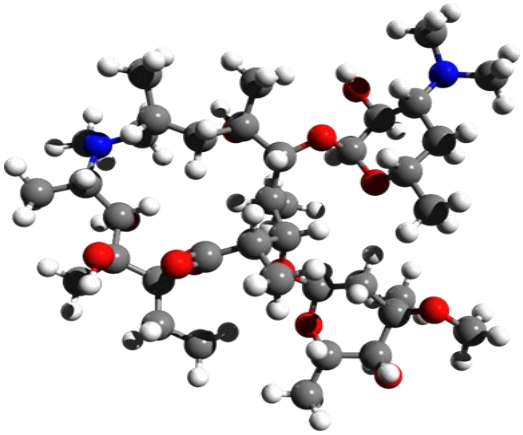


Figure 4:

3-D View of Azithromycin

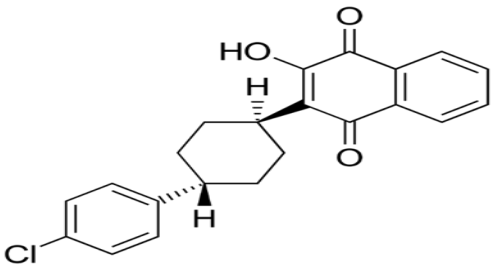


Figure 5: Atovaquone

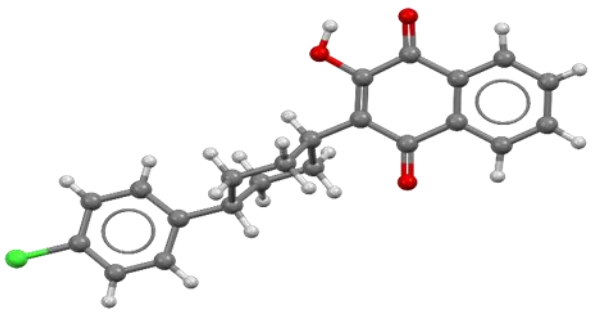


Figure 6: 3-D view of Atovaquone

Molecular docking:

Studying its interactions with elements of the malaria parasite's electron transport chain, like the cyto chrome bc1 complex, can be facilitated using molecular modelling. Researchers can learn more about atovaquone's mode of action and discover strategies to further its anti-malarial efficacy by mimicking its binding to these targets. extensively used to forecast the mechanism and affinity of small molecule (ligand) binding to target protein (receptor) in drug discovery and design. This is an illustration of a reference article that covers the use of molecular docking. When searching for new drugs, molecular docking is often utilized to screen through huge libraries of tiny compounds and estimate how well they will connect to a target protein. In doing so, it becomes easier to find possible lead molecules that medicinal chemistry can refine. [26]

Protein-protein interactions can also be studied via docking, which can be used to predict how two protein molecules will connect to one another. Designing inhibitors or modulators of protein-protein interactions and comprehending signalling cascades will benefit from this. Docking results can inform the rational design of novel compounds with enhanced therapeutic efficacy [30 31 34]

To estimate azithromycin's binding affinity with its target—typically the bacterial ribosome—conduct molecular docking studies. software application such as Autodock vina or Gold can be used. It is essential to identify the bacterial ribosome's active site and for the ligand (azithromycin) to dock within this site. [27]

Molecular dynamic stimulation:

In structural biology, biochemistry, and drug development, molecular dynamics simulation is an invaluable tool that offers precise insights into bio molecular systems and processes that are frequently difficult to detect empirically.[27, 28]

Validate the binding modes of the lead compounds and predict their dynamic behaviour within the target protein using molecular dynamics simulations. This step helps in understanding the stability of the drug-target complexes and provides insights into their interactions over time. This method is used to predict the interaction of azithromycin and atovaquone for treat babesiosis disease. This allows researchers to explore the dynamic behaviour of bio molecular systems and understand their structure, function, and interactions at an atomic level. They aid in the identification and optimization of lead compounds, prediction of binding modes, and exploration of drug resistance mechanisms.[27 28 30]

Software application for molecular dynamic simulation is GROMACS, AMBER, NAMD, open MM. The choice of software depends on factors such as the nature of the system being studied, computational resources available, and specific research requirements. careful validation and interpretation of simulation results are essential to ensure their relevance and reliability in understanding the behaviour of azithromycin and atovaquone at the molecular level.[28 29]

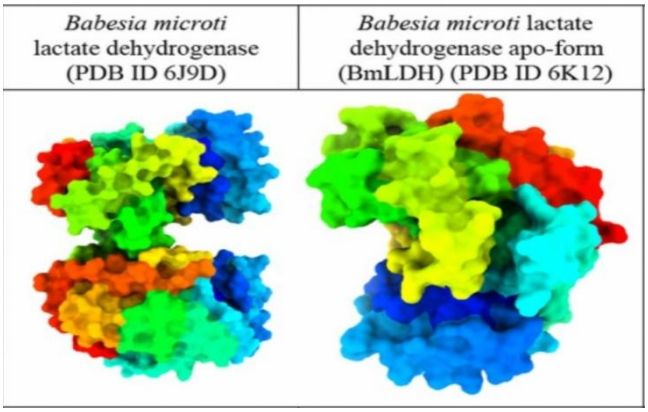


Figure 7: [27]

Binding site prediction:

Understanding the mechanisms of action of small compounds such as azithromycin and atovaquone and directing drug design efforts can be greatly aided by predicting their binding locations. [34]

Researchers can estimate probable binding sites for azithromycin and atovaquone with their target proteins or bio molecules by using these computational approaches. This provides important information for additional experimental validation and drug development efforts. [34] Determine possible binding sites for azithromycin on bacterial ribosome and atovaquone on the parasite cyto chrome bc1 complex. For binding site prediction, use computational techniques like Auto Dock Vina and gold [34]

Structural – activity relationship:

It is also known as lead optimization. Use computational chemistry methods and structure-activity relationship (SAR) research to refine the lead compounds that have been found. To improve the lead compounds' pharmacokinetic, selectivity, and potency characteristics, change their chemical structures. To verify the stability of the lead compounds in complex with their respective targets, do molecular dynamics simulations.[32 33]

Azithromycin and atovaquone's structure-activity relationship (SAR) in connection to babesiosis entails examining how differences in these medications' molecular structures impact their potency, effectiveness, and safety against Babesia parasites.[35]

Azithromycin, a macrolide antibiotic, has shown promise in the treatment of babesiosis, particularly in combination with other drugs like atovaquone. SAR studies for azithromycin in babesiosis may involve exploring modifications to its macro cyclic ring, side chains, or functional groups to enhance its anti-Babesia activity.[35]

SAR studies for atovaquone may involve exploring substitutions on its naphtha quinone ring or modifications to its side chains to improve its efficacy, bioavailability, or resistance profile against *Babesia* parasites. studies of the

structure-activity relationship to clarify the molecular processes behind their anti-Babesia action and direct the creation of more effective and targeted therapies. [35]

DISCUSSION

With these techniques, you can create an azithromycin and atovaquone combination medication that may work in concert to treat parasite infections as well as bacterial infections. Prior to clinical translation, it is imperative to conduct thorough experimental investigations to evaluate the combination's safety and efficacy. The 3D drug designing allows research to design molecules with enhanced therapeutic properties and ultimately improving drug development processes.

CONCLUSION AND FUTURE SCOPE

Comprehensive tools for optimizing atovaquone and azithromycin combination therapy for babesiosis treatment are provided by 3-D drug development approaches. important insight into the molecular mechanism of action, drug receptor interaction, and resistance mechanism are provided by molecular modelling, molecular docking, molecular dynamic simulations, binding site prediction, and structural-activity relationship. Through the utilization of these methodologies, researcher can optimize the effectiveness, safety and selectivity of atovaquone and azithromycin combination therapy, hence leading to better treatment result for patient with babesiosis. By embracing theses emerging trends across discipline, it can collectively contribute to advancing knowledge and addressing complex global challenges.

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