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ARTEMISININ PROPHYLACTIC EFFECT AGAINST HEPATOCELLULAR CARCINOMA IN SCHISTOSOMA MANSONI AND HEPATITIS C VIRUS CO-INFECTION: A REVIEW

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is one of the most common leading causes of cancer related deaths. Chronic *Schistosoma mansoni* and HCV co-infection accelerates the progression of liver disease increasing incidence of early development of HCC. Anti-parasitic rule of artemisinin together with its anti-viral and antitumor effects make this drug a good target for investigation as a prophylaxis against HCC. Molecular Docking and Dynamics Simulation have improved the quality of healthcare studies through providing high quality predictions of in silicon effect of drugs. This review aims to discuss repositioning artemisinin as a prophylactic treatment against development of HCC in patients co infected with *Schistosoma mansoni* and HCV, pointing out the rule of Molecular docking and dynamics in predicting the rate of success of this drug.

Keywords: Schistosomiasis, HCV, HCC, Artemisinin, Molecular docking & dynamics simulation.

Introduction

Hepatocellular Carcinoma: Liver cancer is still considered a global health challenge. The incidence of liver cancer is growing worldwide, estimated by 2025, >1 million individuals will be affected by liver cancer annually (CDC, 2022). Hepatocellular carcinoma (HCC) is the most common form of liver cancer and accounts for more than 90% of cases. HCC is the fourth common cause of cancer related death (Llovet *et al*, 2016). The pathogenesis of HCC varies according to the genotoxic insults and aetiologis. Although general understanding of the pathophysiology and causes of the disease has improved, this knowledge needs to be translated to clinical practice. Llovet *et al.* (2018) in USA summarized the molecular targets and therapies for the management of HCC and discuss the advancements expected in the near future, including biomarker-driven treatments and immunotherapies. Villanueva, 2019 has reported that Hepatocellular carcinoma is the fourth leading cause of cancer-related mortality and has an increasing incidence worldwide. They added that locoregional therapies, defined as imaging-guided liver tumor-directed procedures, play a leading part in the management of 50–60% of HCCs. The diagnosis of HCC is usually based on non-invasive criteria, Hence there is a great need for molecular characterization of the tumor using tissue biopsies in clinical practice (Kim *et al* 2019). Simon *et al*. (2020) in China reported that Prevention of HCC is considered a challenge, beyond vaccines preventing HBV infection and anti-viral therapies for HBV and HCV infection, cumulative data support the preventive role of coffee and aspirin. The management of HCC has markedly improved since the early 2010s (Llovet *et al*, 2021). Tabrizian *et al.* (2022) in USA reported that in a large, multicenter cohort of HCC patients successfully down-staged to within MC, 10-year post-LT outcomes were excellent, validating national down-staging policies and showing a clear utility benefit for LT prioritization decision making. HCC surgical management recurrence after LT was associated with improved survival in well-selected patients and should be pursued, if feasible.

Review and Discussion

Hepatitis C Virus: Chronic HCV infection is the most common underlying liver disease among patients with HCC in North America, Europe and Japan (Akinyemiju *et al*, 2017).

Unlike HBV, HCV is an RNA virus that didn't integrate into the host genome and, therefore, the risk of HCC is primarily limited to those who develop cirrhosis or chronic liver damage with bridging fibrosis. With the use of direct-acting antiviral (DAA) therapy, an increasing proportion of patients with HCV infection were successfully treated to achieve a sustained virological response (SVR) resulting in a 50-80% redu-ction in the HCC risk (Kanwal *et al,* 2017). Additionally, patients with HCV-induced cirrhosis continue to have a persistent risk of developing HCC (>2% a year) even after SVR and should therefore remain under close surveillance (Ioannou *et al*, 2019).

Mutation and malignant transformation of HCV infected cells are triggered by the HCV protein expression (Ezzat *et al,* 2021). In Egypt, HCV increased prevalence can be explained by the initiation of the mass schistosomiasis treatment campaigns in the 1950s and the 1960s (Elgharaby *et al*, 2017).The prevalence of schistosomiasis and HCV co-infection was approximately 50% and other studies reported about 27.3% (Mazigo *et al*, 2017). Interestingly the exposure risk for co-infected patients with HCV and schistosomiasis was two and half times greater than that in chronic HCV patients without schistosomiasis. The patients with hepatosplenic schistosomiasis associated with HCV were reported to have marked depression in cell-mediated immune responses (Omar *et al*, 2017). The effects of the hepatotropic virus in these patients may modify the Th2-dominated chronic granulomatous phase of schistosomiasis. The induction of strong-specific T cell response, is dominant together with infiltration of large number of specific interferon (IFN)-γ-producing CD8+ cells in hepatic parenchyma. These immunological changes lead to decrease cytokine levels via down-regulation of the production of Th2 cytokine which is dominant during *S. mansoni* infection. Schistosomiasis and HCV co-infection causes advanced liver disease and increases risk of development of complications, this is more evident in patients with high HCV-RNA titers, which increased the incidence of liver cirrhosis and hepatocellular carcinoma (Kamal, 2018). Measuring T helper cells either Th1 or Th2 together with the specific subset of memory CD8+ T cells assessed the immune response to *S. mansoni* co-infection with HCV (Omar, 2019).

Schistosomiasis, is considered a public health problem in many countries. With increasing prevalence annually, it was estimated to affect at least 290.8 million people, claiming 24,068 lives globally (McManus *et al,* 2018). It was highly debilitating, leading to an estimated loss of 1.43 million all-age disability-adjusted life years (Kyu *et al*, 2018). Chronic *S. mansoni* infection is normal sequence of the disease. The deposition of schistosome eggs in tissues, particularly liver, and immunological responses against them are the main causes of chronic hepatosplenic schistosomiasis (Mangoud *et al,* 2004). Schistosomiasis acute phase is a usual presentation of patient who travel to endemic areas and exposed to fresh water. The clinical presentation varies according to the severity of the disease, which depends on the infection dose and patient's immunological response to the parasite's eggs, which affect the levels of circulating immune complexes in patient's blood (Newlan, 2019). The development of chronic schistosomiasis is a common sequel of the disease the transition into a chronic state is due to the entrapment of the parasite eggs that are continuously deposited in the host tissue by the host immune responses led to granuloma formation around these trapped eggs, followed by formation of large tracts of fibrotic material along the liver vasculature (Costain *et al,* 2018)

The progressive periportal fibrosis (PPF) led to restriction of blood flow through the liver leading to the development of portal hypertension associated collateral vasculature and esophageal varices and often accompanying ascites (Abdel-Bary *et al,* 2021). Death can occur as a result of repeated at-

tacks or one severe attack of hematemesis caused by the rupturing of esophageal varices entrapment of schistosomiasis eggs in the liver leads to activation of immune system. This activation of the immune system causes a moderate type 1 helper (Th1) response. A dominant Th2 immune response then develops and eosinophils are recruited. Initiation of a fibrinogenic process in the liver leads to formation of multiple granulomas around the eggs. Inspite of the importance of these immunological events to the infected person, since granuloma formation block the hepatotoxic effects of parasite egg antigen, they always lead to many harmful effects on the hepatobiliary system due to fibrosis with excessive accumulation of collagen and extracellular matrix proteins in the periportal space (Carbonell *et al*, 2021). The balance that happens between both TH1- and TH2-type cytokines, influence the extent of pathology and also the occurrence and development of fibrosis, granuloma formation always leads to marked portal and perilobular fibrosis. After granuloma formation a critical process always happens in the lesion, which is angiogenesis. Angiogenesis has unique mode of action since through participating in fibrogenesis and in fibrosis degradation (Masamba and Kappo, 2021).

Treatment of *Schistosoma mansoni*: The Sub-Saharan Africa carries the highest global burden of schistosomiasis, and so since 2003, large-scale mass drug administration (MDA) programs of praziquantel (PZQ), as a preventative chemotherapy (PC), was implemented across much of SSA. In many countries morbidity control has been, generally successful (Deol *et al*, 2019). all these facts lead to a revision of the World Health Organization (WHO) strategic plan for a vision of "a world free of schistosomiasis", which included controlling morbidity of schistosomiasis by 2020 (defined as prevalence of heavy-intensity infection (WHO, 2021). Likewise, the newly-launched revised WHO 2021-2030 NTD Roadmap aims to eliminate schistosomiasis as a public health problem in all endemic countries by 2030. Complete cessation of transmission (reduction of infection incidence to zero) is a target in selected African regions by 2030 (WHO, 2021). Mawa *et al*. (2021) in Uganda reported that for intestinal schistosomiasis, severe morbidity manifests as periportal fibrosis (PPF) in which large tracts of macro-fibrosis of the liver, visible by ultrasound, can occlude the main portal vein leading to portal hypertension (PHT), sequelae such as ascites and collateral vasculature, and ultimately fatalities. For urogenital schistosomiasis, severe morbidity manifests as the pathogenic throughout the urinary system and genitals, and is a definitive cause of squamous cell bladder carcinoma. They added that preventative chemotherapy (PC) programs, delivered through mass drug administration (MDA) of praziquantel (PZQ), were at the forefront of schistosomiasis control programs in the sub-Saharan Africa since their commencement in Uganda in 2003.

It was clearly shown that reduced susceptibility of schistosomes to PZQ can be selected as a cause for increased prevalence of heavy-intensity infection and extending the limit for WHO programs till 2030 this resistance comes with a cost in terms of reduced schistosomes reproductive fitness and genetic diversity. Hence there was a strong variability of response to annual MDA observed by field-based studies which implement large-scale intervention trials to reach optimal treatment (Binder *et al,* 2020). The *Schistosoma* spp. infection fails to decline in prevalence and/or intensity to expected levels despite multiple years of annual MDA, affecting the success of control strategies in several endemic areas is thus likely to be affected by hostparasite-drug interactions and these associated trade-offs have raised concerns there may be reduced drug efficacy, especially in communities with a more intensive history of PZQ treatment, Consequently, there is an urgent need for new anti-schistosomal drugs (Mawa *et al,* 2021).

Artemisinin anti-parasitic activity: Artem-

isinin is a phytochemical derived from *Artemisia annua* (Utzinger *et al*, 2002). This medicinal plant has been used in Chinese medicine for more than two millennia to treat fever and chills. In 1972, artemisinin was identified as an active principle of *A. annua* (Eichhorn *et al*, 2013). *Artemisia judaica* belongs to the family Asteraceae one of the largest families of angiosperms and contains 1600 to 1700 genera with 24,000 species distributed worldwide (Hussain *et al,* 2017). Known as shih in the Middle-East, *A. judaica* is an aromatic shrub found mainly in the deserts of the Middle-East, Egypt, and serval North African countries and is traditionally used as an anthelmintic drug (Abdou *et al,* 2022). The therapeutic value of artemisinin against malaria infections has been shown in a large number of clinical trials since its first discovery and artemisinin-based combination therapies (ACT) now are an indispensable part of modern malaria treatment worldwide (Krishna *et al*, 2014). Researchers revealed that its mechanism of action as antimalarial drug is due to special internal structures called endoperoxide linkages (peroxide bridges). When the malaria parasites invade the human body, they digest a large amount of hemoglobin in host erythrocytes to obtain the nutrients necessary for growth and maturation. Hemoglobin digestion releases abundant heme and free ferrous iron. This heme and iron activate artemisinin, cleaving the peroxide bridge and producing free radicals that alkylate malaria membrane-associated proteins and impair mitochondria functions, as well as reactive oxygen species (ROS), which induce parasite damage and eventual death (Ho *et al*, 2014). In Schistosoma species, as in the case of plasmodia, artemisinins action may be either a heme initiated formation of free radicals Retraction of redox homeostasis by the artemisinins interacting with reduced flavin cofactors of flavin disulfide reductases. Notably within S. mansoni, the multifunctional disulfide reductase thioredoxin glutathione reductase (TGR) functionally replaces TrxR and GR of plasmodia and therefore TGR is a potentially important drug target (Gold *et al*, 2017).

Artemisinin antiviral activity: Besides its antischistosomal properties, it was HCV, it was shown that peroxide treatment (which results in ROS induction), at concentrations that were not toxic to the cells, resulted in the disruption of active HCV replication complexes through reduction of the amount of NS3 and NS5A in the replication complexes (Pawlotsky, 2012). The anti-HCV activity of ART induced by peroxides could be negated by L-N-Acetylcysteine (L-NAC), the molecule that inhibits ROS generation. Obeid *et al*. (2013) reported earlier that ART inhibits in vitro HCV replicon replication at concentrations that have no effect on host cell growth. ART also exerts in vitro Inhibition of replication of infectious HCV, through the cleavage of the endoperoxide bridge within the ART molecule results in the release of carbon radicals and reactive oxygen species (ROS) at concentrations that were not toxic to the cells, resulted in the disruption of active HCV replication complexes through reduction of the amount of NS3 and NS5A in the replication complexes

Artemisinin antitumor activity: The endoperoxide linkage and production of ROS as a vital feature in artemisinin as antimalarial, antischistosomal and antiviral activity, also is considered as a key to liver protection antioxidant, anti-inflammatory, pro-apoptotic, and carcinostatic mechanisms. Thus, artemisinin deserves further examination to determine its clinical usage. Although artemisinin may play a promising role in liver disease treatment, no review has been conducted to systematically clarify the potential use and mechanism of artemisinin and its derivatives in the treatment of liver diseases (Greenshields *et al,* 2017). Increasing evidence has shown that artemisinin and its derivatives have anti-tumor effects, Also, artemisinin and its active metabolite dihydroartimesinin (DHA) decreased cancer cells, induced apoptosis and inflammatory cell infiltration in

tumor sections. Research has recently indicated that the IL-6/JAK/STAT signaling pathway was involved in the development and progression of HCC (Lokau, *et al*, 2019).

Artemisinins can also play a role against HCC by antagonizing fibrogenesis at the pathological level in its end-stage, also by inhibiting angiogenesis, invasion, and metastasis in the development of HCC. Inhibition of fibrogenesis by ART was shown through inhibit ion of activation of primary HSC cells induced by CCl4, and its effect was associated with ferroptosis and activation of ferritin autophagy in mice (Kong *et al*, 2019). In the presence of various liver injuries, quiescent HSCs are activated, suggesting the beginning of fibrosis, followed by cirrhosis and HCC (Barry *et al,* 2020).

The important antitumor activities of artemisinins could be divided into four aspects: antioxidant, anti-inflammatory, pro-apoptotic, and carcinostatic. These four effects interact together to resist the onset and progression of cellular damage that eventually leads to the development of hepatitis, followed by cirrhosis and HCC (Xiong and Huang, 2021).

Previous pharmacokinetic studies suggest that artemisinins are mainly metabolized by liver microsomes and can trigger auto-induction; thus, the half-life of artemisinin is short in vivo. Simultaneously, artemisinins affect the metabolism of other drugs by regulating enzymes related to metabolism. Some animal studies showed that certain doses of artemisinin produce toxic effects to varying degrees. Nevertheless, there are few toxic effects when artemisinins were used to treat malaria in humans. A possible reason for this is that smaller doses over longer periods are more toxic than larger doses over shorter periods. Therefore, this should be considered when artemisinin is used in the future. (Xiong and Huang, 2021). Despite all the accumulating evidence for the application of artemisinins, their use as treatment for chronic hepatic disease in routine clinical practice is extremely limited. Due to the lack of reliable way to assess the success rate and formulate the treatment regimen before application of controlled clinical trials. The discovery of various conventional and advanced techniques including molecular docking and dynamics simulation seems to docking and dynamics simulation seems to be a promising solution.

Molecular docking and dynamics simulation: Molecular modeling, docking, and simulation strategies depend on a rigid view of the receptor–ligand interaction by using computational resources (Meng *et al,* 2011). The concept was to simulate how two (or more) molecular structures (protein or enzyme, nucleic acid, drug…etc.) interact together (Ferreira *et al*, 2015). Protein ligand (small molecule), protein nucleic acid, and protein-protein docking always play a crusial role in predicting the ligand's orientation and binding affinity in the active site of the target protein. The properties of binding affinity always point out the binding strength of a ligand with a target molecule. Protein-protein docking is usually applied to predict the complex structure from known configuration of the individual proteins. The protein-DNA or protein-RNA interaction plays important role in the biological process, replication, transcription, and protein synthesis. The results of molecular docking always depend on binding energies, the number of hydrogen bonds, and potential hits found in the protein-ligand complex structure (Wójcikowski *et al*, 2017).

Molecular docking and dynamics simulation are always, applied at earlier stages of the drug design process, helping focusing on new drug positioning and repurposing by providing valuable understanding of its chemical pathway in a virtual manner, these studies are usually complementary to experimental studies but with more precise results. Molecular docking is an "in-silico" method a computational in vitro- that gives insight to binding targets of small compounds or macromolecules in contact with a receptor predicting their molecular interac-

tions. This increases the availability of ranking these drugs and derivatives according to a hierarchy determined using very specific scoring functions. The scoring function was important for predicting the drug orientation, identifying the intermolecular complex structure. The SF is important to rank to which degree ligand is relative to another. Designing the SF is a Key aspect and is considered a fundamental step (Xu *et al,* 2018). The docking reliability depends on the exact level of accuracy of the SFs, which is important to define the mode of binding and the ligand site. The SF identifies the potential drugs that lead to a specific protein target. Finding a rapid and accurate prediction is considered a great challenging task in this process (Guedes *et al,* 2018). Many protocols that offer Molecular docking and dynamic simulation as a logical approach to improving the drug discovery process have been implemented (Santos *et al*, 2019).

An important challenge that faces studies using Molecular "docking" in structure-based drug designing is the inability to capture the conformational changes and flexibility of the interfacing molecules. Molecular "dynamics" (MD) simulation approach evolved to solve this challenge and to estimate the time dependent behavior of a molecular system. It is a thermodynamic based method, which can be widely used to understand the receptor–ligand interaction complex or docked complex by conformational detail at atomic level (Santos *et al*, 2019).

Molecular "dynamics" (MD) is important in studying the energy landscape of protein – ligand interaction and pointing out their conformational changes, which are defective in high resolution experiments. It is also crusial for the structural refinements of post docking complexes, which can identify the exact degree of compatibility between the receptor–ligand complexes and enhance the complex state, allowing rescoring of the docked complex. MD simulation is important in investigating the biomolecular processes, that is, protein-ligand, protein –nucleic acid, and protein-peptide binding, and their conformation alterations pointing out all atomic behavior at femtosecond (Singh and Pathak, 2020). Thus, MD simulations have many additional advantages over Molecular docking as it considers the important physiological parameters essential to predict actual mode of interactions (Moitessier *et al,* 2008). MD simulation are widely used for knowing the structure-based drug design, the binding dynamics of a ligand molecule with a protein target, protein unfolding problems, conformational/ compactness analysis of the molecular system, and impact of mutations, or drug resistance (Singh *et al*, 2020)

Conclusion

Artemesinin play a prophylactic role against development of HCC in *S. mansoni* & HCV co-infection. Highlighting the rule of in silico prediction of the success rate and formulating the treatment regimen before clinical application.

Recommendations

In spite of promising effects of artemisinin for schistosomaiasis, HCV & HCC, chronic infection in clinical practice was extremely limited. This is due to lack of randomized controlled clinical trials. Evaluation of repositioning Artemisinin as a potent and safe drug should be further standardized. Using molecular docking and dynamics is important to uncover the potential drug effect. Further computational studies are needed to form conclusive insight on drug efficacy of repurposing molecules to fight HCC development in risky patients.

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