1. Introduction

Malaria is currently a disease of global concern and major health problem especially in countries where it is endemic. Historically, malaria has killed more people than any other infectious disease and still shows significant levels of mortality and morbidity in developing countries including India (Reviewed by Ahmad and Tuteja, 2012). The estimated global number of clinical cases of malaria is about 350 - 500 million per year with an estimated 1.1 million deaths each year while recent WHO report showed decrease in the number of death (~219 million cases and an estimated 660 000 deaths) due to malaria (Murray et al., 2012; WHO-Malaria-Report, 2011 and 2012). This is why malaria has been considered one of the most important parasitic diseases with higher morbidity and mortality. Recent climate changes have been of great interest as potential future impact on malaria eradication (Patz et al., 2005; Lafferty, 2009; Gething et al., 2010). As the global temperature is rising, it has been proposed that spread and intensification of disease, and increase in morbidity and mortality rates of malaria will occur (Tanser et al., 2003; McMichael and Woodruff, 2004; Ermert et al., 2012). Thus it is expected that it will severely influence existing global health policy.

Malaria is a parasitic disease caused by Plasmodium species. More than 100 species of Plasmodium can infect animal species such as reptiles, birds and various mammals (Tuteja, 2007b, 2007c) but only four species of parasite can infect humans under natural conditions: viz. \textit{Plasmodium falciparum}, \textit{Plasmodium vivax}, \textit{Plasmodium ovale} and \textit{Plasmodium malarie}. Emergence of fifth species of Plasmodium which can infect human have been reported recently (Kantele and Jokiranta, 2011). Thus out of the five species, \textit{P. falciparum} malaria is severe, potentially fatal and is responsible for most of the malaria cases (Nosten et al., 2004; Dev et al., 2006; Girard et al., 2007; Tuteja, 2007b, 2007c). Human malaria parasites complete their life cycle and spread by infecting two types of hosts: asexual life cycle in humans and sexual life cycle in female Anopheles mosquitoes (Tuteja, 2010). The asexual erythrocytic stage of parasites develop successively into four different stages viz ring, trophozoite, schizonts and then merozoites. This asexual stage is responsible for most of the clinical symptoms of malaria.

The emergence of drug resistant parasite has been serious threat to the malaria eradication. The current scenario for the prevention and treatment of malaria is becoming difficult due
to the emergence of drug resistant *P. falciparum* parasite. The first case of malarial drug chloroquine resistant parasite was reported in 1957 and consequently chloroquine had become futile for the treatment of malaria. Artemisinin combination therapies are currently being used to treat the uncomplicated *P. falciparum* malaria in most of the malaria endemic countries (WHO-Malaria-Report, 2012). Recently, it has also been reported that partial artemisinin-resistant *P. falciparum* malaria has emerged (Noedl et al., 2009). The resistant strains have the potential to spread to different parts of the world and subsequently become a global threat for malaria control and treatment (Dondorp et al., 2010). Despite the development of several artemisinin derivative drugs which are being used for the treatment of uncomplicated malaria (Baird, 2005, Guidelines for the treatment of malaria, second edition Geneva: WHO, 2011), the control of malaria in endemic region is limited by drug resistance, relatively high cost and limited availability of newer drugs (Rosenthal, 2008). There are currently no alternative drugs to replace artemisinin derivatives. Considering the future problem and complication of drug resistant parasite, it is necessary to unravel the molecular aspects of pathogenesis of malaria in order to facilitate the development of novel approaches and identification of some novel targets for drug and vaccine candidates. Several efforts have been made to develop vaccine against malaria but their trials failed due to a number of problems while some are still under clinical trials. Like vaccine against malaria, it is equally important to develop next generation antimalarial to treat the drug resistant parasite. After the availability of complete genome sequence of *P. falciparum* at Plasmodb (www.PlasmoDB.org), it has been possible to study the essential genes important for parasite biology and pathogenesis (Girard et al., 2007). The parasite specific genes important for various pathways can serve as good targets for antimalarial therapy. Recently our lab has reported a genome wide analysis of *P. falciparum* helicases suggesting parasite specific helicases can be good antimalarial drug targets (Tuteja, 2010).

*P. falciparum* RuvB like proteins are homologs of bacterial RuvB protein and seems close to AAA+ class of proteins. Two homologs of RuvB in yeast (ScRuvBL1) and ScRuvBL2 (Qiu et al., 1998) have been studied in detail and the knockout of ScRUVBL1 demonstrates its essentiality in yeast growth. Yeast RuvBs (Rvbp1 and Rvbp2) and human RuvBs (Pontin and Reptin) have been studied under different names. Alternate names of RuvB1/RuvB2 are as RuvBL1/RuvBL2, RUVBL1/UVBL2, Pontin/Reptin, TIP49/TIP48, TAP54α/TAP54β, p50/p47, ECP54/ECP51, INO80H/INO80J, TIH1/TIH2, and
TIP49A/TIP49B (Jha and Dutta, 2009; Huen et al., 2010; Ahmad and Tuteja, 2012). To avoid the confusion of names, in this thesis RuvB1 and RuvB2 will be used whenever required.

RuvB1 and RuvB2 are essential components of several multiprotein complexes and play crucial role in diverse cellular activities. It is expected that their mode of function was very similar in these wide range of complexes (Huen et al., 2010). Considering all the above roles and involvement in several important cellular pathways in different system, *P. falciparum* RuvB like proteins are very similar to those of *Saccharomyces cerevisiae* RuvB Proteins and most likely play essential role in the parasite biology. Further high transcriptome level of *P. falciparum* RuvB like proteins during differentiation (schizonts stage) of parasite indicates the requirement of these proteins during this stage (plasmodb.org). Thus we are expecting that these proteins play very important or essential role during cell cycle progression. Therefore it has been of recent interest to explore the RuvB family of proteins from *P. falciparum* in detail and study their role in various activities in the malaria parasite. Here in this study we will focus on RuvB proteins of *P. falciparum*, along with their homologs in yeast, *E. coli*, human and other systems. Based on the previous studies in different organisms and structural similarity with RuvBs of *E. coli*, yeast and human, it can be speculated that *P. falciparum* RuvBs might be playing crucial role in parasite biology and thus can be expected as a good drug target for control of the malaria (Ahmad and Tuteja, 2012).

HsRuvB1 and HsRuvB2 (Pontin and Reptin) proteins are reported to be involved in several human cancers (Huber et al., 2008) and the inhibition of RuvBL2 (Reptin) resulted into the blockage of cancerous growth (Menard et al., 2010). Thus the human RuvB1/RuvB2 has been of recent interest and is considered as suitable drug targets for cancer therapy. Contrary to human and yeast RuvBs, *P. falciparum* contains an additional RuvB protein (Tuteja, 2010; Ahmad and Tuteja, 2012). Hence the question which needs to be addressed is why malaria parasite requires three instead of two RuvB like proteins. To answer the reason, it is necessary to first explore the biochemical role to understand their activities in the parasite. Considering these crucial roles of human RuvBs proteins, and the presence of additional RuvB like protein in *P. falciparum* has fascinated us to explore the biochemical role in order to get the insight of roles of PfRuvBs in malaria parasite which will help further to establish it as potential drug target for the control of malaria.