ABSTRACT

The increasing number of multi-drug resistant strains of *Plasmodium* is posing a great threat to healthcare of people in the endemic areas. The problem is further aggravated by the absence of an effective malaria vaccine and evolution of insecticide resistant vectors. Hence, there is a need to look for newer alternatives to control the disease. Traditional medicinal plants have played an important role in antimalarial chemotherapy. The best known antimalarials till date (quinine and artemisinin) are plant derived. The present study was undertaken to evaluate the *in vitro* and *in vivo* antiplasmodial efficacy of traditional medicinal plants *Sonchus brachyotus* (leaves), *Thalictrum foliolosum* (leaves), *Thlaspi arvense* (whole plant) and *Bergenia ciliata* (leaves and rhizomes).

In the present study, the extracts were evaluated for their potential *in vitro* antiplasmodial activity against *P. berghei* as well as the chloroquine resistant (RKL-9) and sensitive (MRC-2) strains of *P. falciparum*. All the extracts (ELESB, ELETF, EWETA, ELEBC and EREBC) exhibited high *in vitro* activity against NK-65 strain of *P. berghei* with IC50<5µg/ml. ELESB, ELETF and EREBC were observed to be highly active (IC50<5µg/ml) while EWETA (IC50=5µg/ml) and ELEBC (IC50=6.4µg/ml) exhibited promising activity against the RKL-9 strain of *P. falciparum*. ELESB, EWETA, ELEBC and EREBC exhibited high activity against the MRC-2 strain with IC50<5µg/ml, while ELETF showed promising activity (IC50=5.89µg/ml).

*In vitro* cytotoxicity studies were also carried out to determine the 50% cytotoxic concentration (CC50) of the plant extracts. All the extracts were observed to be non-toxic to both cancerous (*HeLa*) and normal (dermal fibroblasts) cell lines with CC50>1000µg/ml. The selectivity index (SI) for all the extracts was calculated to be >10. High SI establishes the safety of the extracts and points the presence of specific antiplasmodial activity without any general toxicity.

The observed antimalarial efficacy can be attributed to the presence of different phytoconstituents like alkaloids, terpenoids, quinones, flavonoids, etc., which have been implicated in the antiplasmodial activity of plant extracts. ELESB revealed the presence of diterpenes, alkaloids and phytosterols, while ELETF tested positive for alkaloids, saponins, phenols, triterpenes, phytosterols. Anthraquinones, steroids, diterpenes, triterpenes, phytosterols were detected in EWETA. ELEBC was observed to contain flavonoids, phenols,
diterpenes and steroids, whereas, presence of phenols, saponins, anthraquinones, steroids, triterpenes, cardiac glycosides, tannins and phytosterols was evident in the rhizome extract (EREBC).

The *in vivo* suppressive, preventive and curative activity of the extracts was assessed against *P. berghei*. The acute toxicity of ELESB, ELETF and ELEBC was observed to be >5g/kg, while EWETA and EREBC recorded LD50>4g/kg, indicative of their safety for oral administration at higher and intermediate doses respectively. In the suppressive test, based upon their ED50 value EWETA and EREBC were classified as very good antimalarials (ED50<50mg/kg), ELESB as a good antimalarial (ED50<250mg/kg) and ELEBC (ED50=616.70mg/kg) and ELETF (ED50=579.56mg/kg) as inactive against early infection of *P. berghei*. In the preventive test, EREBC showed best preventive activity at a dose of 500mg/kg, while ELETF, EWETA and ELEBC were found to exhibit good preventive activity at lower doses. ELESB exhibited considerable preventive potential at all the tested doses (100-750mg/kg). Best curative activity was evident at intermediate doses of ELESB (500mg/kg), EWETA (100mg/kg) and ELEBC (750mg/kg).

The biochemical and histopathological studies were also performed to assess the effect of extract administration on hepatic and renal function of the host. Treatment with the extracts resulted in slightly increased serum levels of liver (ALP, bilirubin, SGOT, SGPT) and kidney (creatinine, urea) function biomarkers as well as some histopathological alterations in transverse sections of liver and kidney of the surviving mice on day 28. However, the increased hepatic and renal function biomarker levels and the changes in the normal tissue architecture were comparable to the chloroquine treated mice. Also, more biochemical and histopathological changes were evident at higher doses of the extracts. All these observations illustrate the safety of extracts to the liver and kidney of the host at lower doses.

The present study highlights considerable *in vitro* and *in vivo* antiplasmodial potential of these medicinal plant extracts along with their safety to the liver and kidney function of the host at lower doses. Thus, the study provides scientific evidence to the traditional use of these plants as fever reducing agents. The extracts can be formulated in the form of a phytomedicine against malaria. Alternatively, further studies can be carried out to isolate the active phytoconstituents responsible for the observed activity.