Recent Advances in Medicinal Chemistry to Treat Filariasis and Helminthiasis

Lymphatic filariasis (LF), commonly known as elephantiasis is a neglected tropical disease (NTD) caused by *Wuchereria bancrofti*, *Brugia malayi* and *B. timori*. It has been ranked as the second leading cause of long-term chronic disability world-wide. Around 856 million people from 52 countries worldwide are at risk by LF and seek prophylactic treatment to control the expansion. This disease affects the poorest populations who are living in areas with poor sanitation and housing, causing chronic manifestations such as hydrocele, lymphoedema and elephantiasis associated with impaired mobility and social activity, reduced work capacity, sexual dysfunction, severe psycho-social problems, stigma and bad marital prospects.

In this regard, the World Health Organization launched the Global Programme to Eliminate Lymphatic Filariasis (GPELF) using diethylcarbamazine (DEC) or ivermectin (IVM) or albendazole alone or in combinations and the results were encouraging as out of 72; twenty countries successfully reduced the infection prevalence to such a level that transmission will not be sustainable. However, due to serious technical difficulties the programme is facing problems in the eradication of this endemic disease as DEC and IVM both are microfilaricid with poor or no activity on adult parasites. Furthermore, resistance has also emerged against albendazole and ivermectin. This depressing perspective demands, an urgent need of intensive drug discovery to develop new, more effective, affordable and accessible macrofilaricidal possessing novel modes of action, which could reduce the time and burden of drug resistant.

In this thematic issue, I collected several reviews and research articles contributed by the experts in the area of medicinal chemistry, including current developments in rational drug design, synthetic chemistry, bioorganic chemistry, new and emerging drug targets, natural products, and structure-activity relationships. This issue begins with a research article on “*In Vitro* and *In Silico* Studies of Glycyrrhetinic acid derivatives as Anti-Filarial Agents” by Rekha Tyagi and Santosh Kumar Srivastava, reporting antifilarial activity in glycyrrhetinic acid (GA) derivatives. These derivatives reduced the motility of *Brugia malayi* adult worms by up to 74% while the GA and DEC reduced only up to 49%. Further, GA and most of its derivatives exhibited two times more reduction in the MTT assay when compared to the standard drug DEC. These derivatives also showed 100% reduction of microfilariae and good interactions with Bm-TPP protein. These results may be of great help in developing QSAR model for optimizing a new class of antifilarial lead from a very common, inexpensive, and non toxic natural product [1].

Peroxides are widely used in various areas of life. The rapid development of medicinal chemistry of organic peroxides began in 1971 and is associated with the discovery of antimalarial drug, artemisinin. The second article of this issue is a review article on “Bioactive natural and synthetic peroxides for the treatment of helminth and protozoan pathogens: synthesis and properties” by Prof. Alexander O. Terent’ev and his group. The review is focused on structures and synthesis of peroxides active against parasites causing neglected tropical diseases and toxoplasmosis, describing promising active natural, semi-synthetic and synthetic peroxides compounds found till date [2].

The third article of this issue is also a review on “Strategies to Control Human Lymphatic Filarial Infection: Tweaking Host’s Immune System” by Dr. Puvvada Kalpana Murthy. The review is focused on the advances made in this area such as enhancing the immune competence of host by immunomodulation, combining immunomodulation with antifilarials, identifying immunoprophylactic parasite molecules (vaccine candidates) and identifying parasite molecules that can be potential drug targets [3].

Schistosomiasis is a neglected disease which affects millions of people in developing countries. Its treatment relies on a single therapeutic alternative, praziquantel. This situation may lead to drug resistance; hence there is urgent need for the search of new antischistosomal agents. The fourth article of this issue is a research article on “Vanillin-Related N-Acylhydrazones: Synthesis, Antischistosomal Properties and Target Fishing Studies” by Prof. Josué de Moraes and his group reporting good antischistosomal activity (47.91 μM) for the N-acylhydrazone compound GPQF-407. Further, confocal laser scanning microscopy revealed that it triggered severe tegumental destruction and tubercle disintegration. Target fishing studies pointed out some probable targets, such as the serine-threonine kinases, dihydroorotate dehydrogenases and carbonic anhydrase II. The GPQF-407 can be easily synthesized on large scale from commercially available materials [4].

The fifth article of this issue is a research article on “*In Vitro and In Vivo* Antifilarial Activity of Standardized Extract of *Calotropis procera* Flowers against *Brugia malayi*”, by Dr. P. Kaplan Murthy and her group reporting the microfilaricidal and macrofilaricidal activity of ethanolic extract (A001) and hexane fraction (F001) of *C. procera* flowers *in vitro*. In animal models, A001 killed 49-54% adult worms. In *M. coucha* model F001 killed 12-60% adult worms in a dose (125-500 mg/kg) dependent manner; A001 and F001 suppressed microfilaraemia till days 91 and 35 post initiation of treatment, respectively.
HPTLC analysis revealed presence of lupeol (0.61%), β-sitosterol (0.50%) and 1.50% triacontanol (1.50%) in F001. This is the first report on antifilarial efficacy of flowers of C. procera [5].

In order to develop vaccine and specific diagnostic tests, it is important to characterize different stages of the filarial worms. Microfilariae (Mf) stage of the roundworm is found in host blood or lymph vessels and can be important not only for developing better immunodiagnosits but also for understanding immune recognition and its relevance to immune-pathogenesis and protective immunity. The sixth article of this issue is also a research article on “Immunocchemical Characterization of Setaria cervi Microfilarial Antigens using novel antibodies” by Dr. Anuradha Kalani and her group. They prepared four different immune sera against Setaria cervi; intact live, intact live with adjuvant, intact glutaraldehyde fixed with adjuvant and total somatic Mf and used for the immunoccharaterization of Mf antigens. The study revealed that compared to fixed intact Mf, live intact Mf were more immunogenic, as the immune sera generated against intact live Mf showed high ELISA reactivity with Setaria cervi Mf and adult worm antigens. All the four immune sera IgG fractions had surface specificity as determined through considerable ELISA reactivity with S. cervi intact Mf. When tested under native conditions (immunoelectrophoresis and crossed immunoelectrophoresis), all the four immune rabbit sera were able to detect antigens of S. cervi Mf and adult stages. These results can be useful in detail understanding of the complex nature of the Mf and adult antigens, which are prerequisite in the development of vaccine and more specific diagnostic tests [6].

REFERENCES


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