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Glycyrrhetinic acid and its analogs: A new class of antifilarial agents

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ABSTRACT

Although a number of chemicals have been isolated from *Glycyrrhiza glabra*, only a few have been evaluated for their biological significance. As part of our drug discovery program for antifilarial agents from Indian medicinal plants, the roots of *G. glabra* were chemically investigated, which resulted in the isolation and characterization of an antifilarial agent, glycyrrhetinic acid (GA, **1a**) effective against microfilariae (mf) in vitro (LC100: 12.5 μM; IC_{50}: 1.20 μM), but was inactive against adult worms. Further, GA (**1a**) was converted into six analogs (**2a**–**7a**) and their antifilarial potential was evaluated by studying in vitro motility and MTT reduction assays employing mf and adult worms of *Brugia malayi*. The results showed that out of six GA analogs, the benzyl amide analog (**6a**) killed adults and mf at 25 and 50 μM concentration, respectively, and inhibited 49% MTT reduction potential of the adult parasites. The IC_{50} values were found to be 8.8 and 2.2 μM for adults and mf, respectively. The SI of the compound was >60. On the other hand the octylamide analog (**7a**) required much higher concentration to adversely affect the parasites. Finally, both active amide analogs (**6a** and **7a**) were in vivo evaluated using *B. malayi*-jird model, which showed that analog **6a** possesses promising macrofilaricidal activity at 100 mg/kg, s.c. ×5 days and around 40% of the treated animals showed calcified masses of worm fragments in peritoneal cavity of the animals. To the best of our knowledge this is the first ever report on the antifilarial potential of GA analogs. Further work on optimization of the antifilarial lead is under progress.

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Lymphatic filariasis (LF), a longstanding chronic disease caused by *Wuchereria bancrofti*, *Brugia malayi* and *B. timori* is transmitted through the bites of infected mosquitoes. It is prevalent in many parts of the tropics and sub-tropics of the world. Currently over 120 million people are affected by the infection with 40 million people showing chronic disease symptoms.[1] In India, more than 500 million people are exposed to infection and approximately 25 million people are known to harbor circulating microfilariae (mf) and another 19 million people suffer from filarial manifestations.[2] WHO has recognized this major health problem as one of the six important tropical diseases and launched a global programme for elimination of filariasis (GPELF).[3,4]

Diethylcarbamazine (DEC) ivermectin and albendazole are existing antifilarial drugs for human filariasis, of which DEC and ivermectin are principally microfilaricidal with limited or no action on adult parasites. DEC has been in use almost empirically for more than five decades.[5] Ivermectin mainly affects the late stages of microfilarial development while albendazole has a transient effect on early embryogenesis. Also drug resistance to ivermectin appears to be another issue of concern, especially in areas where DEC cannot be administrated. Moxidectin though looks promising in animal studies is still under development. In current therapy DEC and ivermectin are given either alone or in combination with albendazole. Advent of mass drug administration (MDA) strategy raised hope for elimination of this disease, however, unfortunately this disorder is continuing due to the technical limitations of MDA strategy.[6] This depressing perspective demands, an urgent need for new molecular structures associated with macrofilaricidal activity/or sterilizes the adult worms is, therefore, needed[7,8] since adult parasites not only produce millions of mf that are picked up by mosquito vector and transmitted, but are also responsible for the debilitating pathological lesions. Therefore, we need macrofilaricidal agents which not only adversely affect the target but should have very low or no side effect.

Since ages, several medicinal agents have been derived and developed from plants and utilized in traditional therapeutics. India has a rich tradition of using medicinal plants or their products in treating different disease conditions through Ayurveda, Unani and Siddha systems of medicine. A number of natural products with diverse chemical structures have been isolated as anticancer,[8] anti-inflammatory[9,10] and anti-diabetics[11] etc. and many of them have been modified to yield better analogs for activity. Indeed,

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several successful molecules also have emerged as drugs upon modification of the natural leads.

Over the past few years' triterpenoids from higher plants have shown a wide range of biological activities, such as antitumor,[12] antiviral,[13] anti-inflammatory[9,10,14] and anti-HIV.[15] As part of our drug discovery program on antifilarial agents from Indian medicinal plants, the literature search revealed significant antifilarial activity in pentacyclic triterpene, oleanolic acid.[16,17] This prompted us to investigate antifilarial activity in other triterpenoids found in widely used Indian medicinal plants. For this purpose, the roots of *G. glabra* were selected, which contain a unique triterpenic acid 'glycyrrhetinic acid GA (**1a**)' as a major constituent in the form of saponin 'glycyrrhizic acid'. For the isolation of GA (**1a**), the roots of *G. glabra* were extracted and fractionated according to the flow chart (Fig. 1). The TLC profile of all the fractions showed that the desired compound, glycyrrhizic acid was present as a major component in the butanol extract. Hence, the BuOH fraction was chromatographed over Silica gel H on flash. The fractions 42–58 eluted with $CHCl_3$:MeOH (85:15) afforded glycyrrhizic acid (650.0 mg), characterized on the basis of ^1H and ^{13}C NMR spectroscopic data (Fig. 2). Further, glycyrrhizic acid was acid hydrolyzed and the hydrolyzed product after work up was purified over Silica gel H on flash. The fractions 28–46 eluted with $CHCl_3$:MeOH (99:1) afforded GA (**1a**) (250.0 mg), characterized on the basis of its ^1H and ^{13}C NMR spectroscopic data.[18] (Fig. 3)

Finally, BuOH extract which contained glycyrrhizic acid as the major constituent and GA (**1a**) were evaluated for antifilarial activity against *B. malayi* using motility and MTT assays[19–21] and the results are presented in Table 1. From the results it is evident that BuOH extract was inactive against female adult worms as well as mf even at 1000 μg/ml whereas GA (**1a**) at low concn was active against mf (LC100: 12.5 μM; IC_{50}: 1.20 μM), but was inactive against adult worms even at 100 μM concentration. This prompted us to semi-synthesize some analogs of GA (**1a**) to identify better activity.

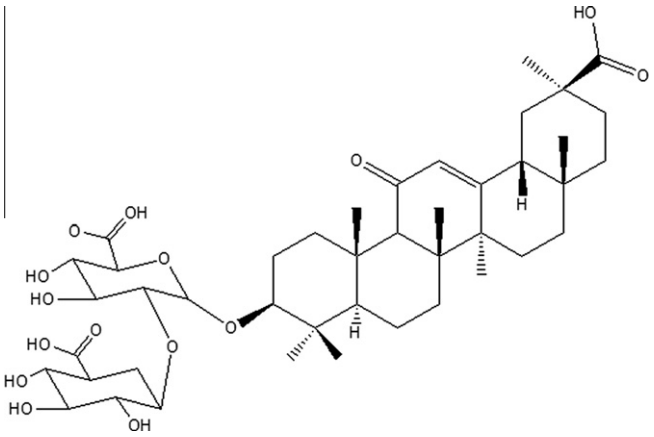


Figure 2. Characterization of pooled fraction 42–58 as Glycyrrhizic acid.

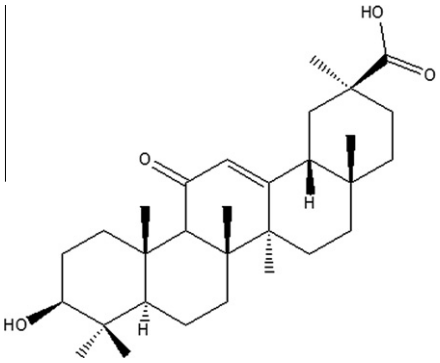
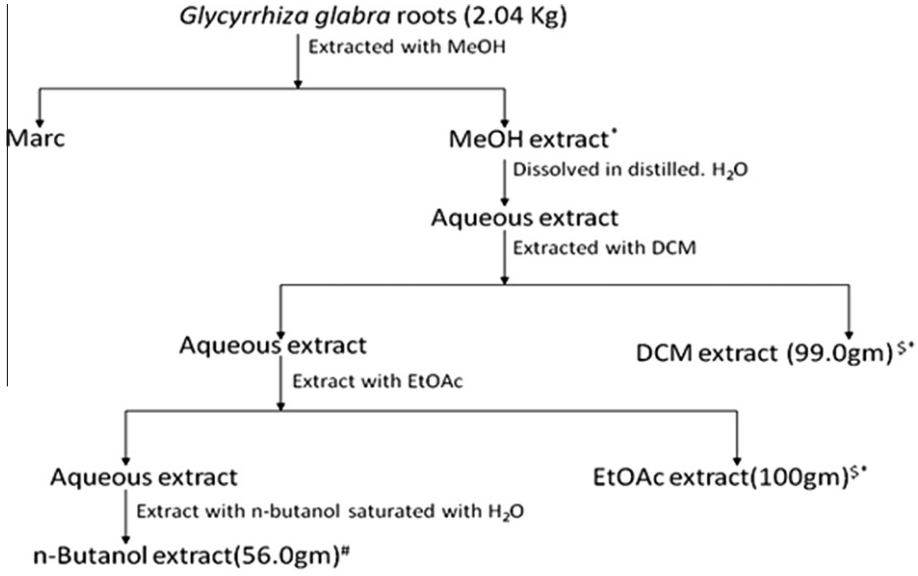


Figure 3. Characterization of pooled fraction 28–46 as Glycyrrhetinic acid.



A schematic procedure for extraction and fractionation of *Glycyrrhiza glabra* roots

$Washed with water and dried over anhydrous Na_2SO_4.
*Solvent was completely removed under vacuum on Buchi Rota Vapour.
#Solvent removed under vacuum by making azeotrop with water

Figure 1. Extractions and Isolation procedure of *Glycyrrhiza glabra*.

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