Journal of Coastal Life Medicine

journal homepage: www.jclmm.com

Original article doi: 10.12980/jclm.4.2016J5-197

Anti-inflammatory, analgesic and antipyretic potentials of marine sponge *Sigmadocia pumila*

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ARTICLE INFO

Article history:
Received 9 Oct 2015
Received in revised form 19 Oct 2015
Accepted 15 Mar 2016
Available online 6 Apr 2016

Keywords:
Sigmadocia pumila
Anti-inflammatory
Analgesic
Antipyretic

ABSTRACT

Objective: To study the pharmacological properties of *Sigmadocia pumila* (*S. pumila*), a marine sponge, through *in-vivo* analysis.
Methods: The anti-inflammatory activity was determined by the carrageenan-induced rat paw edema method. The analgesic activity was analyzed by tail immersion method. Antipyretic activity was done by using Brewer's yeast induced hyperpyrexia method.
Results: The anti-inflammatory activity using methanol extracts in *S. pumila* at the concentrations of 100 mg/kg and 200 mg/kg, (*p.o.*) on rats showed significant decrease in the paw thickness at the 5th h of administration. It was denoted that the *S. pumila* exerted more analgesic activity. As for the antipyretic activity during the 2nd and 3rd h, the 3rd and 4th group of rats showed the reduction in temperature in *S. pumila* at 100 mg/kg and 200 mg/kg dosages.
Conclusions: The present study concludes that the marine sponge *S. pumila* acts as a vital role in exhibiting pharmaceutical activities. It could be used to produce novel drugs.

1. Introduction

Marine sponges of phylum Porifera are considered to be a goldmine due to their diversity of secondary metabolites presenting in it. The secondary metabolites was used to cure various types of diseases[1]. Marine sponges have been excellent sources for natural products that show bio-activity including enzyme inhibitors, cell division inhibitors, antiviral, antifungal, antimicrobial, anticoagulant, immunosuppressive, anti-inflammatory, anti-tumour, antipyretic, analgesic and cardiovascular properties[2]. It was demonstrated that sponge metabolites acted as a possible treatment for tuberculosis since they have the ability to control the growth of the *Mycobacterium tuberculosis*[3]. The order Verongida in sponge contains bioactive compounds that are bromotyrosine derivatives of widely varying complexities, and it was considered as the source of natural products[4]. The marine sponge *Aplysina caissara* obtained from Brazil of the order Verongida, also possesses known bromotyrosine compounds like fistularin-3 and 11-hydroxyaerothionin which showed moderate antibiotic activities against Gram-positive and negative organisms like *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*[5]. IPL 512602 a bioactive metabolite steroid contignasterol from sponge *Petrosia contignata* is in phase II stage trial as a leucocyte suppressing anti-inflammatory drug against asthma[6]. Globostellatic acid is the prototype of the third group of isomalabaricane-type triterpenoids sharing carboxylation at C-4. It was isolated together with derivatives, globostellatic acids B–D, from the marine sponge *Stelletta globostellata* collected in Japan. Other globostellatic acid congeners, F–M, and X methyl esters, were reported from different collections of the Indonesian marine sponge *Rhabdastrella globostellata*. Globostellatic acids revealed the maximum cytotoxicity similar to the stelletins and stelliferins. Globostellatic acids A–D showed significant cytotoxicity against murine leukemia P388 cells with IC_{50} values of 0.2–0.8 μmol/L[7]. The activity of the Red Sea *Suberea mollis* sponge extract on carbon tetrachloride-induced acute liver injury in rats was investigated. The protective effect of the *Suberea mollis* sponge extract against carbon tetrachloride-induced hepatic injury was due to its antioxidant and radical scavenging activity[8]. Several brominated natural products and other aminoacid derivatives presenting in sponges such as cyclic peptides, polymere alkyl pyridinium, sesquiterpene quinones, onamides, mycalamides, macrolides, porphyrins, terpenoids, aliphatic cyclic peroxides and sterols were considered as important

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All experimental procedures involving animals were conducted in accordance to the Sangaralinkam Bhuvaneswari College and approved by the Animal Ethics Committee (Regd. No. 622/02/C/CPCSEA).

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cytotoxic bioactive metabolites[9]. Marine invertebrates that are sessile organisms like sponges were the largest number of organisms in invertebrates with pharmacological properties[10]. Similarly *Hyrtios* sp. extract induced apoptosis via different pathways depending on p53 status and cell death occurring by the induction of p53 and p21 proteins. It dose dependently inhibited viability of human cancer cell lines. Multinucleate, an indication of mitotic catastrophe, was also observed[11]. From 2001 to 2015 marine sponges continued to be the most promising source of marine natural products. The order Dictyoceratida was found to be the most prolific producer of new compounds among all the sponge orders studied. *Dysidea* sp. and *Ircinia* sp. were found to be the most promising genera because of their capacity for producing new bioactive compounds[12]. Considering this, the primary objective of the study was to detect the pharmaceutical applications of the marine sponge *Sigmadocia pumila* (*S. pumila*).

2. Materials and methods

2.1. Marine sponge samples

Samples of the marine sponge *S. pumila* were collected from the coast of Kanyakumari with fish nets during active fishing season. The sponges entangled in the fishing nets were detached and were segregated. They were examined for attached algae and other organisms and they were carefully removed. Details of colour, shape, texture, residency, form and other characteristic features were noted during the time of collection. The sponge of *S. pumila* was transferred directly to new wide mouth plastic containers containing sea water to prevent contact of sponge tissue with air. Another set used for bioactivity studies was transferred to bottles containing methanol.

2.2. Preparation of extracts

Sponges weighing 250 g were made into small pieces and extracted with methanol and then filtered through Whatman No.1 filter paper fitted in a Buchner funnel using suction. Solvents were removed by rotary vacuum evaporator (Buchi-type) under reduced pressure so as to get the extract. The extracts were collected in plastic containers and stored in refrigerator for further use.

2.3. Animals used in the study

Wistar albino rats of either sex, weighing approximately 120-180 g were selected. They were procured from the Department of Pharmacology, Sankaralingam Bhuvaneswari Pharmacy College Sivakasi (Tamilnadu). The experimental mice were fed with pellet diet (Gold Mohur brand) at room temperature in separate cages. Water was given *ad libitum*. All experimental procedures involving animals were conducted in accordance to the Sangaralinkam Bhuvaneswari College and were approved by the animal ethics committee (Regd. No. 622/02/C/CPCSEA) and were used for the present study.

2.4. Anti-inflammatory activity

Inflammatory condition of animals was induced by injecting 0.05 mL of 1% w/v carrageenan (Sigma) subcutaneously into the subplantar region of the right hind paw of albino rats. The paw edema was measured. Rats were divided into four groups of four individuals each. The control group (Group I) was given saline (1 mL/kg) and the standard drug diclofenac sodium (10 mg/kg). Animals in Group II served as the standard reference. Animals in Groups III and IV were treated with *S. pumila* extracts at the doses of 100 and 200 mg/kg (*p.o.*). The thickness of the right paw was measured before and after carrageenan injection at time intervals 0, 1, 2, 3, 4 and 5 h. The data were analyzed by One-way ANOVA followed by Dunnett's test.

2.5. Analgesic activity (tail immersion method)

The analgesic activity was assessed by measuring the sensitivity of the rats tails by gently placing the tip of the tails (the last 1–2 cm) of adult albino rats in warm water with temperature of (55 ± 2) ℃. Only active rats (tail flicking within 5 s) were selected for this study. The Group I (control group) received normal saline and the Group II (standard reference group) was treated with pentazocine (10 mg/kg, *p.o.*). Groups III and IV individuals were treated with *S. pumila* extracts (100 and 200 mg/kg, *p.o.*, respectively). After drug treatment, the basal reaction time of animals of all groups was recorded at different time intervals like 0, 1, 2 and 3 h and the values were expressed as mean ± SD of 4 animals in each group. The data was analyzed by One-way ANOVA followed by Dunnett's test.

2.6. Antipyretic activity

Antipyretic activity was evaluated by Brewer's yeast induced hyperpyrexia method. Wistar rats of either sex weighing 120–180 g were selected. Animals were fasted for 24 h before inducing pyrexia. Pyrexia was induced in albino rats by injecting 15% (m/v) aqueous suspension of Brewer's yeast into the nape of neck subcutaneously. The initial temperature of each animal was recorded. After 18 h, the animals developing 0.5 ℃ rise in the temperature was selected for further studies. Group I (control group) received normal saline and Group II (standard reference group) was treated with (25 mg/kg) aracetamol orally. Group III and IV animals were treated with *S. pumila* extracts (100 and 200 mg/kg, *p.o.*, respectively). The temperature was recorded at 1, 2, 3 and 4 h after administration of the test extracts.

3. Results

3.1. Anti-inflammatory activity

The groups treated with methanol extracts of *S. pumila* at the concentrations of 100 and 200 mg/kg (*p.o.*) showed significant decrease in the paw thickness in a dose-dependent manner as compared to that of the control, at the 5th h of administration as indicated in Table 1. It was comparable with that of standard diclofenac sodium (10 mg/kg). The anti-inflammatory activity results were determined by One-way ANOVA followed by Dunnett's test and expressed as mean ± SEM from 0 to 5 h. Both the concentrations showed significant difference ($P < 0.001$). These results indicated

Table 1

In vivo effect of anti-inflammatory activity by using methanol extracts of *S. pumila*.

Treatment	Group	Dose (mg/kg)	Increase in paw volume (mL)					
			0 h	1 h	2 h	3 h	4 h	5 h
Control	I	-	0.586 ± 0.004	0.928 ± 0.004	0.988 ± 0.005	0.939 ± 0.005	0.847 ± 0.005	0.725 ± 0.005
Diclofenoc sodium	II	10	0.597 ± 0.004	0.767 ± 0.007*	0.748 ± 0.008*	0.648 ± 0.009*	0.617 ± 0.008*	0.598 ± 0.008*
S. pumila	III	100	0.603 ± 0.005	0.785 ± 0.006	0.736 ± 0.007*	0.663 ± 0.010*	0.633 ± 0.008*	0.595 ± 0.008*
S. pumila	IV	200	0.579 ± 0.005	0.820 ± 0.006	0.735 ± 0.007*	0.686 ± 0.007*	0.604 ± 0.008*	0.588 ± 0.009*

Values are expressed as mean ± SEM (n = 4). P value was calculated by One-way ANOVA followed by Dunnett's test. *: $P < 0.001$ (Group II to IV).

the important anti-inflammatory effect which inhibited almost 50% of the induced edema.

3.2. Analgesic activity

The groups treated with extracts of sponge *S. pumila* exerted increase in latency time as compared with the control group. After oral administration with different doses (100 and 200 mg/kg body weight), the percentage of inhibition observed in *S. pumila* at 100 mg/kg was 68.18%, 79.25% and 83.74%. At 200 mg/kg, it was 73.07%, 88.66 %, and 94.35% for 3 h. It was denoted that the *S. pumila* extract exerted more analgesic activity. The percentage inhibition effect using the extracts of *S. pumila* were analysed at the dosages of 100 and 200 mg/kg. The values were compared with the control as well as with the standard drug pentazocine (Table 2).

3.3. Antipyretic activity

A stabilized temperature in antipyretic activity was recorded in 18 h as shown in Table 3. The methanol extracts of *S. pumila* were given orally to Group III to Vl at 100 and 200 mg/kg dosages, respectively. The difference in temperature between 0 h and at the end of 4 h was compared and analysed with that of the standard drug paracetamol. Significant value was noted at $^{*}P < 0.05$ and at $^{**}P < 0.01$, thus indicating high activity. In antipyretic activity during the 2nd and 3rd h the rats of III and IV Groups showed reduction in temperature.

4. Discussion

From those results, it was observed that the *S. pumila* belonging to Demospongiae extract could act as cyclooxygenase (COX) inhibitors and reduced the phospholipase enzyme effect to exhibit anti-inflammatory action. This was seen in the inhibitory effect of carageenan-induced paw edema in rats. Previous studies stated that the anti-inflammatory action was based on the irreversible inhibition of the release of arachidonic acid from membrane phospholipids by preventing the enzyme phospholipase A2 from binding to the membranes. A rise in the intracellular arachidonic acid concentration would lead to the up-regulation of the synthesis of inflammation mediators such as prostaglandins and leukotrienes. Phospholipase A2 inhibition has been recorded not only for sesterterpenes but also for bis-indole alkaloids such as topsentin from sponges classified under the order Dictyoceratida[11]. The extract of *S. pumila* was compared with that of the standard drug diclofenac sodium. Anti-inflammatory effect which inhibited almost 50% of the induced edema could be recorded. The presence of compounds such as the flavones and polyacetylene could also induce the anti-inflammatory action. The anti-inflammatory activity of avarol and avarone (sesquiterpenoid derivatives) of marine metabolites showed inhibition in mice, with effects comparable to those of indomethacin[12], both marine metabolites showed a potency higher than that of mepacrine experimental. It is possible that benzamidines and cinnamaldehyde compunds seen in the sponge *S. pumila* extracts have the ability to produce anti-inflammatory effects by regulating the action of COX-1 and COX-2 enzymes with modulation of gene expression, such as NF-κB[13]. Similarly, a novel anti-inflammatory sterol, clathriol B from

Table 2

Experiments for analgesic activity by using methanol extracts of *S. pumila.*

Treatment	Group	Dose (mg/kg)	Reaction time after drug administration (s)			Percentage inhibition (%)		
			1 h	2 h	3 h	1 h	2 h	3 h
Control	I	-	1.73 ± 0.48	2.72 ± 0.25	2.85 ± 0.29	0.00	0.00	0.00
Pentazocine	II	10	7.50 ± 0.65**	9.25 ± 0.48**	15.25 ± 0.42**	73.07	80.20	99.59
S. pumila	III	100	5.50 ± 0.65*	6.75 ± 0.48**	7.75 ± 0.48**	68.18	79.25	83.74
S. pumila	IV	200	6.50 ± 0.65**	8.25 ± 0.75**	9.75 ± 0.86**	73.07	88.66	94.35

Values are expressed as mean ± SD (n = 4). P value was calculated by One-way ANOVA followed by Dunnett's test. *: $P < 0.01$, **: $P < 0.001$ compared with control group.

Table 3

Study of antipyretic activity by using methanol extracts of *S. pumila.*

Treatment	Group	Dose (mg/kg)	Initial temperature (°C)	Rectal temperature (°C)				
				0 h	1 h	2 h	3 h	4 h
Control	I	-	37.53 ± 0.09	38.15 ± 0.16	38.16 ± 0.09	38.18 ± 0.09	38.20 ± 0.09	37.23 ± 0.10
Paracetamol	ll	45	37.39 ± 0.13*	38.70 ± 0.17*	37.96 ± 0.20**	37.77 ± 0.27**	37.70 ± 0.34*	37.50 ± 0.31**
S. pumila	lll	100	37.49 ± 0.08	37.98 ± 0.11*	37.69 ± 0.10*	37.58 ± 0.21**	37.45 ± 0.20*	37.34 ± 0.17*
S. pumila	lV	200	37.42 ± 0.08	38.08 ± 0.13*	37.83 ± 0.11*	37.65 ± 0.32**	37.57 ± 0.10*	37.42 ± 0.07

Values are expressed as mean ± SEM (n = 4). P value was calculated by One-way ANOVA followed by Dunnett's test. *: $P < 0.05$, **: $P < 0.01$ (Group II to IV).

the New Zealand sponge *Clathria lissosclera* was shown to exhibit the production of superoxide anion from agonist stimulated human peripheral blood neutrophils[14]. The anti-inflammatory activity of *S. pumila* extracts was detected at the range of 100 and 200 mg/kg in rats. The decrease in paw thickness was detected from 1 to 5 h after the administration of extracts[15]. The results of the present study have shown that the extracts of *S. pumila* exhibited very high analgesic activities. *S. pumila* could act as analgesics by blocking the generation of impulses at the chemoreceptor site of pain. The *S. pumila* extracts showed the higher inhibitory effect at 94%. The selective analgesic inhibitors of specific enzymes act against a wide range of diseases, like psoriasis or rheumatic arthritis. Only a few sponge deriving terpenoids have been found to inhibit lipoxygenase, and involved in the analgesic response[16]. Similarly, Curcuphenol, a monocyclic aromatic sesquiterpenoid, isolated from sponge *Didiscus oxeata* was an analgesic compound confirmed through the tail immersion method at the doses of 100, 150 and 200 mg/kg by oral administration[17]. Manoalide from sponge *Luffariella variabilis* was a new compound for drug development with analgesic activity. In marine sponge, *S. pumila* extracts were compared with that of the standard drug pentazocine[18]. The duration of analgesic effect was recorded to be higher in high-dose treated animals as compared to the low-dose treated animals. The extracts of *S. pumila* could inhibit the COX-1 enzyme. COX enzyme is a part of the route of prostaglandins formation. It is known that pain is closely associated with inflammation and hence most of the anti-inflammatory compounds are analgesic as determined by the tail immersion method[19]. The compound cavernolide isolated from sponge *Fasciospongia cavernosa*, contignasterol from *Petrosia contignata* and the compound cyclolinteinone from the sponge *Cacospongia linteiformis* showed anti-inflammatory activities. The actions of these compounds were explained by the inhibition of enzymatic activities, like inhibition of inducible nitric oxide synthase, COX-2 gene expression, plasma exudation *in vivo* in response to ovalbumin and prostaglandin E2[20]. *S. pumila* extracts have compounds such as the monoterpenoids and cyclic peptides which could induce antipyretic activity. As for antipyretic activity, the extract could inhibit significantly through yeast induced pyrexia. The terpenoid 2-tetraprenyl benzoquinol extracted from marine sponge *Disidea pallescens*, 4-hydroxy-3-tetraprenylbenzoic acid from *Ircinia muscarum*, 2-polyprenyl benzoquinols from *Ircinia spinosula* and furospongin-1 from *Spongia officinalis* were considered as good antipyretic agents[21].

Our study identified that the methanol extracts of the *S. pumila* showed anti-inflammatory, analgesic and antipyretic properties through *in-vivo* studies. *S. pumila* is a good source of bioactive compounds. Sponge plays a vital medicinal values. Further studies are necessary to observe the bioactive metabolites and its structural characteristics.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

The authors express the gratitude to Dr. A. Thanga Thirupathi, principal and the management of Sankaralingam Bhuvaneshwari College of Pharmacy, Sivakasi for providing the support and facilities.

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