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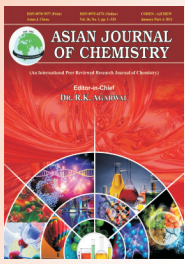

NOTE

Avarol Effectively Inhibits *Bacillus cereus* Growth

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This work extends *in vitro* screening of antibacterial activity of avarol on four selected pathogenic bacteria associated with psoriasis (*Bacillus cereus*, *Clostridium sporogenes*, *Enterococcus faecalis* and *Staphylococcus aureus*). Avarol exhibited a moderate activity with minimum inhibitory and minimum bactericidal concentrations ranged from 0.78-1.56 and 3.12-18.75 µg/mL, respectively. It proved to be more effective against *B. cereus* in comparison to the both positive controls applied, gentamycin and ampicillin. According to the experimental data, this marine natural product may inspire development of new antibiotics with an enhanced therapeutic index, at first place those targeting *B. cereus*.

Keywords: Porifera, *Dysidea avara*, Marine natural product, Antibacterial activity, Psoriasis.

Sponges are sessile organisms with a specific chemical defense of great interest for the natural product chemists. Indeed, their terpenoid quinones and hydroquinones have attracted the most attention[1].

Avarol, a marine sesquiterpenoid hydroquinone possessing a rearranged drimane skeleton, is the main secondary metabolite of the Mediterranean sponge *Dysidea avara* Schmidt [2,3]. Pharmacological properties of this natural product include antibacterial, antifungal and antiviral activities[4]. It has shown to be active against a variety of Gram-positive bacterial and some fungal species. On the other hand, no antibacterial activity has been found for Gram-negative bacteria[5-7].

Avarol exhibits antipsoriatic activity as well[8]. Indeed, recent studies performed in human keratinocytes showed that avarol decreased the production of skin-derived antileukoproteinase (SKALP/Elafin) determined as index of psoriatic keratinocyte differentiation, without affecting cell proliferation. It is supposed that observed biological activity is partially mediated by the downregulation of TNF-α and NF-κB in psoriatic skin[9]. Psoriasis is a common skin disease characterized by epidermal hyperplasia, inflammation in dermis and epidermis and leukocyte infiltration[10]. However, its pathogenesis still remains unclear. Pathogenic organisms that have been associated with psoriasis include *Bacillus cereus*, *Clostridium* sp., *Enterococcus faecalis* and *Staphylococcus aureus*[11,12]. Anthralin is among the most widely used drugs in the treatment of psoriasis. However, its clinical efficacy is limited by the side-effects of irritation and staining of the uninvolved skin[13].

The low toxicity in male mice (lethal dose for 10 % of the mice kill is 111 mg) and no side effects in men (at the dose of 3 mg/kg)[14,15], prompted us to extand *in vitro* antibacterial screening of avarol related to psoriasis. The screening has included four Gram-positive bacteria, namely *Bacillus cereus* ATCC 11778, *Clostridium sporogenes* ATCC 19404, *Enterococcus faecalis* ATCC 19433 and *Staphylococcus aureus* ATCC 25923. Avarol was isolated from the sponge *D. avara*, collected in the Bay of Kotor (Kotor, Montenegro) as previously reported[2,3], while its antibacterial activity was evaluated *in vitro* by a microdilution method[16].

This marine natural product exhibited good activity against all bacteria tested with minimum inhibitory (MIC) and bactericidal (MBC) concentrations ranged from 0.78-1.56 and 3.12-18.75 µg/mL, respectively (Table-1).

The most sensitive bacterium was *B. cereus* with MIC/MBC values reached at 0.78 and 3.12 µg/mL, respectively. In comparison, both positive controls used, gentamycin and ampicillin, were less effective towards this strain (MIC/MBC values 2.50/10.00 µg/mL and 2.00/4.00 µg/mL, respectively). It's worth noting that avarol did show selectivity against the Gram-positive bacteria screened inhibiting *B. cereus* and *E. faecalis* in a bactericidal rather than in a bacteriostatic manner

TABLE-1
MINIMUM INHIBITORY (MIC) AND BACTERICIDAL (MBC) CONCENTRATIONS OF AVAROL

Bacteria	Avarol[*¥]	Gentamycin[*#¥]	Ampicillin[*#¥]
Bacillus	0.78 ± 0.02	2.50 ± 0.03	2.00 ± 0.06
cereus ATCC 11778	3.12 ± 0.03	10.00 ± 0.02	4.00 ± 0.08
Clostridium	1.56 ± 0.06	2.50 ± 0.02	64.00 ± 0.06
sporogenes ATCC19404	18.75 ± 0.03	>20	>128
Enterococcus	1.56 ± 0.03	5.00 ± 0.06	16.00 ± 0.03
faecalis ATCC 19433	6.25 ± 0.06	>20	>128
Staphylococcus	1.56 ± 0.08	2.50 ± 0.06	8.00 ± 0.06
aureus ATCC 25923	12.50 ± 0.06	10.00 ± 0.03	>128

[*]MIC/MBC (µg/mL), [#]positive control, [¥]$p < 0.05$

(MBC/MIC = 4). This study confirms avarol potential related to psoriasis and indicates the need for the antibacterial activity screening at *in vivo* conditions. Indeed, its chemical structure may inspire development of new and more effective antibiotics targeting *B. cereus*, the bacterium known to cause chronic skin infections that are difficult to eradicate.

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