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Research review paper

Recent advances in marine drug research

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ABSTRACT

Structures and properties of promising marine anti-cancer, anti-inflammation and anti-infectious (HIV, HSV, malaria, leishmania) compounds reported during 2008–2011 are discussed. Wherever possible, attempts have also been made to highlight their possible biogenesis or structure–activity relationships (SAR). Since the stress is on identifying and short-listing potential drug molecules, this review is restricted to only those compounds exhibiting promising *in vitro* activity, the arbitrary cut off being $IC_{50} < 15$ μM, reported during the above period.

Contents

1. Introduction

Ocean, covering more than 70% of the Earth's surface is home to nearly one million multicellular (plants and animals) and one billion unicellular (distributed under 100 different phyla) organisms, (Burgess, 2012). Living in a highly competitive environment, many of these organisms have perfected the technique of survival through chemical defense. Evolved over millions of years, they are a goldmine of genetic diversity and novel secondary metabolites. Due to several reasons, *viz.*, inaccessibility of their habitats, very low yield of bioactive metabolites, *etc.*, systematic chemical and pharmacological investigations of these organisms were not popular till a few decades ago. However, the recent advances in underwater exploration, natural products chemistry, genome mining and bioassays have led to a great surge in the search for novel biomolecules from this rather underexploited habitat. A cursory review of the literature indicates that more than 70% of marine metabolites are obtained from marine sponges, corals and microorganisms. The contribution from other organisms like molluscs, ascidians and algae adds up to only 30% (Blunt et al., 2007). The importance of marine metabolites in modern day drug research is revealed by the fact that around 50% of the US FDA approved drugs during 1981–2002 consist of either marine metabolites or their synthetic analogs. Their low effective dosage, better selectivity against target malignant tissues and relative non-vulnerability to resistance development as compared to compounds of terrestrial origin, render them useful target molecules. According to US National Cancer Institute estimates, more than 1% of marine natural products show antitumor properties as against only 0.01% amongst their terrestrial counterparts.

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Though serious research in the field of marine pharmacology is of very recent origin, a few products (or their analogs) have already appeared in the market as therapeutic drugs or health food. This includes ω-3 poly unsaturated fatty acids (PUFA, cholesterol-lowering), Ara-C (Cytarabine, anticancer), Ara-A (antiviral), ziconotide (analgesic), Trabectidin (anti-cancer) *etc.* In addition, several more compounds such as bryostatin, didehydrodidemnin, eribulin mesylate, dolastatins, kahalalide F, KRN 7000, squalamine, *etc.*, are at different stages of clinical trials (Mayer et al., 2010).

The advances in the field of marine metabolites exhibiting diverse biological properties up to early 2008 period have recently been compiled (Mayer et al., 2011). Subsequently, 3079 new compounds have been added to the literature during the next 4 year period, 2008–2011, (Blunt et al., 2010, 2011, 2012). As the purpose of this review was to short-list marine compounds of therapeutic potential for common human ailments like cancer, inflammation and infectious diseases, only compounds having IC_{50} values < 15 μM are included here. Thus, this review lists 136 cytotoxic, 31 anti-infectious and 24 anti-inflammatory compounds reported during the years 2008–'11 (Fig. 1). But for a handful of compounds, which displayed activity at concentrations higher than 10 μM, most of these compounds were active at submicro-molar levels. Broadly, these bioactive compounds may be classified into diverse structural types: terpenes, non-terpenes, alkaloids and peptides. The non-terpenoid compounds belong to both acetogenic (C2) and propionate (C3) biosynthetic pathways. Peptides may be either linear or cyclic, including lipopeptides, depsipeptides, *etc.* Many of these peptides contain L- or D-amino acids, β-amino acids, or other structurally modified amino acids of non-ribosomal origin.

2. Marine sponges

Marine sponges (Phylum: Porifera) constitute one of the most primitive multicellular organisms (>600 million years old) on earth. Due to their long evolutionary history, these organisms possess vast genetic diversity, producing several novel metabolites of potential biomedical applications. The isolation of sponge-derived antiviral and anticancer nucleosides (spongothymidine and spongouridine) in early 1950s heralded a new era in modern biomedical research. Subsequent studies over the last six decades have led to the discovery of several novel metabolites, displaying promising biological properties. Herein we report the most active cytotoxic and anti-infectious compounds from 28 sponges reported during the last four years under review. Among these, ten sponges yielded non-nitrogenous compounds (**1**–**5**, **7**–**11** and **13**–**26**), while six animals each yielded alkaloids (**6**, **12**, **27**–**40**), usual cyclic peptides of 7–9 amino acid residues (**41**–**51**), or unusual peptides/depsipeptides (**52**–**68**) (Table 1) (Fig. 2). Perhaps, the occurrence of novel peptides of possible non ribosomal peptide synthetase (NRPS) or polyketide synthase (PKS) biogenesis indicates their probable microbial origin.

Gukulenins A (**1**) and B (**2**) are tetraterpenoid bis-tropolone derivatives, isolated from a Korean sponge *Phorbas gukulensis*, active against 4 human cancer cell lines (pharynx, stomach, colon, and renal cancer cell lines) at concentrations below 1.0 μM (Park et al., 2009). The novel γ-lactone containing sesterterpenoids, aplysinoplides A–C (**3**–**5**) were reported from the Japanese sponge *Aplysinopsis digitata* (Ueoka et al., 2008). These sesterpenoids have close structural similarities with manoalide, the antipsoriatic compound, previously reported from the sponge *Luffariella variabilis* (De Silva and Scheuer, 1980). Aplysinoplides A and B were active against P388 mouse leukemia cells at IC_{50} of 1 μM. Axisonitrile-3 (**6**), a spiro sesquiterpene nitrile active against HepG2 liver carcinoma cells was reported for the first time as a natural product from a marine sponge *Halichondria* sp. (Prawat et al., 2011).

Pandarosides E–J, the new steroidal glycosides with unique 15-keto-16-ene and *cis* C/D ring geometry were reported from a Caribbean sponge *Pandoras acanthifolium* (Regalado et al., 2010). These compounds as well as their methyl esters displayed promising antiprotozoal activity against *Trypanosoma brucei rhodesiense* and *Leishmania donovani*. Among these, Pandaroside G (**7**) and its methyl ester (**8**), having unsaturation

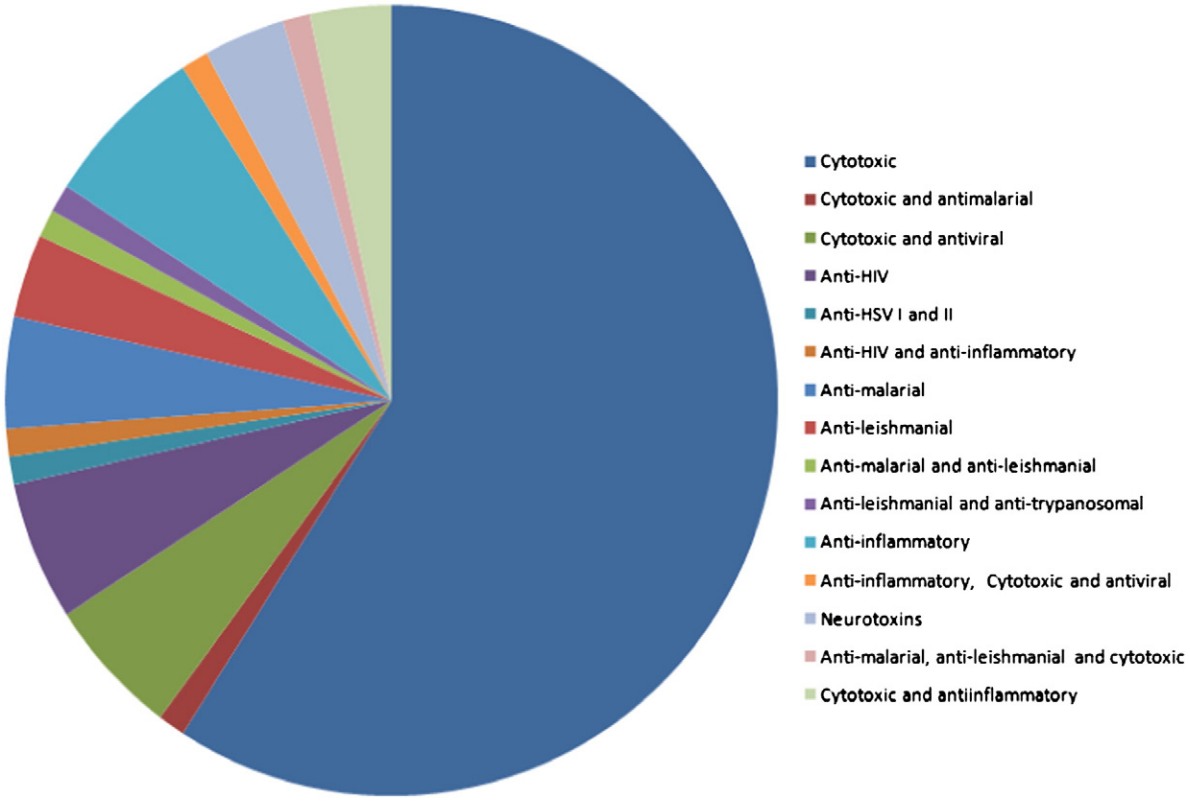

Fig. 1. Classification of compound based on their bioactivity.

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