Biotechnology Advances 32 (2014) 1364–1381

Contents lists available at ScienceDirect

Biotechnology Advances

journal homepage: www.elsevier.com/locate/biotechadv

Research review paper

Advances in algal drug research with emphasis on enzyme inhibitors

Kannan R.R. Rengasamy, Manoj G. Kulkarni, Wendy A. Stirk, Johannes Van Staden *

Research Centre for Plant Growth and Development, School of Life Sciences, University of KwaZulu-Natal Pietermaritzburg, Private Bag X01, Scottsville 3209, South Africa

ARTICLE INFO

Article history:
Received 20 May 2014
Accepted 24 August 2014
Available online 3 September 2014

Keywords:
Algal drugs
Enzyme inhibitors
Dementia
Diabetes
Drug likeness
Inflammation
Structure activity relationship

ABSTRACT

Enzyme inhibitors are now included in all kinds of drugs essential to treat most of the human diseases including communicable, metabolic, cardiovascular, neurological diseases and cancer. Numerous marine algae have been reported to be a potential source of novel enzyme inhibitors with various pharmaceutical values. Thus, the purpose of this review is to brief the enzyme inhibitors from marine algae of therapeutic potential to treat common diseases. As per our knowledge this is the first review for the potential enzyme inhibitors from marine origin. This review contains 86 algal enzyme inhibitors reported during 1989–2013 and commercial enzyme inhibitors available in the market. Compounds in the review are grouped according to the disease conditions in which they are involved; diabetes, obesity, dementia, inflammation, melanogenesis, AIDS, hypertension and other viral diseases. The structure-activity relationship of most of the compounds are also discussed. In addition, the drug likeness properties of algal inhibitors were evaluated using Lipinski's 'Rule of Five'.

Contents

Introduction

About 70% of the Earth's surface is covered by ocean with one million multicellular and one billion unicellular marine organisms (Burgess, 2012). This provides enormous opportunities for the natural product chemists to explore new and promising drugs from marine resources. The global market for marine-derived drugs was approximately $4.8 billion in 2011 and is projected to reach $8.6 billion by 2016 at a compound annual growth rate (CAGR) of 12.5% for the five year period of 2011 to 2016 (BCC Research, 2011). About 50% of the US FDA approved drug during 1981–2002 consisted of either marine metabolites and their synthetic analogs. This is due to effective dosage of marine metabolites at a lower level, better selectivity against target malignant tissues and relative non-vulnerability to developing resistance as compared to terrestrial compounds (Vinothkumar and Parameswaran, 2013). Among these marine metabolites, 70% are obtained from various marine animals and microorganisms while the contribution of algae and others in marine pharmacology is up to 30% (Blunt et al., 2007). After extensive research in the field of marine pharmacology, some

* Corresponding author. Tel.: +27 33 2605130.
E-mail address: rcpgd@ukzn.ac.za (J. Van Staden).

http://dx.doi.org/10.1016/j.biotechadv.2014.08.005
0734-9750/

therapeutic drugs from marine source are available in the market such as vidarabine (Ara-A), cytarabine (Ara-C), ziconitide (Prialt®) and trabectin (Yondelis®).

Marine macroalgae or seaweeds are lower cryptogams which are classified into three main phyla: Phaeophyceae, or brown seaweeds, Chlorophyceae, or green seaweeds and Rhodophyceae, or red seaweeds. Globally there are about 1500 brown, 900 green and 4000 red species of seaweeds (Dawes, 1998). Red and green seaweeds are found mostly in subtropical and tropical waters, while brown seaweeds are more common in cooler, temperate waters (Khan and Satam, 2003). Seaweeds are basically exposed to various environmental conditions and many of these seaweeds develop chemical defense mechanisms to survive through chemical defence. This chemical defence includes many novel compounds. Advances in the field of algal biotechnology have identified numerous structurally diverse secondary metabolites such as terpenoids, polyphenols, alkaloids, steroids, peptides, polysaccharides and others (Hu et al., 2012). The antiangiocardiopathy drug propylene glycol alginate sodium sulfate (PSS) (Fig. 1) is a clinically available marine algal drug used for the treatment of heart and brain diseases with a production value of about US$140 million per year (Hanzhi et al., 2012).

Modern drug therapy is targeted to identify two main classes of biological macromolecules namely enzymes and G-protein coupled receptors. Among these two main classes, enzymes are gaining much attention from natural product researchers (see recent reviews) (Birari and Bhutani, 2007; Copeland et al., 2007; Feldhammer et al., 2013). Enzyme inhibitors are molecules that cause their pharmacological effects by the inhibition of particular enzymes and account for half of the oral drugs in clinical use (Hopkins and Groom, 2002). These are primarily classified into competitive, uncompetitive and noncompetitive types based on their mechanism of action. The competitive inhibitors are further classified into two special types that bind very strongly to the target enzyme - namely transition state analogs and tight-binding inhibitors (Smith and Simons, 2004). Enzyme inhibitors are now included in many kinds of drugs used to treat most human diseases including communicable, metabolic, cardiovascular, neurological diseases and cancer (Copeland et al., 2007). The worldwide market for enzyme inhibitory drugs was estimated at US$104.4 billion in 2010 and reached nearly $104.6 billion in 2011. It is estimated to reach $127.4 billion by 2016 with an annual increase of 4% (BCC Research, 2012). Fig. 2 summarises enzyme inhibitors that are currently approved and used in treating human ailments.

The purpose of this review is to discuss the enzyme inhibitors from marine algae of therapeutic potential to treat common diseases such as diabetes, obesity, dementia, inflammation, melanogenesis, AIDS, hypertension and various viral diseases. Thus, this review lists 86 algal enzyme inhibitors reported during 1989–2013. As per our knowledge, this is the first review for the potential enzyme inhibitors of marine origin.

Fig. 3 explains about the distribution of enzyme inhibitors among the seaweed phyla and highlights the predominance of brown seaweeds. Seaweeds belonging to the order Laminariales and Ceramiales were reported to be the most active enzyme inhibitors due to the presence of polyphenols and terpenoids discussed here. See Figs. 4A–E for chemical structures and Tables 1–9 for the summary of enzyme inhibitory properties of 86 algal enzyme inhibitors.

Diabetes mellitus

Diabetes mellitus (DM) is a complex disorder characterized by hyperglycemia and represents one of the world's most serious health concerns, developing increasingly with increasing obesity and advancing age amongst the global population. In 2010, 285 million people were affected by diabetes according to the World Diabetes Foundation (WDF), which was about 4.6% of the world's population. The WDF projected that these figures will escalate to 438 million (7.8%) by 2030. The disease is primarily classified into insulin dependent diabetes mellitus (type I diabetes) and non-insulin dependent diabetes mellitus (type II diabetes). Type II diabetes is responsible for 85–95% of all diabetes in high-income countries and may account for an even higher percentage in low- and middle-income countries (Shaw et al., 2010). Type II diabetes may be treated by α-amylase and α-glucosidase inhibitors which delay glucose absorption. Synthetic α-amylase and α-glucosidase inhibitors such as acarbose, miglitol and voglibose are widely used for the treatment of patients with Type II diabetes, but are also reported to cause various side-effects. Therefore, safer natural α-amylase and α-glucosidase inhibitors are desired and many such compounds have been reported from plant sources.

The other major enzymes, protein tyrosine phosphatases (PTP1B) are directly involved in the regulation of insulin and leptin receptors which makes them ideal therapeutic agents for Type II diabetes. Several reports have demonstrated that PTP1B is a key player in immune responses and cancer (Feldhammer et al., 2013). So far there are 250 published papers on the development of PTP1B inhibitors covered in recent reviews (Barr, 2010; Feldhammer et al., 2013; He et al., 2013). However, no PTP1B inhibitors have yet entered clinical trials. See Table 1 for a summary of algal metabolites that inhibit enzymes linked to diabetes.

Fucodiphloroethol G (**1**), Dieckol (**2**), 6,6′-bieckol (**3**), 7-phloroeckol (**4**) and Phlorofucofuroeckol A (**5**) are phlorotannins isolated from the brown seaweed *Ecklonia cava* that are active in inhibiting α-amylase and α-glucosidase at micro molar concentrations with Dieckol (**2**) being the most active (Lee et al., 2009). Studies have confirmed the antidiabetic effect of Dieckol (**2**) both *in vitro* and *in vivo* using diabetic mice (Kang et al., 2012a; Lee et al., 2010; 2012a, b). This compound also exhibited hepetoprotective activity (Kang et al., 2012b; 2013). These reports suggest that Dieckol can be used as a potent source for the development of new therapeutic drugs.

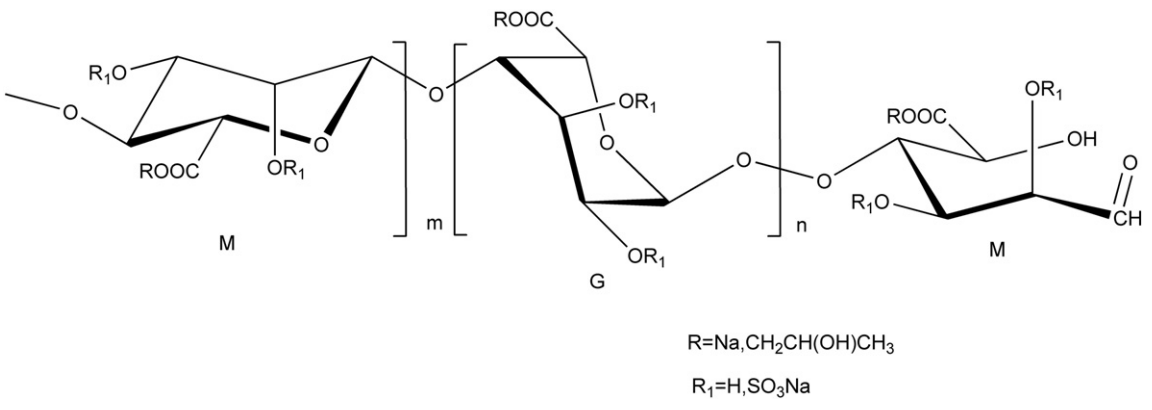

Fig. 1. Marine algal drug used for antiangiocardiopathy.