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MINI-REVIEW

Natural Products as Potential Antiviral Drugs: The Specific Case of Marine Biotoxins

Jean-Louis Kraus[1]

Institut de Biologie du Développement de Marseille (IBDM), UMR-7288 CNRS Aix-Marseille University, Marseille Cedex, 13288 France

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Abstract—To fight against various viral infections researchers turned to new chemical structures resulting from natural medicinal plants and more recently from "marine origin" as sources of active molecules against viral infections. The present manuscript describes complex marine origin drugs, their chemical complex structure, their therapeutic use, and their antiviral properties. Emphasis is placed more particularly on the properties of ionic channels (Na^+, K^+, Ca^{2+}) blockers compounds from marine origin, named *Dinotoxins*, derived from "dinoflagellates microalgae". These compounds are of particular pharmaceutical interest since *ionic channels blockers* could be used to fight against a wide diversity of viruses, including SARS-CoV2 virus.

Keywords: marine products, biotoxins, SARS-CoV2, dinoflagellates, ionic channels blockers

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1. INTRODUCTION

The study of nature's enormous arsenal of new bioactive compounds and natural metabolites has historically led to immense benefits with respect to drug discovery [1]. From natural plants medicinal mixtures were identified interesting chemical scaffolds such as flavonoids, chalcones, tanshinones, cinnamic amides, diarylheptanoids, phlorotannins (list not exhaustive) which represent the active ingredients of a wide diversity of bioactive drugs It should be underlined that the number of compounds of marine origin is higher than that of terrestrial origin including antiviral properties [2–5]. The great diversity of these molecular scaffolds found in natural products has stimulated the search for natural molecules to fight against "*Severe Acute Respiratory Syndrome Coronavirus 2*" (SARS-CoV 2). Some natural plant compounds [6], target more specifically SARS-CoV 2 cellular receptors, like angiotensin converting enzyme (ACE2) [7] while some others, target specific proteases, such as papain-like protease or SARS-CoV 2 chymotrypsin-like protease [3CL(pro)] [8, 9]. The interaction of new ligands with the molecular structure of these specific SARS-CoV 2 receptors has enabled the identification of new drugs targeting infected cells, which have shown efficient antiviral activities in vitro [10, 11].

[1] Corresponding author: phone: (33) 0413 94 2425; e-mail: jean-louis.kraus@univ-amu.fr.

2. SEARCH FOR IN VITRO ACTIVE ANTI SARS-CoV 2 DRUGS

2.1. Drug Repositioning and High Throughput Screening Methods

The first technique was "*drug repositioning,*" also known as drug re-purposing, re-profiling, re-tasking, or therapeutic switching. This approach is to repurpose a drug approved for the treatment of a given disease, or for a new therapeutic application or medical condition, different from which it was originally developed. This repositioning initiative has been used to identify drugs as first-line therapy for treating /preventing COVID-19 infection [10]. Drug repositioning is a "universal strategy" which allows: to reduce the number of required clinical trial steps, to reduce time and costs for the medicine to reach market and to facilitate formulation and distribution. Besides the screening of FDA approved drugs, "*large generalist chemical libraries*" around 10000 to 100000 of compounds with great diversity of chemical structures, available through different suppliers have been screened using High Throughput Screening (HPTS) robotic methods. HPTS methods [12, 13] which allow to quickly conduct millions of chemical, genetic, or pharmacological tests have led the discovery of numerous approved drugs applied to cure various kind of rare diseases [14, 15]. Applied to the search for new COVID-19 antiviral drugs, those library screening methods have led to some encouraging results since some compounds (Hydroxychloroquine, Remdesivir, Clofoctol) were found active in vitro on SARS-CoV 2

cellular cultures but their clinical activity has still not been demonstrated [16].

Unfortunately, after several world wild clinical trials, to date none of these in vitro active drugs were found active in vivo. Additionally, since the X-ray crystal structure of SARS-CoV 2 M protease was fairly available to the whole international scientific community both virtual and in vitro screening compounds have been performed in order to design and screen potential SARS-CoV 2 protease inhibitors. Some active inhibitors have been identified, unfortunately to date, no in vivo activity has been reported [17].

3. MEDICINAL PLANTS PRODUCTS AS SARS-CoV 2

Medicinal plants as possible sources of active molecules against SARS-CoV 2 were explored largely [18]. As a first selection, 39 plants recognized by botanists and pharmacologists for their widespread use in respiratory related diseases were identified [19]. The effectiveness of 39 herbal medicines were selected and their antiviral activities were compared to that of the three chemical molecules (codein, ibuprofen, paracetamol) commonly recommended against Covid 19 common symptoms (headaches, fever or chills, cough). Among these 39 herbal medicines, 5 were identified as very likely to appeal to the COVID19 patient. *Althaea officinalis* (marshmallow), *Commiphora molmol* (myrrh), *Glycyrrhiza glabra* (licorice), *Hedera helix* (climbing ivy), *Sambucus nigra* (black elderberry).These herbal medicines do not cure or prevent the flu but may both improve general patient well-being and offer opportunity to personalize therapeutic approaches.

4. MARINE DRUGS AS PROMISING SOURCES OF ACTIVE DRUGS AGAINST SARS-CoV 2

Numerous marine drugs [20] have shown in vitro activity on a large panel of viruses: HIV, Influenza A and B, Herpes simplex 1 and 2, Measles and Cytomegalovirus. Most of these active compounds present a large diversity of chemical structures: sulfated polysaccharide, sterol, depsipeptide, flavones, fatty acids, alkaloids, furanoterpenes, shikimate. None of them have been approved for human use. Following, the results gained on the antiviral properties of numerous marine derived natural products, a known library of marine natural compounds (14064 compounds) were screen in silico against SARS-CoV 2 [21]. Some products have been shown to be excellent in vitro inhibitors of the SARS-CoV 2 protease in particular heptafuhalol and bieckol [22], but their in vivo possible clinical use remains to be demonstrated.

4.1. The Particular Case of Dinoflagellates Microalgae Biotoxins

Considering the potential represented by marine microalgae in terms of sources of new molecules not yet identified, and in terms of unknown biological properties, microalgae constitute a living organism of choice for the research of new molecules and their possible applications in the field of antiviral infections in particular. Microalgae [23, 24] could be seen as "*cells mills producing recombinant commercial molecules.*" Among the myriads of microalgae species, the family of dinoflagellates [25] is of particular interest since they produce wide varieties of complex chemical structures called *Dinotoxins*. The chemical structure of these dinotoxins extracted from dinoflagellate microalgae species are presented on Fig. 1. Dinotoxin producers as well as dinotoxins biological effect, biological target and toxicity are given in Table 1.

Dinoflagellates are a unique class of unicellular planktonic microalgae [26] and a source of a wide variety of biotoxins which present a potential for human health, and unexpected applications as pharmacological drugs. Their potential uses in biotechnological fields and more specifically in the war against viruses have been reported [27, 28]. Due to the molecular structure complexity of these marine biotoxins [26], their synthesis of an industrial scale is too expensive, time consuming and too difficult to implement. The case of *palytoxin* is a significant example of complex molecule with 64 stereogenic centers [29], its chemical synthesis requires more than 140 steps [30].

5. VOLTAGE GATED IONIC CHANNELS BIOTOXINS FROM DINOFLAGELLATES AS POTENTIAL CANDIDATES TO TARGET SARS-CoV 2

Ionic channels are expressed in human diseases (e.g. malaria parasite) and infective agents such as bacteria and viruses. Therapeutic approaches relative to genetic ion *channelopathies* have been already described [31] and more specifically applied to viral infections [32], since SARS-CoV 2 included in its genomic structure ionic channel genes [33, 34], those genes represent suitable targets to tackle SARS-CoV 2 infection. An interesting paper from Wang [35] provides a brief overview of the origin, the structure and the voltage gated ionic channel properties of dinoflagellates biotoxins presented in Table 2.

Saxitoxin and related analogues Gonyotoxins [36, 37] block sodium channels in binding to a receptor located in the outside surface of the membrane very close to the orifice of the sodium channel, without affecting the potassium channel. Similar to saxitoxin derivatives, lipid-soluble polyether drugs, brevetoxins [38] from *Karina brevis*, are also voltage-gated sodium channels blockers. In contrast, yessotoxins [39], maitotoxins [40, 41], azaspiracids [42], target specifically

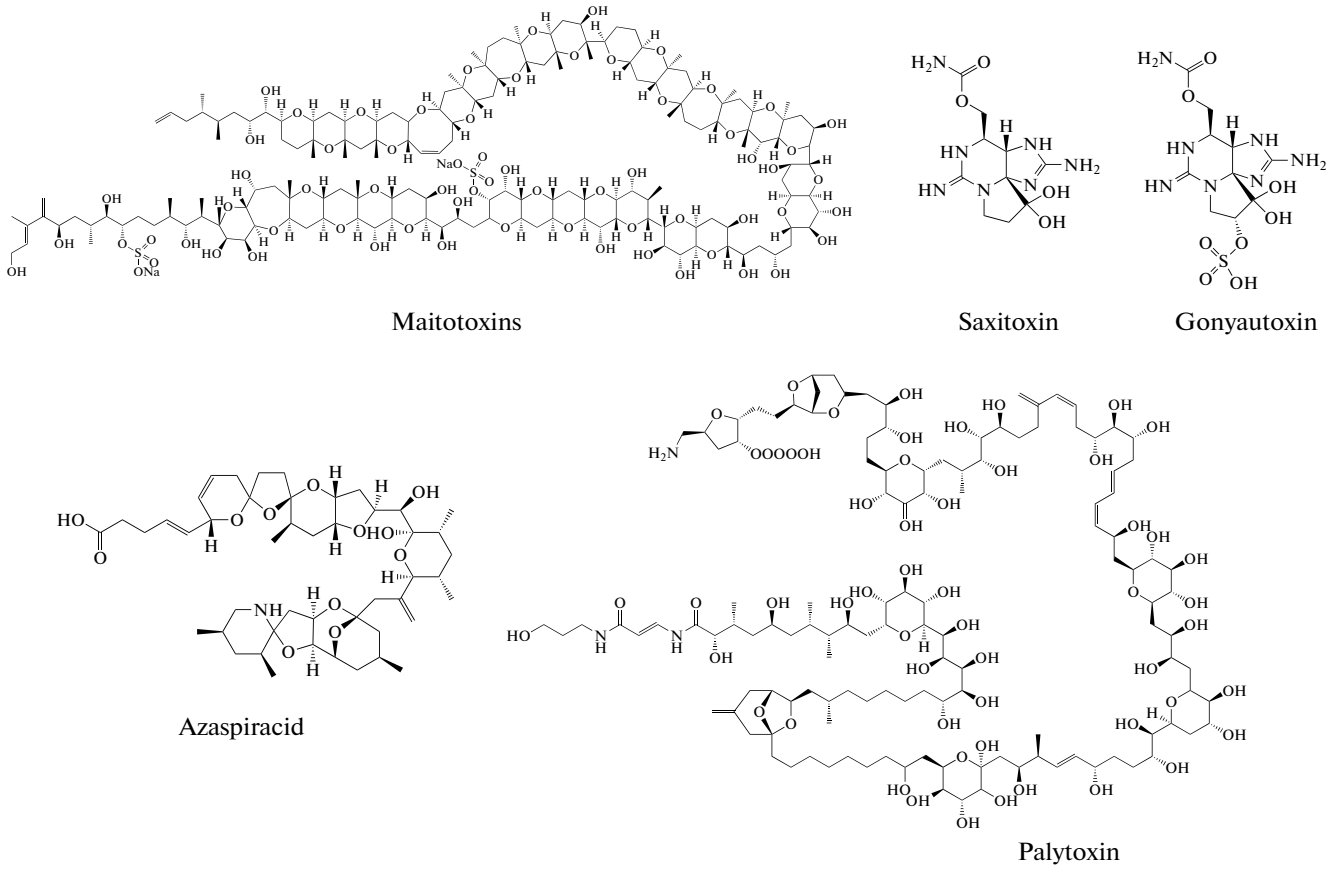


Fig. 1. Dinotoxins chemical structures.

Table 1. Dinoflagellates microalgae biotoxins biological properties

Biotoxins	Dinoflagellates species biotoxin producers	Biological effect	Target on action	Toxicity
Saxitoxin	*Alexandrium (minutum tamarense, catenella)*	Long acting pain blocker	Voltage-gated sodium channel blocker	Potent neurotoxin
Karlotoxin	*Amphidinium* genus	Haemolytic activity Antifungic	Ionic permeability membranes perturbator	Ichthyotoxic
Palytoxin	*Ostreopsis*	Vasoconstrictor	Sodium potassium pump protein	Clupeotoxic
Tetrodotoxin	*Alexandrium tamarense*	Nerve and muscle conduction blocker	Voltage-gated sodium channel blocker	Neurotoxic
Okadaic acid	*Procentum* genus	Myalgia, ataxia, bradycardia	Protein phosphatase inhibitor	Abdominal pain diarhea
Brevetoxin	*Karenia brevis*	Respiratory Gastrointestinal	Voltage-gated sodium channel blocker	Neurotoxic
Gambierol	*Gamberdicus genus*	Respiratory system paralysis	Voltage-gated sodium channel blocker	Neurotoxic
Amphidinolide	*Amphidium genus*	Antifungic, anticancer	Cell aggregation	Cytotoxic

Table 2. Voltage-gated channels dinotoxins blockers

Dinotoxins	Sources of toxins	Channel ions target	References
Saxitoxins	*Alexandrium* genus	Voltage-gated Na^+ channel 1	37, 38
Gayautoxins	*Gymnodinium*, *Pyrodinium*	Voltage-gated Na^+ channel 1	37, 38
Brevetoxins	*Kerenia brevis*, *Chatonella marina*	Voltage-gated Na^+ Channel 5	39
Yessotoxins	*Protoceratium reticulatum*, *Llingulodinium polyedrum*	Voltage-gated Ca^{++}/Na^+ channels	40
Mailtoxins	*Gambierdiscus toxicus*	Voltage-gated Ca^{++} channel	40, 41
Azaspiracids	*Protoperidinium crassipies*	Voltage gated Ca^{++} channel	42
Palytoxins	*Ostrepsis siamensis*	Na^+/K^+ ATPase	43

Ca^{2+} channels, leading to an increase of Ca^{2+} influx in brain stem cells. (Chemical structure on Fig. 1.) Other dinoflagellate toxins such as palytoxin [43] interact with the Na^+,K^+-ATPase, enzyme involved in the induction of ionic channel, regulating ions concentrations to get into and out of cells. A general survey of pharmacological properties of ionic channel blocker compounds reports that the following group of synthetic chemical drugs: amiodipine, felodipine, nifedipine, gliclazide, nemantine, recognized as voltage-gated ionic blockers, were found active in vitro on SARS-CoV 2 virus replication [44].

One can ask the question: is the property for a drug to be *ionic channels blockers* a sufficient condition to endow the drug with SARS-Cov 2 antiviral properties? In contrast to dinotoxins, the following group of known marine drugs: amphinolide, karlotoxin, astaxanthin [45] (Fig. 2), and sulfated exopolysaccharides [46, 47] found active on SARS-CoV 2 virus, are not voltage-gated ionic blockers.

Following these observations, it could be suitable to screen if the marine biotoxins listed in Table 2, which ionic voltage gated channel activity have been demonstrated, are active molecules against SARS-CoV 2 infected cells. Different observations argue in favor of this hypothesis: It has been recently reported that the synthetic drug Gliclazide (Fig. 3) an antidiabetic drug, which belongs to the family of sulfony-

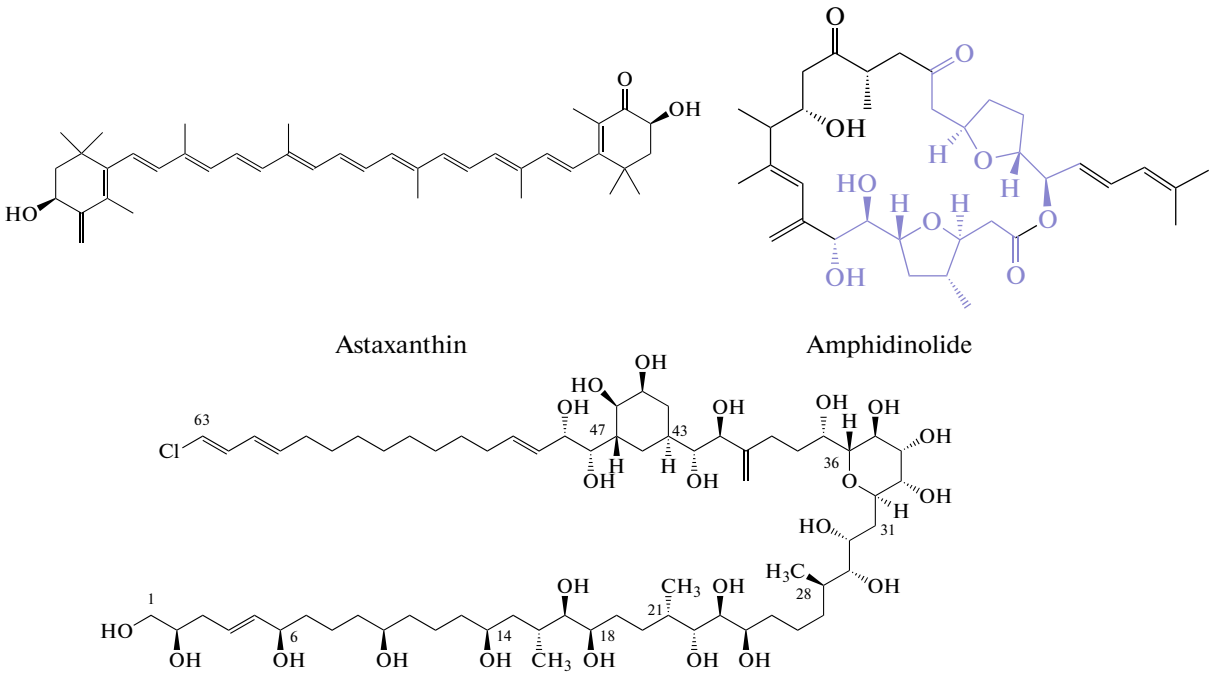
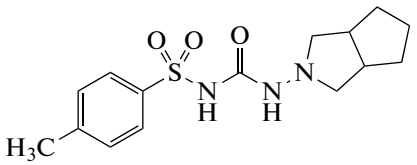


Fig. 2. Chemical structures of dinotoxins active in vitro on SARS-CoV 2 Virus: amphidinolide, karlotoxin, astaxanthin.



Glicazide

Fig. 3. Glicazidechemical structure: synthetic antidiabetic drug active in vitro on SARS-CoV 2.

lureas, launched in 2010, widely used in the management of diabetes mellitus type 2, has demonstrated remarkable antiviral properties in vitro against SARS-CoV 2 [35] moreover Gliclazide act as inhibitor of the K^+/Na^+ATPase enzyme, an enzyme involved in the induction of ionic channels, which regulates ionic species concentrations to get into and out of cells [48].

CONCLUSIONS

Unfortunately Gliclazide, is a synthetic drug with several known side effects, and its synthesis required polluting synthetic processes. In contrast dinotoxins are marine natural compounds from natural algae, for which several dinoflagellates producers have recently developed new biotechnical processes allowing the quantity production of dinotoxins at reasonable prices [49]. Their unique properties as selective ionic channels blockers which play key roles in almost all facets of cellular physiology represent a new approach to discover new antiviral drugs which target specifically viral voltage-gated ionic channels. For these reasons, the search for new natural antiviral agents from marine sources [50] not only to fight against SARS-CoV2 infection, represents a hope for the development of new active antiviral molecules.

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COMPLIANCE WITH EHICAL STANDARDS

This article does not contain any studies involving human participants performed by any authors and does not contain any studies involving animals performed by any of these authors

Conflict of Interests

The author declare no conflict of interest.

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