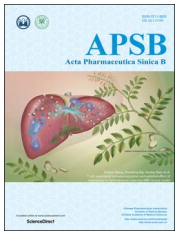
Acta Pharmaceutica Sinica B ▮▮▮▮;▮(▮):▮▮▮–▮▮▮

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



REVIEW

Insects: an underrepresented resource for the discovery of biologically active natural products

Lauren Seabrooks[a,*], **Longqin Hu**[a,b,**]

[a]*Department of Medicinal Chemistry, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA*
[b]*Cancer Institute of New Jersey, New Brunswick, NJ 08901, USA*

Received 6 March 2017; received in revised form 27 April 2017; accepted 2 May 2017

KEYWORDS

Natural products;
Insects;
Entomotherapy;
Traditional medicine;
Drug discovery

Abstract Nature has been the source of life-changing and -saving medications for centuries. Aspirin, penicillin and morphine are prime examples of Nature's gifts to medicine. These discoveries catalyzed the field of natural product drug discovery which has mostly focused on plants. However, insects have more than twice the number of species and entomotherapy has been in practice for as long as and often in conjunction with medicinal plants and is an important alternative to modern medicine in many parts of the world. Herein, an overview of current traditional medicinal applications of insects and characterization of isolated biologically active molecules starting from approximately 2010 is presented. Insect natural products reviewed were isolated from ants, bees, wasps, beetles, cockroaches, termites, flies, true bugs, moths and more. Biological activities of these natural products from insects include antimicrobial, antifungal, antiviral, anticancer, antioxidant, anti-inflammatory and immunomodulatory effects.

*Corresponding author. Tel.: +1 732 5944653. Current address: Merck Research Laboratories, 2000 Galloping Hill Road, Kenilworth, NJ 07033, USA.
**Corresponding author. Tel.: +1 848 4455291.
E-mail addresses: les02d@gmail.com (Lauren Seabrooks), longhu@rutgers.edu (Longqin Hu).

Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

http://dx.doi.org/10.1016/j.apsb.2017.05.001

Please cite this article as: Seabrooks Lauren, Hu Longqin. Insects: an underrepresented resource for the discovery of biologically active natural products. *Acta Pharmaceutica Sinica B* (2017), http://dx.doi.org/10.1016/j.apsb.2017.05.001

1. Introduction

The chemical and structural diversity of natural products are unparalleled by any synthetic based library and have inspired a wealth of life-changing and -saving medicines for centuries[1]. In 1803, the remarkable pain-relieving natural product, morphine, was isolated from the *Papaver somniferum* plant and in the 1870's served as the template for codeine[2]. Two decades later, salicin, the medicinally active natural product from the willow bark, *Salix alba*, was isolated and characterized by Henri Leroux[2,3]. From this acetylsalicylic acid, an anti-inflammatory agent known commercially as aspirin was synthesized by the Bayer scientist Felix Hoffman. Aspirin has been a commercial success for the Bayer Company since its market debut in 1899. Thirty years later penicillin was isolated from the fungus *Penicillium notatum* by Alexander Fleming and proven to be a groundbreaking antibiotic by Howard Florey and Ernest Chain[2,4,5]. This discovery revolutionized medicine, earning Fleming, Chain and Florey the 1945 Nobel Prize in physiology or medicine for their efforts[2,5]. Then in 1971, the most effective malarial treatment to date was discovered while scientists were reviewing ancient tomes on traditional Chinese medicine[4]. It was within these texts that artemisinin was identified as a promising drug discovery lead. The head scientist, Youyou Tu, earned the Lasker prize in 2011 and the 2015 Nobel Prize in physiology and medicine for this impressive discovery[4,5].

The aforementioned examples and the fact that 33% of drugs approved from 1981–2010 and a staggering 68% of all approved antibacterial drugs are natural products or derivatives thereof prove that nature is an important source of new target molecules[6,7]. However, the focus of natural product medicine has been overly focused on terrestrial plants, various algae and fungi. An underrepresented source of inspiration, entomotherapy, has been in practice for as long as and often in conjunction with medicinal plants. Entomotherapy is the use of insects as medicine and is an important alternative to modern therapy in many parts of the world including India, Mexico, Korea, China, Spain, Brazil, Argentina, Ecuador and various African countries today[8–22]. Honey, a sweet bee byproduct, is valued as an antioxidant and antimicrobial agent, suitable for the battle against heart disease and skin disorders[23–27]. Propolis, a gap filling "glue" used in the construction of the beehive, has been evaluated extensively for its potential antioxidant, antimicrobial, anti-inflammatory, cardioprotective, immunomodulatory and antiangiogenic properties[28–30]. Venom, especially from bees, has been studied as an alternative medicine for inflammation and cancer therapy[31–34]. Success has also been achieved in identifying biologically active isolates from insect bodies, excretions and secretions. Antimicrobial peptides, an innate component of insect immunity within the hemolymph (blood), have shown activity against fungi, parasites, viruses and most importantly antibiotic resistant bacteria[35–37]. Insect toxin isolates pederin and cantharidin from defense secretions of the rove and blister beetles, respectively, have peaked scientific interest as potential anticancer therapies[38,39].

Insects as natural product resources have also been featured in reviews published from 2010–2015[14,38,40–44]. However, the scope of the aforementioned articles often includes other arthropods, covers a limited selection of insects, focuses heavily on insect byproducts and incorporates uses outside of pharmaceutical applications. This review focuses on the continued cultural use of insects as medicine worldwide, validation of their medicinal properties and identification, characterization and synthesis of insect natural products and derivatives.

Like plants and other invertebrates, insects are hosts for many types of microbial endophytes that include bacteria and fungi. These endophytic microorganisms may be involved or working together with their insect hosts in the production of a natural product reported. The potential involvement of endophytes should be taken into account when we isolate the natural products from insects[45].

Insects belong to the kingdom Anamalia, phylum Arthropoda, and class Insecta. Members of this class are further divided into 29 orders though 81% belong to one of the following four orders: Coleoptera, Diptera, Hymenoptera and Lepidoptera[46,47]. This review article is split into sections based on the different orders and occasionally further subdivided by families. Sections are titled with scientific nomenclature with common names in parentheses.

2. Hymenoptera (bees, wasps, ants and sawflies)

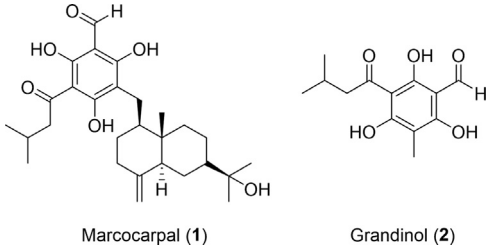
2.1. *Symphyta (sawflies, wood wasps, and horntails)*

The family Symphyta is the smallest of the hymenoptera representing only 7% (8000–10,000 species) of the order[48]. Like ants, they feed on leaves or burrow into wood earning them the position as pests by most foresters. In 2013, researchers out of China and Australia found medicinal value in these pests. Two small molecules with strong antimicrobial activity (Fig. 1) were isolated from the methanolic extract of Australian sawfly larvae[49]. The novel macrocarpal (**1**) and known grandinol (**2**) were evaluated against *Bacillus subtilis* (*B. subtilis*) and exhibited inhibition zones of 8.0 and 7.0 mm, respectively.

Additionally, the hemolymph of sawfly larvae has been found to be rich in phenolic compounds, such as novel flavonol oligoglycosides, flavonoid glycosides and naphthodianthrones, all with known potential health benefits that were not evaluated in the studies[50,51].

2.2. *Formicidae (ants)*

Ants are one of the most familiar members of the hymenoptera order. This is a social family with an impressive life span, the record being 29 years[48]. In 2005, the number of valid described species was approximately 12,000. Ants and ant byproducts are widely used in traditional folk medicine across the globe. In southern India, mud from the interior portion of an anthill is applied topically for the treatment of scabies by the Paniyan tribe[16]. In northern India, scabies, wounds and boils are treated through the topical application of a paste made from the crushed black ants, *Bothroponera rufipes*[11]. Additionally, ground *B. rufipes* mixed with water is gurgled to relieve toothaches and daily consumption of 1–2 whole ants reportedly reduces blood



Marcocarpal (**1**) Grandinol (**2**)

Figure 1 Structures of two compounds with antimicrobial activity isolated from Australian sawfly larvae.

Please cite this article as: Seabrooks Lauren, Hu Longqin. Insects: an underrepresented resource for the discovery of biologically active natural products. *Acta Pharmaceutica Sinica B* (2017), http://dx.doi.org/10.1016/j.apsb.2017.05.001