2 Prospecting Arthropod Biomolecules for Medicinal and Therapeutic Use: Recent Breakthroughs

Anudita, V. Varunrajan, and B.M. Deepa

Abstract

Arthropods, particularly insects, are endowed with the richest chemical diversity which needs to be harnessed. Arthropods are reservoirs of neurotoxins, peptides, terpenoids, saponins, sugars, etc., that have the potential to cure modern human ailments like HIV, dengue, chikungunya, Ebola virus, Japanese encephalitis, and other syndromes. Basic knowledge of chemical interactions among and between organisms is important to understand the nature of disease treatment, controlling pest and food production, to name a few examples. In order to achieve improved livelihoods, it is necessary to use the chemistry of nature and to use it in a sustainable manner. Isolation, characterization of the molecule, and mass production need a holistic understanding of the chemical and physical properties of the substances arthropods produce. Pharmacognosy is still naive and needs to be further explored.

Keywords

Biomolecules • Entomotherapy • Pharmacognosy • Venom

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2.1 Introduction

Arthropods use a wide variety of chemical substances for ecological adaptations, and this is the encircling idea of the field of chemical ecology. Progress in the field has advanced rapidly. There are enormous potentials for discovering natural products with numerous medicinal values from members of the phylum Arthropoda. Insects represent 80–90 % of the world's biodiversity, and hence, it is the largest and the most diverse group on earth. So far, 950,000 species of insects have been described, with some authors estimating that there are approximately 4,000,000 insect species on earth. Like all other organisms, insects and related arthropods mainly utilize chemistry to adapt to environments such as defense against predation or infection, communication and socialization, life cycle development, and surviving. The sheer number of insect species, to say nothing of the diversity of niches they inhabit or the huge variety of ways they interact with other species and their environment through chemistry, is awesome.

2.2 Entomotherapy and Ethnoentomology

The use of insects to treat medical ailments is termed as entomotherapy. Larval therapy is a method wherein the damaged and decaying tissues of the wound are allowed to be fed by the maggots of *Lucilia sericata* fly to heal the wound. Such practices were used by traditional medicine followers in countries such as Australia, Asia, and South America (Horobin et al. 2003; Wolff and Hansson 2003). Costa-Neto (2005) summarizes a list of different arthropods, both aquatic and terrestrial forms which include 14 orders spanning across insects, centipedes, and arachnids, which are used by different communities around the globe. The commercial value of the products based on insects was estimated to be worth more than hundred million US dollar. Studying the nature of insects was one of the most important aspects of chemical ecology. The exodus began for the isolation of "bombycol" from silk moth by Butenandt et al. (1959); since then the beneficial aspects of insects were explored for exploitation in the field of medicine, food, and industry. The early record of using bee sting and bee venom for arthritis treatment was described by Hippocrates (460–377 BC), and elsewhere leeches were used to remove "bad blood."

Costa-Neto (2005) describes in his review how people of different cultures use insects. The Arawak community of Guiana allow their babies to be stung by *Paraponera clavata* to facilitate them to walk early. The adults tolerate the sting so that they can gain immunity to the future stings. Marahna, a tribe from Brazil has a different way of using a related species of ant (*Pachycondyla commutata*). The women of the community undergo the stinging, and as a ritual these ants were woven into strings and tied across the forehead and chest by the subject. A South American tribe uses insects in an indirect way. They gather poisonous dart frogs (Dendrobatidae) for the poison secreted in their skin. The frogs produce poison as result of ingesting toxic arthropods which accumulate on their skin. This toxin was used to poison their arrows to kill during hunting. Asian medicine even today has exotic ingredients such as insects. From the early literatures of Chinese Materia

Medica by Read and Shennong Pharmacopoeia (100–200 AD), a useful list of medicinal arthropods is available, viz., bees, wasps, hornets, silkworm, caterpillars, mantises, flies, stink bugs, cicadas, mole crickets, silverfish, cockroaches, dragonflies, locusts, and lice; and extending the list are other arthropods such as spiders and scorpions. A few more to the list was provided in Compendium Materia Medica (1578). Both Chinese and European medicines use the blood of Spanish fly which contains cantharidin, is a potential blistering agent.

2.3 Venom and Neurotoxins

The class insecta embraces numerous poisonous insects. Among the arthropods, more poisonous species are represented by centipedes, chelicerates, and hymenopteran insects. Exclusively venomous arthropod groups are represented among scorpions and spiders (King and Hardy 2013). Therefore, arthropod's venom is a rich source of biologically active molecules in the natural world (Cherniack and Cherniack 2011; Pimenta and de Lima 2005; Schwartz et al. 2012).

The most popular venom to be explored is from spiders. Spiders, although a small group and less diverse among the arthropods, possess diverse neurotoxins to paralyze the prey. Some toxic compounds known from spiders include acylpolyamines, toxic peptides, sulfated nucleosides, polyamine compounds, and polyamine neurotoxins. Estrada et al. (2007) compiled a list of acylpolyamines, toxic peptides from different groups of spiders which have numerous potentias to treat pain and diseases related to malfunctioning of central nervous system such as Alzheimer, Parkinson, and Huntington disease. A study conducted by Schroeder et al. (2008) has identified novel sulfated nucleosides and polyamine compounds using NMR technology from more than 70 different spider species. Common pests such as the violin spider (*Loxosceles reclusa*) and hobo spider (*Tegenaria agrestis*) which were known for their toxicity for many years have such compounds. An array of polyamine neurotoxins from spiders are mostly found on the sensory receptors, which can be explored for drug discovery.

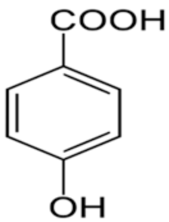
The venom of the spiders has different modes of action. Argiotoxin, isolated from the venom of *Agelenopsis aperta,* was effective against seizures which were audiogenic and N-methyl-D-aspartate (NMDA) induced. The most extensively studied spider for more than two decades, *Phoneutria nigriventer,* has some unique neurotoxins such as PhTx-3 (Tx-3) with an inhibitory effect on Ca^{2+}-dependent glutamate release. On the other hand, the colonial spider *Parawixia bistriata* and Chilean giant pink tarantula *Grammostola spatulata* have different modes of action; the latter uses a combination of toxins to kill its prey. The toxic mixture acts on the ion channels and inhibits their functions (Laurent et al. 2005). Voltage-gated calcium channels like N, P, and Q type were targeted by grammotoxin SIA, a neurotoxin isolated from the venom of spider *G. spatulata*; because of the targeted site of action, there are lots of avenues for potential research. There are few compounds with structural and functional similarity between some neurotoxic compounds found in spiders and other arthropods; one such compound is philanthotoxin which was first discovered from a predatory wasp species *Philanthus triangulum*.

Later such compounds were found in spider venom as well. This suggests a plausible convergent evolutionary relationship between these two neurotoxins in bringing down the prey. Philanthotoxin acts at the nerve junctions as a noncompetitive antagonist of both glutamate receptors and nicotinic acetylcholine receptors.

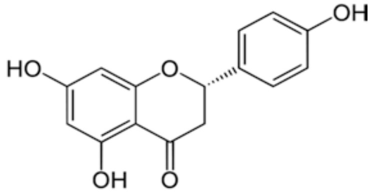
Many insect-related compounds have been developed as drugs. Structure–activity relationship (SAR) studies have used a chemical approach of producing over 100 analogs of philanthotoxin to improve specificity. Photolabile analogs are used to probe receptor structure and to design more selective antagonists of specific human receptors, with the goal of generating more useful compounds with therapeutic potential. Neurotoxins from invertebrates are diverse, and compounds such as philanthotoxin demonstrate numerous potentials and hence valuable in basic neuroscience research. Insects, like many arachnids, have diverse compounds in their venom such as poneratoxin, pederin, and philanthotoxin, to name a few. Poneratoxin is produced by bullet ant (*Paraponera clavata*). Bite by this ant is most painful, and the protein poneratoxin acts on the voltage-dependent ion channels in the insects. Further exploiting this phenomenon in control of insects was proposed using expression of this protein in insects using viral vectors. The suitability of using this compound and its analogs from other ant species needs to be explored. Pederin and philanthotoxin from rove beetle *Paederus fuscipes* and digger wasp *Philanthus triangulum,* respectively, have high potential as compounds for human medicine (Estrada et al.2007; Schroeder et al. 2008; Schwartz et al. 2012; King and Hardy 2013).

2.4 Honey

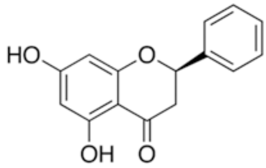
Honey has rich tradition in human civilization, be it for therapeutic or cultural reasons. Honey is produced by few genera of hymenopteran insects which include genera *Apis*, *Partamona*, *Tetragonisca*, *Plebeia,* and *Melipona*. Meda et al. (2004) list a few uses of honey in medical ailments such as topical applicator for treatment of burns, cold, sore throats, flu, irritable bowel syndrome, and tuberculosis. Honey in combination with lemon juice is used in the western cultures commonly against sore throats, flu, and colds. Efem et al. (1992) suggested honey for wound dressing owning to its antibacterial effects against both primary and secondary infections. Honeybees in addition to honey collect propolis, a waxy material from flowers which they use to seal the gaps in the comb. In addition to its structural function, it also has antimicrobial, antimutagenic, and antioxidant properties (Wang et al. 2002). Antimicrobial and antioxidant properties of honey and also four phenolic compounds, chrysin, pinocembrin, p-hydroxybenzoic acid, and naringenin, depend on the food source the bees forage.Hence, the antimicrobial and antioxidant properties of the honey differ among species of bees and plants (Basson and Grobler 2008). Honey is used in the treatment of skin disorders in combination with beeswax and olive oil. Royal jelly, a food source for developing queen larva, contains many compounds, of which 24-methylenecholesterol, 10-hydroxy-trans-2-decenoic acid, and 10-hydroxydecanoic acid have gained importance in traditional medicine and are widely used (Figs. 2.1 and 2.2) (Suzuki et al. 2008; Leung et al. 1997; Miyata 2007).



P-hydroxybenzoic acid

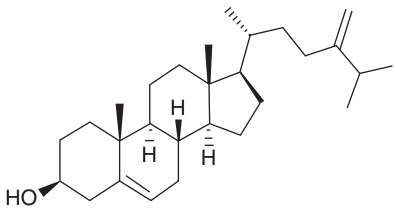


Naringenin

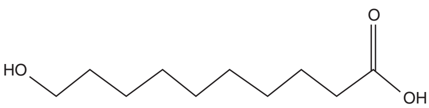


Pinocembrin

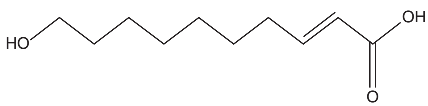
Fig. 2.1 Phenolic compounds in honey (Noda et al. 2005)



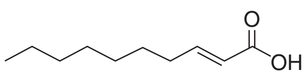
24-methylenecholesterol



10-hydroxydecanoic acid



10-hydroxy-Trans-2-decenoic acid



Trans-2-decenoic acid

Fig. 2.2 Royal jelly constituents (Noda et al. 2005)

2.5 Medical Entomology/Pharmaceutical Entomology

Laurent et al. (2005) reviewed the literature on chemical molecules in insects, and gave the application of such molecules in insect defense and medicinal application.

Ramos-Elorduy (1988, 1999) suggested that "insects may prove a valuable source of prototype drugs." For instance, there are different species of cockroaches found in the world; among them particularly species such as *Eupolyphaga sinensis* and *Opisthoplatia orientalis* are mass cultured in China to be used as medicine for "trauma and vulnerary." On the other hand, other species of cockroaches are used for internal feverish chills. Early writings found in Jing Shi Zheng Lei Da Guang Ben Cao, a traditional medical writing by the Chinese during the Song Dynasty (1280 AD), identify a list of medicinal insects and their uses (Namba et al. 1988). The practice of using insects as medicine is increasing nowadays. In the orient, 43 species of insects have been identified for use as medicine. They belong to 16 families and 6 orders.

Only two large-scale surveys of arthropods have been conducted to date: one in the 1960s, which continues today in the group led by Pettit, and a second group led by. Arthropod-based drug discovery by the Trowell group since 2002 at Australia's Commonwealth Scientific and Industrial Research Organization (CSIRO) and spun off into the company Entocosm. Those studies began with over 1,000 arthropod species, of which 80 % were insects that included representatives from 17 different orders of insects. Both Entocosm and Entomed (Dimarcq and Hunneywell 2003) were founded with the mission of discovering drugs from arthropods. The pharmaceutical company Merck has patented a scorpion toxin called margatoxin for use as an immunosuppressant (Costa-Neto 2005). In 1991, the National Biodiversity Institute of Costa Rica (INBio) entered into a US$1 million agreement with Merck to test insect extracts for their efficacy against infections, AIDS, cancer, and inflammatory conditions. New advances in analytical chemistry, new disease models for more efficient and high-throughput drug screening, and epidemics of emerging pathogens and other diseases provide significant rationale for deeper exploration of arthropods as sources of new drugs.

2.6 Cytotoxins and Anticancer Compounds

Arthropods have different groups of chemicals in their venoms and hence are desirable candidates for drug development. These chemicals are often used to paralyze prey by virtue of their toxicity and to ward off predators. Most often even humans are known to have physiological responses to these chemicals (Fox and Serrano 2007). The compounds with cytotoxic properties are often examined for their potential as anticancer chemotherapeutics. Farnesyl lamin, a cytotoxic compound, has the ability to inhibit farnesyl protein transferase; pharmacological properties of this compound were studied even before it was discovered from the natural source, an ant species *Monomorium fieldi* from Australia. Oldfield (1984, 1989) reported that among the 800 terrestrial arthropods studied which include centipedes, millipedes, crustaceans, insects, and spiders, around 4 % of the extracts were found to have at least some anticancer properties. To treat snake bites and headache, centepedes were ground into paste and used.

Maggot therapy, in addition to helping in the healing of bone tissue, also cleans the dead tissues, by the action of endogenous antibiotics and the secreted ammonia, and calcium carbonate provides a quick healing platform. Cantharidin is an example of a cytotoxic compound from blister beetles (Meloidae) (Figs. 2.3a, b and 2.4) and is being explored for potential medical application. Cantharidin, which is terpenoid in nature, is derived from *Lytta vesicatoria* (Spanish fly), *M. cichorii* (Chinese blister beetles), and the bodies of blister beetle, *Mylabris phalerata,* and is used in traditional Chinese and Vietnamese medicine as an ingredient to treat esophageal cancer, hepatoma, and skin diseases, and it has been found to inhibit the cancer cell proliferation in cancer cell lines (Moed et al. 2001; Rauh et al. 2007; Liu and Chen 2009). Blister beetles when disturbed produce droplets of blistering blood poured out from their leg joints so that it rubs off on the attacker. Blister beetles traditionally have been used to remove warts and for cancer treatment, and Greeks used it for enhancing sexual libido. Spanish fly is currently restricted for use only in animal husbandry and wart treatment in the United States. Unlike most chemotherapeutic

Fig. 2.3 Maggots of *Lucilia sericata*

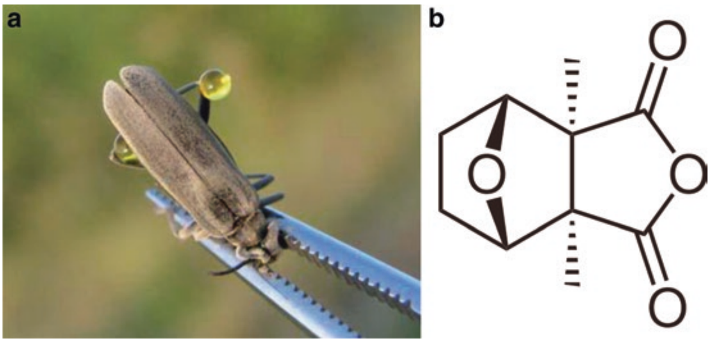


Fig. 2.4 (**a**) Blister beetle (*Epicauta* sp., family Meloidae) deploying its typical defensive secretion of blood (hemolymph) enriched in the blistering agent. (**b**) Cantharidin (Source: Aaron 2010)

agents, cantharidin is found to act on leukemia progenitor and stem cells (Dorn et al. 2009). Commercial products synthesized from cantharid will be available in the supermarkets soon (Moed et al. 2001; Dorn et al. 2009).

Several fatty acids from insects also possess anticancer properties. Yoo et al. (2007) reported that numerous compounds were isolated from the flower beetle *Protaetia brevitarsis*. The scarab grubs were extracted in dichloromethane and further fractionated on silica gel. The fraction which contained anticancer activity was further analyzed by both NMR and GC-MS, which predominantly had two fatty acids: palmitic acid and oleic acid. They have also reported that an authentic standard of palmitic acid induces apoptosis in colon cancer cells. At high concentrations, fatty acids cause cell death by apoptosis or necrosis. Thus palmitic acid induces apoptosis in cancer cell lines, especially in colon cancer (Yoo et al. 2007) (Figs. 2.5, 2.6, and 2.7).

Pettit's (1977) anticancer activity compounds are from insects, namely, Asian rhino beetle (*Trypoxylus* (*Allomyrina*) *dichotoma*), the Asian butterfly *Catopsilia crocale,* and the wasp *Vespula pensylvanica*. Few current examples include the Texas lubber grasshopper *Brachystola magna* and the Asian butterfly *Byasa polyeuctes termessus*. From grasshoppers (*Brachystola magna*) collected from Texas in 1967 and preserved in isopropanol, three antineoplastic agents were isolated. New cytotoxic substances from butterfly extracts were identified by Pettit et al. (1991).

Fig. 2.5 Chinese red-headed centipede (Source: https://www.sciencenews.org/article/centipede-venom-fights-pain)

Fig. 2.6 The forest or wood scorpion (*Cercophonius squama*) (Source: http://www.australiangeographic.com.au/news/2013/12/venom-of-deadly-scorpions-has-medical-use)

Fig. 2.7 Leech, *Hirudo medicinalis* (https://commons.wikimedia.org/wiki/File:Hirudo_medicinalis.jpg)

Ethanolic extracts of *Byasa polyeuctes termessus* were subjected to activity-guided fractionation and were tested against the mouse-derived leukemia model P388. This resulted in "papilistatin," a new cancer cell growth inhibitor with the structure of aristolochic acid. This is present in other Asian butterflies that feed on food plants of the same genus (Aristolochia) as *B. polyeuctes termessus* (Pettit et al. 1991).

The nests of wasps is a store of anticancerous substances. "Paper wasps" (family Vespidae) build their nests with cellulosic plant material collected from different sources. Fujiwara et al. (2008) reported the first anticancer quinine 7, 8-seco-para-ferruginone from nests of the social wasp *Vespa simillima*. 7, 8-Seco-para-ferruginone and precursor ferruginol occur in the bark of Japanese cedar (*Cryptomeria japonica*) plants and is collected by the wasps for nest construction. The polyketide derivative pederin is a compound discovered in the hemolymph of *Paederus fuscipes* (Family: Staphylinidae). It was discovered in 1953 by Pavan and Bo from the extract of over 25 million field-collected beetles and this is another potential anticancercompound. Pederin is the primary component responsible for anticancerous property. It is produced by an internal symbiont present in the beetle, *Pseudomonas aeruginosa*, and it functions as a chemical defense, effective against spiders.

2.7 Antibiotics

Antimicrobial substances are important tools in the innate immune system for many animals such as insects, which are likely to function as a defense against microbial attack and infection. One such substance is the insect antimicrobial peptide. Cecropins were the first antimicrobial peptides to be discovered, whereas defensins are another common class of antimicrobial peptides which are found in a wide variety of organisms from plants to insects to humans, and their biological activity against bacterial and fungal pathogens has been reported. Melittin, a major component in the sting venom of honeybees and cecropins, is effective against Gram-negative bacteria. Genes encoding insect with antimicrobial peptides have even been identified for their potential use in transgenic plant production. An antimicrobial factor, lucifensin from the maggot species *Lucilia sericata*, is used clinically for better and faster wound healing (Opletalová et al. 2012). This peptide was found in different tissues of the insect as well as its secretions and also found to be effective against *Micrococcus luteus*.

Fly larvae (maggots) have been used for centuries to aid wound healing by removing dead tissue quickly while simultaneously protecting against infection. The isolation of antimicrobial substances from fly larvae was evident from several recent studies (Horobin et al. 2003). In addition to the previously mentioned lucifensin, several substances isolated from larvae of *Lucilia sericata* have been shown effective against a range of bacterial pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA). Similarly an antimicrobial lipid, 1-lysophosphatidylethanolamine (C16:1), has been isolated from the common house fly (*Musca domestica*) (Meylaers et al. 2004). Another insect antimicrobial substance is 5-S-GA, which is effective against both Gram-positive (*Micrococcus luteus*) and Gram-negative (*Escherichia coli* and *Staphylococcus aureus*) bacteria (Leem et al. 1996).

Aquatic beetles produce p-hydroxybenzoic acid, probably to prevent microbe attachment to beetles, which would disrupt their ability to repel water. A similar compound, p-hydroxycinnamaldehyde, is an antimicrobial isolated from another Dipteran, the sawfly *Acantholyda parki*. Additionally to this cyclic proline dimer, other dipeptides isolated from flesh flies, *Sarcophaga peregrina* (Leem et al. 1996) and *Neobellieria bullata* (Meylaers et al. 2004) have been shown to possess antimicrobial properties. Apart from Lepidoptera and Diptera, antimicrobial properties have also been discovered from Coleoptera and Hymenoptera. Glandular secretions present in the nests of ants have also been shown to possess antifungal properties. Other social insects, such as social bees, also use antimicrobial substances to construct their nests.

2.8 Antiviral

Melittin and cecropins have been reported for anti-HIV activity. Melittin (from the sting venom of honeybees) and its analogs have also been shown effective against other viruses such as herpes simplex virus (Baghian et al. 1997; Matanic and Castilla 2004) and Junin virus (Matanic and Castilla 2004). Alloferons are another group of insect-derived antiviral peptides, originally discovered in the hemolymph of experimentally infected blowflies (*Calliphora vicina*). These peptides have been shown effective against influenza and herpes simplex virus. A detailed study found that one likely mode of action for alloferons against viruses could be activation of the NF-kB signaling pathway, which is found in nearly all animal cell types and is involved with cell stress, free radicals, and antigens from viruses and bacteria.

Various modern bioassays with silkworm powder have been tested and shown to inhibit absorption of glucose in human intestinal epithelium cells and reduce vasopressin expression in the hypothalamus of diabetic mice. The constituents responsible for the antidiabetic activity of silkworm powder are likely to include sugar-mimetic α-glucosidase-inhibiting alkaloids such as 1-deoxynojirimycin (DNJ) and other sugar-mimetic alkaloids including 1,4-dideoxy-1,4-imino-D-arabinitol (D-AB1) (67) and 1,4-dideoxy-1,4-imino-D-ribitol (Han et al. 2007; Konno et al. 2006).

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