Review

Plant-derived medicinal entomochemicals: an integrated approach to biodiscovery in Australia

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Abstract

Despite an ancient and well-established use of insects in traditional medicine, our understanding of their bioactive compounds (entomochemicals) lags far behind that of medicinal plants (phytochemicals). In this review, we focus particularly on insect–plant interactions, to examine the possible dependence of the medicinal properties of insects on phytochemicals that they bioaccumulate or chemically modify. We suggest that a cross-disciplinary approach including ethnobiology, insect ecology and phytochemistry can provide new opportunities in bioprospecting. Such opportunities lie not only in identifying medicinal entomochemicals that are based on phytochemical accumulation or modification but also on using insects as bioindicators of what plants may contain novel phytochemicals that have not yet been studied. Firstly, evidence is drawn from the international literature on the medicinal use of insects, many of which have pharmacological properties now well established in the Western scientific paradigm. Secondly, we highlight the value of a cross-disciplinary approach to bioprospecting in an Australian context, where records of traditional Aboriginal use of medicinal insects are scant. Particularly, we explore the Aboriginal use of Lepidoptera as a case study, including witchetty grubs, hawkmoths and processional caterpillars. We conclude that opportunities remain to connect traditional, ecological and chemical knowledge for biodiscovery, in collaboration with Indigenous communities. Ultimately, the success of any such endeavour is dependent on the successful conservation management of insect biodiversity into the future.

Key words

Aboriginal Australians, bioactive compounds, bioprospecting, ethnomedicinal insects, Indigenous knowledge, insect–plant interactions, Lepidoptera, phytochemistry, sequestration, witchetty grubs.

INTRODUCTION

Insects have been used in traditional medicine all over the world for millennia, and this ethnobiological knowledge often guides the search for new bioactive compounds (Pemberton 1999; Costa-Neto 2002; Ding et al. 2005; Senthilkumar et al. 2008; Meyer-Rochow 2017). However, the ecological interactions that underlie and often drive the pharmacological properties of insects are generally ignored. In this review, we explore ecologically guided research as an exciting new approach to biodiscovery in both insects and plants. We demonstrate that investigations of plant–insect relationships have the potential to reveal novel compounds in both organisms, as well as helping to scientifically validate and understand their traditional use.

The ongoing search for new medical treatment options along with increasing concern about drug and pesticide resistance continues to drive global demand for novel pharmaceuticals and biologically active compounds. Although plants have provided the vast majority of natural products to date, there is a growing recognition of the enormous bioprospecting potential offered by insects and other invertebrates (Dimarcq and Hunneyball 2003; Cherniack 2010; Dossey 2010; Anudita and Deepa 2016; Seabrooks and Hu 2017). However, rapid and ongoing declines of global insect biodiversity have recently been brought to light by Sánchez-Bayo and Wyckhuys (2019), with Lepidoptera and Hymenoptera among the terrestrial insect groups most affected. Amid such dire predictions, it is imperative that the ecological implications of harvesting insects be recognised, particularly with respect to their host–plant interactions. Considerations for the conservation of edible insects have been highlighted by Yen (2009) and apply equally to medicinal insects and the plants they interact with. While insects may guide the discovery of novel compounds, we stress that conservation of insect biodiversity is paramount, lest undiscovered compounds and interactions be lost before they can be studied (Sands 2018; Taylor et al. 2018). As such, entomochemicals should only be used as precursory models from which synthetic compounds can be developed for commercialisation. Furthermore, any profitable enterprise must recognise local traditional knowledge through benefit sharing arrangements.

Simpson et al. (2016) presented the advantages of integrating ecological knowledge with the more traditional ethnobotanical and chemotaxonomic approaches to bioprospecting in...
plants. Here, we combine ethnobiology, insect ecology and host plant chemistry to explore the feasibility of such an approach in insects. Given that many phytophagous insects can bioaccumulate, concentrate or modify phytochemicals, examination of plant–insect interactions could provide a powerful yet underutilised pathway for biodiscovery. We begin with an overview of medicinal insect use worldwide, their therapeutic properties and the chemical drivers of plant–insect interactions. We then discuss the potential of an integrated approach in an Australian context and use Lepidoptera as a case study. Specifically, we ask, ‘Could the possible therapeutic properties of insects be inferred by the plants they feed on?’ or, conversely, ‘Can phytophagous insects help target the search for novel phytochemicals?’ We conclude by highlighting how both questions address the knowledge gap of how ecological interactions between insects and plants could underpin a novel and cost-effective approach to biodiscovery.

**ENTOMOCHEMISTRY OF MEDICINAL INSECTS**

Costa-Neto (2005) reports 411 medicinal insect species recorded worldwide; however, this is likely to be much higher according to a recent review by Meyer-Rochow (2017). For example, over 300 insect species are thought to be used as part of traditional medicine in China alone (Feng et al. 2009). Species, mostly from Lepidoptera, Coleoptera, Hemiptera, Hymenoptera, Orthoptera and Homoptera, are ingested or applied in all sorts of ways to treat a vast range of internal and external ailments (Costa-Neto 2005; Dossey 2010; Meyer-Rochow 2017). The ethnomedicinal applications of insects and their pharmacological properties have been detailed in several excellent reviews (Dossey 2010; Ratcliffe et al. 2014; Anudita and Deepa 2016; Meyer-Rochow 2017; Seabrooks and Hu 2017). Bioactive compounds such as phenols, flavonoids, terpenes, saponins, sugars, alkaloids, glycosides and fatty acids have been characterised from a wide variety of insects and shown to have pharmacological properties have been detailed in several excellent reviews (Dossey 2010; Ratcliffe et al. 2014; Anudita and Deepa 2016; Meyer-Rochow 2017; Seabrooks and Hu 2017). Bioactive compounds such as phenols, flavonoids, terpenes, saponins, sugars, alkaloids, glycosides and fatty acids have been characterised from a wide variety of insects and shown to have biological activities including antioxidant, anti-inflammatory, antiproliferative, cytotoxic, analgesic, immunomodulatory, anti-diabetic, cardioprotective, anti-hypertensive, antimicrobial and insecticidal properties. A well-known example is that of the monoterpene, cantharidin, derived from blister beetles (Meloidae) which are traditionally used to treat cancers, warts and skin diseases and to stimulate sexual arousal. Extensive analyses of cantharidin and its analogues or derivatives have revealed powerful anti-inflammatory, cytotoxic and immunomodulatory activities, making them promising anticancer and immunosuppressive agents; reviewed in Ratcliffe et al. (2014) and Seabrooks and Hu (2017).

Insect secondary metabolites (entomochemicals) play important roles in an insect’s life history, as chemical defences against predators (e.g. toxins) or pathogens (e.g. antimicrobials), as reproductive signals (e.g. pheromones), or as venoms against prey. Chemicals can be stored in specialised glands, produced as secretions, or can be found in hemolymph, body tissues, excrement or exuviae. While entomochemicals can be synthesised de novo by some insects, we will focus on those that are plant derived for the purposes of exploring their potential role in novel approaches to biodiscovery.

Most plant families synthesise secondary metabolites as protection against herbivores, pathogens and competitors and in response to environmental stressors (Jay-Allemand et al. 2015). In turn, many invertebrates have developed diverse strategies to counteract plant defence mechanisms or even use them to their advantage. Such strategies include impermeable gut membranes and/or rapid excretion to avoid absorption of toxins; metabolism of compounds into less toxic products; detoxification through symbiotic relationships with microorganisms; and accumulation and storage of plant chemicals (Schoonhoven et al. 2005; Opitz and Müller 2009). Some insects sequester plant secondary metabolites in their tissues or glands, to be used for their own chemical weaponry against predators or for communication (e.g. sex pheromones). From a biodiscovery perspective, these interactions are of particular interest due to the relative lack of attention paid to them thus far. Opitz and Müller (2009) reported sequestration of plant secondary metabolites in more than 250 species of insects from at least 40 plant families. While most compounds were accumulated through leaf herbivory, insects feeding on roots, flowers, seeds and fruits were also shown to sequester phytochemicals. Furthermore, sequestered metabolites were found in all insect life stages, from eggs through to adults. Classes of sequestered phytochemicals include a variety of aromatic compounds, alkaloids, terpenoids, cyanogenic glycosides, cardiac glycosides, fatty acid derivatives as well as other nitrogen-containing and sulphur-containing metabolites (Rosenthal and Berenbaum 1991; Opitz and Müller 2009; Gronquist and Schroeder 2010; Nishida 2014). The importance of secondary metabolites is perhaps best highlighted by the findings that several insect taxa actively ingest plants to take up phytochemicals rather than nutrients, a process known as pharmacophagy (Nishida 2002; Nishida et al. 2004; Zaspel et al. 2014).

A variety of enzymatic pathways have been described in several insect taxa. These enable herbivores to neutralise or metabolise plant toxins (e.g. alkaloids, terpenoids and glucosinolates) through processes such as hydrolysis, de-esterification, oxidation or glycosylation (Rosenthal and Berenbaum 1991; Schoonhoven et al. 2005; Heckel 2014). Some lepidopteran and dipteran species have been shown to use plant-derived compounds as precursors in the synthesis of sex pheromones or defence compounds (Nishida 2014). Symbiotic microbes (yeasts, bacteria and fungi) present in the gut of insects can also play important roles in enzymatic detoxification processes (Rosenthal and Berenbaum 1991; Schoonhoven et al. 2005). Modification of phytochemicals by insects therefore provides a valuable source of novel bioactive compounds that are not found in the original host plants.

While humans have appreciated the medicinal values of plants since time immemorial, the pharmacological connection between plants and the insects they interact with has largely been overlooked. Compared to medicinal plants, relatively few medicinal insect species have had their bioactive chemistry characterised, and of these, only a handful of studies have
examined whether these chemicals are plant derived. Phytochemicals sequestered and stored intact should prove easier to ascribe a plant origin to, but plant-derived compounds that are chemically modified by the insect to produce novel molecules may provide a greater challenge (Gronquist and Schroeder 2010). Identifying similarities between bioactive and/or ethnomedicinal properties of host plants and their associated insect herbivores may also provide clues about the origin of entomochemicals.

Surprisingly, few insects that are known to sequester or modify plant metabolites have been recognised for their medicinal properties. Silkworms (Bombyx mori) and their products are used to treat a variety of ailments in Chinese medicine, ranging from respiratory, intestinal and cardiac conditions to hypertension, diabetes and inflammatory disorders (Singh and Jayasomu 2002). The antidiabetic activities of silkworm larvae have been attributed to α-glucosidase inhibiting alkaloids sequestered from their mulberry host (Morus alba) and concentrated to levels almost three times those found in the plant leaves (Asano et al. 2001; Konno et al. 2006; Han et al. 2007). Furthermore, silkworm larvae metabolise and sequester quercetins from the mulberry plant into their cocoons, and these flavonoids have antioxidant and cardioprotective properties (Simmonds 2003; Hirayama et al. 2013; Khan et al. 2014). Similarly, isoquinoline derivatives from the Texan grasshopper have anticancer properties, and these alkaloids are also thought to have host plant origins (Pettit et al. 2005). Stink beetles (Pentatomidae), used medicinally worldwide for numerous conditions (Meyer-Rochow 2017), contain a suite of bioactive compounds many of which are presumed to be plant derived. Several studies have detected high concentrations of alkaloids, flavonoids, cardiac glycosides, steroids, triterpenoids and free-reducing sugars in extracts of South African stink beetles, Encosternum delegorguei, demonstrating antioxidant and antimicrobial properties (Teffo 2006; Zvidzai et al. 2013; Musundire et al. 2014). Indeed, the host plants of these sap-sucking insects themselves have pharmacological properties, but further research is required to conclusively demonstrate the plant origin of bioactive compounds in these beetles (Teffo 2006). Surprisingly, no concerted attempt appears to have been made by the pharmaceutical industry to capitalise on these insect-derived bioactive compounds despite a long history of capitalising on chemicals from plants.

**AN INTEGRATED APPROACH TO BIOPROSPECTING IN AUSTRALIA**

Australia has around 200 000 species of insects (Austin et al. 2004; Cranston 2017), yet there are only a few records of insects or insect products used for medicinal purposes by Australian Aborigines. Here, we review current ethnobiological records from Indigenous Australians with a view to consolidating existing literature, identifying knowledge gaps and hopefully encouraging the documentation of more information before it is lost. The benefits of applying a multifaceted approach to bioprospecting was recently discussed by Simpson et al. (2016). In particular, the authors highlighted the importance of combining ethnobotanical knowledge with ecologically guided research to enhance biodiscovery in arid land plants. It is argued that harsh climatic conditions are likely to drive the production of defensive or protective plant secondary metabolites, and hence, arid zone flora should be recognised as a potentially rich source of novel biochemicals (Harlev et al. 2012; Simpson et al. 2016). Naturally, this rationale could easily be extended to the insects associated with such plants.

We suggest that a similar approach using recorded Indigenous knowledge, insect–plant associations and plant chemistry could be applied to guide the discovery of biologically important compounds in Australian insects. We have based our review on ethnomedicinal information obtained from published literature; however, we acknowledge and respect that this Indigenous knowledge is the intellectual and cultural property of Aboriginal and Torres Strait Island people. We present examples of phytophagous insects known to be medicinally important to Indigenous Australians and explore the possibility that these insects contain bioactive substances derived from their host plants. It has been demonstrated that apospermic insects can be used as indicators of plants that produce bioactive compounds (Hlson et al. 2009); however, to our knowledge, the reverse situation employing host plant chemistry to discover biologically important insects has not yet been explored.

There is no doubt that insects are of immense cultural importance in Indigenous Australian society, attested by their totemic associations, their presence in Dreamtime mythology, art, rituals and ceremonies, and their use in calendars and as place names. Not only a valuable food source, insects serve as indicators of changing seasons, of the location of certain plant species or other foods (e.g. honey), and as medicines. However, given Australia’s insect diversity, there are surprisingly few records of insects or their products used for medicinal purposes (Table 1). Possible explanations for this seemingly undercapitalised potential may be related to Australia’s harsh and unpredictable environment. Yen (2010) proposed that the underrepresentation of some insect taxa in the diet of Australian Aborigines might be associated with large temporal variations in insect abundance and the concentration of unpalatable essential oils and other phytochemicals characteristic of much of Australia’s flora. Similarly, unreliable access to insects would make their medicinal use far less practical compared to more readily available plants, which are the mainstay of traditional medicine. While it is possible that the therapeutic properties of some insect taxa were simply never discovered, it is very likely that much of the Indigenous knowledge was lost before it could be systematically recorded in the literature. This is especially relevant for southern Australia where Aboriginal communities were displaced by European settlement earlier than in other parts of the continent. As such, the overwhelming majority of records come from central and northern Australia.

For the purposes of this review, we draw on recorded Indigenous uses of phytophagous insects for which medicinal properties may be related to the phytochemistry of host plants. We
provide detailed case studies of medicinally used lepidopterans to demonstrate the potential of combining ethnopharmacology with contemporary ecological and biochemical investigations. From this, we hope to inspire the exploration of insect–plant relationships as potential sources of bioactive compounds based on known secondary metabolites produced by the host plants.

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Table 1 Records of insects or their products used for medicinal purposes by Australian Aborigines

| ORDER | Insect species | Ethnomedicinal use and/or conditions treated (insect part used) | References |
|-------|----------------|---------------------------------------------------------------|------------|
| BLATTODEA | *Cosmozosteria* spp. (Bush cockroach) | Bites & stings (whole adult); pain relief, healing of cuts & wounds (adult innards) | (ACNT 1993; Wijnjorrotj et al. 2005) |
| Termitidae | *Amitermes*, *Macrotermes* spp., *Drepanotermes* spp., *Nasutitermes triodiae*, *Tumulitermes pastinator*, (Termites) | Diarrhoea, stomach & hunger pain, promotion of lactation, burns, infant fever, menstrual & pregnancy pain, mineral deficiency, respiratory complaints, protective plaster for broken bones, sun protection for infant fontanelle, sores (mound material); respiratory complaints (smoke from mound resin); stomach pain, infant diarrhoea, respiratory complaints, colds (eggs); headache (pupae); respiratory complaints, sores (alates) | (Foti et al. 1989; ACNT 1993; Peile and Bindon 1997; Tiwi Land Council 1998; Wightman 2003; White et al. 2009; Roberts et al. 2011; Bordulk et al. 2012; Hector et al. 2012; McTaggart et al. 2014; Lowe 2015; Long et al. 2016) |
| COLEOPTERA | *Cnemoplites edulis* (Mallee witchetty grub) | Sores, wounds, burns, boils, sores eyes (larvae) | (Peile and Bindon 1997) |
| DIPTERA | Calliphoridae (Blow fly) | Treatment of suppurating ear (pus formation) (larvae) | (Peile and Bindon 1997) |
| HEMIPTERA | Cicadidae (Cicada) | Sores, wounds, burns (adults) | (Peile and Bindon 1997) |
| Eriococcidae | *Cystococcus pomiformis* (Coccid) | Burns, sunburn, muscle aches (immature stages within gall) | (Peile and Bindon 1997) |
| HYMENOPTERA | Apidae | Antiseptic for sores, tinea, ichy skin conditions, sore eyes (brood); constipation (honey, pollen) | (Levitt et al. 1981; Isaacs 1987; Hector et al. 2012) |
| Formicidae | *Camponotus* spp. (Honey pot ant) | Colds, sore throat (honey from abdomen) | (Turpin and Ross 2012; Martin 2014) |
| *Oecophylla smaragdina* (Green tree ant) | Colds, ichy skin conditions, sore throats, antiviral for stomach aches (adults); headaches, colds & flu (adults & nests); colds, flu, coughs, congestion, toothache & mouth sores, gastrointestinal complaints, ichy skin (nests & eggs); colds & flu (queens); skin sores, colds & flu (eggs) | (Berndt 1982; Isaacs 1987; Cherry 1991; ACNT 1993; Lindsay et al. 2001; Wightman 2003; Wijnjorrotj et al. 2005; White et al. 2009; Karadada et al. 2011; Roberts et al. 2011; Bordulk et al. 2012; Martin 2014; McTaggart et al. 2014; Long et al. 2016; Cheinmora et al. 2017; Purdie et al. 2018) |
| Formicidae | *Ochetellus flavipes* (Spinifex ant) | Sickness, colds (resin from nest) | (Dymock 1979) |
| LEPIDOPTERA | Cossidae | *Endoxyla* spp. (Witchetty grub) | (O’Connell et al. 1983; ACNT 1993; Turner and Dobson 1996; Peile and Bindon 1997; Deegan et al. 2010; Latz 2018) |
| Unspecified spp. (Witchetty grubs) | Headache (larvae) | (Isaacs 1987) |
| Sphingidae | *Coenosites* spp. (Hawk moth) | Caterpillar used medicinally (details not provided) | (Walsh et al. 2014) |
| Thaumetopoeidae | *Ochrogaster luniger* (Processionary caterpillar) | Poultice or protective dressing for wounds and burns (silken bag shelter) | (ACNT 1993; Walsh et al. 2014) |
LEPIDOPTERA AS A CASE STUDY

Witchetty (witjuti) grubs

Witchetty grubs are arguably one of the most well-known food sources for Australian Aborigines, yet the taxonomy and life history of these insects remain poorly understood. This has been further complicated by the general use of the term ‘witchetty grub’ to include any species of wood- or ground-dwelling lepidopteran (e.g. Hepialidae and Cossidae) or coleopteran (e.g. Buprestisidae and Cerambycidae) larvae (Ramson 1988; Yen 2005). Yet, Aboriginal people’s understanding of the importance of plant–insect relationships is demonstrated by a binomial naming system which often includes the name of the plant that an edible grub is collected from (Yen 2010).

In its strictest sense, ‘witchetty grub’ refers to the Cossid moth larvae found on the roots of the Witchetty (Witjuti) shrub, Acacia kempeana in Central Australia, but this species has still not been formally identified and described. Tindale (1953) identified larvae feeding on the roots of Acacia ligulata in northern South Australia as Endoxyla (syn. Xyleutes) leucomochla, and most resources also apply this name to the witchetty grubs found on A. kempeana in central Australia. However, recent DNA analysis has revealed that witchetty grubs collected from A. kempeana were distinct from Endoxyla leucomochla (Yen et al. 2018). The extent of host plant specificity among edible grubs is also unclear. Yen et al. (2018) suggest that a single host plant species may harbour several different species of edible grubs and that the same plant species may be host to different grub species across their geographical range. Cossid moth larvae are wood borers in stems, branches, trunks or roots of trees and shrubs. The majority of edible wood-dwelling grubs are collected from Acacia, Corymbia and Eucalyptus species, but they are also found in a wide variety of other host plants including Salsola, Senna, Atalaya, Codonocarpus, Sterculia and Bombax species (Table S1).

Although witchetty grubs (in the broad sense) are an extremely important food source for Indigenous people across Australia (Fig. 1), their medicinal use is mainly recorded from central Australia. Barr et al. (1988) and ACNT (1993) describe the effective use of a paste made from pounded witchetty grubs (cossid moth larvae associated with the roots of A. kempeana and A. ligulata), applied thickly to serious burns and wounds. It is thought that this fatty paste provides protection against desiccation and infection and promotes healing. Walpiri people of central Australia use a similar paste to treat sore eyes (Latz 2018), while Arrernte people squeeze the inwards of witchetty grubs from A. kempeana onto sores and sore nipples (Turner and Dobson 1996). Interestingly, Turner and Dobson (1996) describe a similar medicinal use for the inwards of a small grub found in the roots of Acacia victoriae and specify that unlike the larger edible grub found in the roots of the same tree, the small species is not consumed. ACNT (1993) also report that wood borers found in Eucalyptus trunks are not used medicinally. Isaacs (1987) mentions the rubbing of yellow uncooked matter from grubs onto foreheads to relieve headaches; however, the type of larvae, its host plant or the region where this medicinal use was recorded is unclear. Glenn Wightman’s substantial Northern Territory Botanical Bulletin series records the consumption of edible grubs collected from at least 40 plant species within nine plant families across Northern Australia (e.g. Deegan et al. 2010; Hector et al. 2012; Doonday et al. 2013; McTaggart et al. 2014; Long et al. 2016; see Table 2 and Supplementary Table S1 for examples and references). Yet, with over 20 regions surveyed in these studies, only the Jaru people from the south-east Kimberley/western Northern Territory describe medicinal consumption of grubs from various Acacia and Eucalyptus species to clear up stomach disorders (Deegan et al. 2010) (Table 2).

The broad range of medicinal uses suggest that the therapeutic properties of witchetty grubs are associated with their chemical composition rather than their physical properties alone. This is further supported by the fact that not all grubs are used medicinally and that grubs from different host plants have different uses. Indeed, native languages make clear distinctions between grubs found in different host plants or different plant parts (Yen 2010; Turpin and Si 2017). It is therefore feasible that some of the therapeutic properties of witchetty grubs are associated with phytochemicals derived from their food plants. Observations that medicinal uses of witchetty grubs are predominantly recorded from the arid zone also support a potential link to secondary metabolites produced by plants growing in stressful conditions.

Many lepidopteran taxa have been shown to sequester plant secondary metabolites such as phenols, terpenes, alkaloids and cyanoglycosides (Nishida 2002). Arguably, the most cited example is the Monarch butterfly (Danaus plexippus), whose larvae store cardenolides from milkweed (Asclepias) host plants, rendering the adults particularly unpalatable to avian predators (Brower and Moffitt 1974). Although the pharmacological properties of the Cossidae have not yet been investigated, a number of species contain bioactive chemicals that serve as pheromones or defence chemicals in larvae and adult moths (Brown and Moore 1977; Reyes-Garcia et al. 2011; Herrera et al. 2016).
## Table 2  Phytochemical properties of host plants associated with medicinally important witchetty grubs and caterpillars as well as other edible insects or insect products: (M) Medicine; (F) Food. Plant parts utilised: (A) Ash/charcoal, (G) Gum or Sap, (F) Flowers, (L) Leaves/Phyllodes, (B) Bark, (P) Pods, (R) Roots, (S) Seeds, (Sm) Smoke, (St) Stems

| Host plant species | Insect associations (and Indigenous use) | Ethnomedicinal use of host plant/conditions treated | Pharmacological or therapeutic activity | Bioactive compounds |
|--------------------|----------------------------------------|-----------------------------------------------|---------------------------------------|---------------------|
| **FABACEAE**       |                                        |                                               |                                       |                     |
| *Acacia aneura*    | Processionary caterpillars (M) (Floater 1996); Red scale (*Austrotachardia acacia*) honeydew (F); Honey pot ants (F); Wasp galls (F) (Latz 2018) | Pain relief (B); treatment of newborn (Sm); colds, pain relief (A) (ACNT 1993; Peile and Bindon 1997; Williams 2010) | None recorded | Saponins, steroids, terpenoids, flavonoids (Pedrotti and Fox 1979; ACNT 1993) |
| *Acacia bivenosa*  | Witchetty grubs (M, F); Stingless bees (F) (Deegan et al. 2010) | Note: *A. bivenosa* ssp. *wayi*, syn. *A. ligulata* from central Australia is a distinct species: colds, coughs (B); headache (L) (Peile and Bindon 1997; Wickens and Penncaccio 2002; Latz 2018) | Antibacterial (L) (Penacchio et al. 2005) | None recorded |
| *Acacia gonoclada* | Witchetty grubs (M, F); Stingless bees (M, F) (Wightman 2003; Deegan et al. 2010) | None recorded | None recorded | None recorded |
| *Acacia implexa*   | Processionary caterpillars (M) (Floater 1996) | Skin conditions, wounds (B) (Lassak and McCarthy 2011; Williams 2011) | Antimicrobial, antioxidant, anti-diabetic, anticancer (B, L) (Lassak and McCarthy 2011; Akter et al. 2016; Subhan 2016) | None recorded |
| *Acacia kempeana*  | Witchetty grubs (M, F); Red scale (*Austrotachardia acacia*) honeydew (F) (O’Connell et al. 1983; ACNT 1993; Latz 2018) | Colds, chest infections, wound disinfectant (L); general illness (L, B); post-partum treatment (Sm) (ACNT 1993; Bindon 1996; Latz 2018) | Antimicrobial, antioxidant, anti-diabetic, anticancer (L) (Palombo and Semple 2001; Gulati et al. 2012; Gulati et al. 2015) | Phenolics, flavonoids, essential oils (L); linoleic & oleic fatty acids (S) (Brown et al. 1987; ACNT 1993; Gulati et al. 2012) |
| *Acacia ligulata*  | Witchetty grubs (M, F) (ACNT 1993; Latz 2018) | Coughs, medicinal wash, dizziness, nervous conditions (B); post-partum treatment & diaphoretic for nervous conditions (Sm); head lice (S) (ACNT 1993; Bindon 1996; Peile and Bindon 1997; Latz 2018) | Antimicrobial, antioxidant, anti-diabetic, anticancer (P) (Gulati et al. 2012; Jaeger et al. 2018) | Phenolics, flavonoids, triterpenoid saponins (L, P); linoleic & oleic fatty acids (S) (Brown et al. 1987; ACNT 1993; Gulati et al. 2012; Jaeger et al. 2017; Jaeger et al. 2018) |
| *Acacia lysiphloia*| Witchetty grubs (M, F) (Deegan et al. 2010) | Colds, flu, congestion, muscle & joint pain, headache, sores (L); skin conditions (R); post-partum treatment (Sm) (ACNT 1993; Peile and Bindon 1997; Jones et al. 2011; Williams 2011; Hector et al. 2012; Latz 2018) | None recorded | Saponins, alkaloids (L); linoleic & oleic fatty acids (S) (Brown et al. 1987; Barr et al. 1988; ACNT 1993) |
| *Acacia synchronica*| Witchetty grubs (M, F) (Deegan et al. 2010) | Boils, diuretic (L) (Maslin et al. 2010) | None recorded | None recorded |
| *Acacia victoriae* | Witchetty grubs (M, F) (Turner and Dobson 1996; Latz 2018) | None recorded | Anticancer, antioxidant, anti-inflammatory, antihypertension (P, S) (Haridas et al. 2001; Jayatilake et al. 2003) | Triterpenoid saponins (P); phenolics, linoleic & oleic fatty acids (S) (Brown et al. 1987; Haridas et al. 2001; Jayatilake et al. 2003) |

(Continues)
Plant-derived medicinal entomochemicals

| Host plant species | Insect associations (and Indigenous use) | Ethnomedicinal use of host plant/conditions treated | Pharmacological or therapeutic activity | Bioactive compounds |
|--------------------|-----------------------------------------|----------------------------------------------------|-----------------------------------------|---------------------|
| **MYRTACEAE** | Eucalyptus camaldulensis | Witchetty grubs (M, F); Lerp (Pyilliidae) (F); Everard et al. 1988; Deegan et al. 2010; Widdijburn et al. 2010; Doonday et al. 2013; Latz 2018 | Colds, flu, congestion, medicinal wash, headache (L, B); joint pain (L); colds & flu (Sm); diarrhoea (G) (ACNT 1993; Wightman 2003; Deegan et al. 2010; Lassak and McCarthy 2011) | Antioxidant, antibacterial, antifungal, antiviral, analgesic, cytotoxic, anti diabetic, insecticidal (L) (Williams 2011; Gakauhi et al. 2017; Dhakad et al. 2018) | Phenolics, terpenoid essential oils (e.g. 1,8-cineole and α-pinene, γ-terpinene) (L, B); kinottonic acid, catechin (G) (ACNT 1993; Lassak and McCarthy 2011; Williams 2011; Gakauhi et al. 2017; Dhakad et al. 2018) |
| Eucalyptus coolabah | Witchetty grubs (M, F); Lerp (Pyilliidae) (F); Galls (Eriococidae) (F) (Deegan et al. 2010; Latz 2018) | Colds, flu, internal pains, joint pain, skin sores, pruritus, headache (L, B); toothache, medicinal wash (B) (ACNT 1993; Peile and Bindon 1997; Bordulk et al. 2012) | Antibacterial, antifungal, antioxidant, insecticidal (L) (Gaffar et al. 2015; Maghsoudlou et al. 2015; Nikbakht et al. 2015; Siddique et al. 2017, 2018) | Terpenoid essential oils (e.g. 1,8-cineole and α-pinene) (L, F) (ACNT 1993; Bignell et al. 1997; Gaffar et al. 2015; Maghsoudlou et al. 2015; Nikbakht et al. 2015; Siddique et al. 2017, 2018) |
| Eucalyptus microtheca | Processionary caterpillars (M) (Walsh et al. 2014) | Sores, respiratory complaints (B); boils (S) (Peile and Bindon 1997) | Antioxidant, antimicrobial, insecticidal (L) (Negahban and Moharramipour 2007; Safaei-Ghomi and Ahd 2010; Safaei-Ghomi et al. 2010) | Essential oils (e.g. 1,8-cineole) (L), phenolic acids (Sedikop et al. 2006; Safaei-Ghomi et al. 2010) |
| **PROTEACEAE** | Grevillea striata | Processionary caterpillars (M) (Floater 1996; Walsh et al. 2014) | Sores, burns, cuts (G) (Bindon 1996) | Antitumour activity (L, St) (Collins et al. 1990) | Saponins, phenolic compounds (Lassak and McCarthy 2011) |
| **SCROPHULARIACEAE** | Eremophila longifolia | Hawkmoth caterpillars (Sphingidae) (M, F) (Walsh et al. 2014) | Skin lesions, bites & stings, muscle & joint pain, headaches, colds, flu, fever, eye wash, relaxant (L); post-partum treatment, stimulation of lactation; headache (Sm) (ACNT 1993; Bindon 1996; Latz 2018) | Antimicrobial, antioxidant (L, Sm, St); modulation of platelet activity (anti-headache) (L, F); cardiovascular effects (L) (Pennacchio et al. 1996; Rogers et al. 2000; Hayhoe and Palombo 2011) | Terpenoid essential oils, iridoid glucoside (geniposidic acid), alkaloids, phenyl propanoids (L); genifuranal (Sm); phenolics (St) (Pennacchio et al. 1996; Saddgrove et al. 2011; Sidog et al. 2013; Saddgrove et al. 2014) |

References are provided within each subheading. Note: the terms ‘witchetty/edible grubs’, ‘lerp’ and so forth may constitute many different species.

1 E. coolabah and E. microtheca are closely related species and often taxonomically confused, so data for both species has been combined.

2 Stingless bees (Tetragonula and Austroplebeia spp.) are recorded only when the reference specifies nectar and/or pollen collection (rather than nest presence alone).

Whether these compounds are plant-derived or synthesised de novo has not been determined; however, it is not unreasonable to expect that this insect family can acquire phytochemicals from their host plants. For example, Herrera et al. (2016) suggest that one of the main components of a sex pheromone produced by the South American cossid moth, Chilecomadia valdiviana, is derived from a linoleic acid precursor. This essential fatty acid is found mostly in plant oils, and while de novo synthesis has been...
demonstrated in several insect species, none are from the Lepidoptera (Malicka et al. 2018). In Saudi Arabia, the stem-boring larvae of another cossid, *Semitocossus johannes*, feed on a milkweed from the Apocynaceae, a plant family known for their association with insect specialists that sequester toxic cardiac glycosides as defence chemicals (Al Dhafer et al. 2013).

To explore this connection further, we turn our attention to the host plants of medicinally used witchetty grubs. *Acacia kempeana, A. ligulata* and *A. lysiphloia* are themselves important medicinal plants for Indigenous people in central and northern Australia (Table 2). A decoction made from leaves is used as a medicinal wash and for the treatment of colds, flu and congestion, while the smoke from branchlets and leaves is an important component of post-partum recovery. An infusion made from the root bark of *A. ligulata* helps relieve coughs (ACNT 1993; Latz 2018). The therapeutic properties of these plants have been supported by the detection of several bioactive compounds including phenolics, flavonoids and saponins, with antibacterial, antioxidant, anticancer and antidiabetic activities (Table 2). Although there are no medicinal uses recorded for *A. victoriae*, the pods and seeds of this species have also been shown to possess similar biological activities. Interestingly, all the *Acacia* species contain linoleic acid, a potential precursor for the synthesis of sex pheromones in cossid moths. The four *Eucalyptus* species known to host therapeutic witchetty grubs have applications in traditional medicine as well and contain essential oils with anti-septic and other biological activities (Table 2). Of particular interest are compounds in bark and leaf extracts of *A. ligulata* shown to inhibit strains of pathogenic bacteria that cause skin and wound infections (Jaeger et al. 2018). This provides a tantalising link between the plant’s medicinal uses, its chemical properties and the use of associated witchetty grubs in the treatment of burns, sores and serious wounds. Similarly, the application of witchetty grub gut contents for skin sores (Turner and Dobson 1996) could be directly attributed to the antimicrobial properties of *A. kempeana* plant material ingested by the larvae.

Many of the host plants of medicinal and edible grubs are also associated with other highly valued invertebrate foods such as lerps and galls (produced by Hemiptera or Hymenoptera species) and native bee products (Tables 2 and S1). Although it is beyond our scope to discuss the possible medicinal attributes of these foods, recognition of their potential to contain plant-derived compounds offers another avenue for natural product exploration. Likewise, the search for interesting entomochemicals could be extended to include edible grubs more generally, beginning with those that are associated with medicinally important host plants (Table S1).

**Hawkmoth caterpillars**

The consumption of foliage feeding caterpillars by Australian Aborigines appears to be confined to central Australia. For the Arrernte people, the larvae of four Sphingidae hawkmoth species (*Coenotes eremophila*, *Hyles livornicoides*, *Hippotion celerio* and possibly *Agrius convolvuli*) have totemic significance and are at the centre of Dreamtime creation stories (Cresswell and Murphy 2016). They were once a valuable food source, either starved to clear their gut contents or eaten directly after removing the head and squeezing out the innards (Turner and Dobson 1996; Latz 2018). This practice suggests that the digested plant material contains unpalatable or toxic compounds.

There are scant records for the medicinal use of *Coenotes* caterpillars (Fig. 2) feeding on the enu bush *Eremophila longifolia* (Walsh et al. 2014). These are most likely the larvae of *C. eremophila*; however, no details for their preparation or therapeutic applications have been provided. Again, the host plant is considered a powerful medicine (Table 2) and is still used by contemporary Indigenous Australians. Essential oils from leaf, stem and smoke extracts have a range of antimicrobial properties (reviewed by Singab et al. 2013). In addition, leaf and flower extracts have been shown to modulate platelet activity involved in the aetiology of migraine, supporting their traditional use as a headache remedy (Rogers et al. 2000). Geniposidic acid, a non-volatile iridoid glycoside isolated from the leaves is reported to have cardioactive properties (Pennacchio et al. 1996).

At least nine geographically defined chemotypes have been characterised for *E. longifolia* each with different essential oil yields and composition, particularly monoterpenes and ketones (Sadgrove and Jones 2014). For example, the authors show that essential oils in a chemotype from Alice Springs (central Australia) are dominated by α-pinene and limonene, and are very different to extracts from Australia’s far west which consist almost entirely of two potentially hepatotoxic and carcinogenic compounds, safrole and methyl eugenol. These geographical variations in host plant chemistry may account for the apparently restricted medicinal use of *C. eremophila* larvae to parts of central Australia.

The larvae of sphingid moths have therapeutic applications elsewhere in the world, and Meyer-Rochow (2017) lists seven species used in Japan to treat tuberculosis, gastrointestinal complaints, fever, tumours and even snakebite. Furthermore, members of the sphingidae have been shown to sequester several

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**Fig. 2.** Hawkmoth caterpillar, *Coenotes* spp. (possibly *C. eremophila*). Photo courtesy of Simon Ong taken at Kununurra, Western Australia. Image used under CC BY-NC-SA 4.0 and cropped for use here with permission from creator.

https://www.inaturalist.org/observations/26046241.
classes of phytochemicals including cardiac glycosides, iridoid glycosides, tropane alkaloids, pyrrolizidine alkaloids and ingenane diterpenes as protection against vertebrate and invertebrate predators (Nishida 2002; Opitz and Müller 2009). Indeed, larvae of Ceratomia catalpa feeding on Catalpa host plants were found to contain almost 15% of their dry weight as catalpol, with over 50% of this iridoid glycoside sequestered in their haemolymph (Bowers 2003). As the host plant of C. eremophila also contains iridoid glycosides, it is quite feasible that these or their derivatives are sequestered by the larvae.

**Processionary caterpillars**

The silken bag shelter constructed by larvae of the Processionary or Bag Shelter moth, Ochrogaster lunifer (Thaumetopoeinae) (Fig. 3), has an important place in Aboriginal medicine as a wound dressing. Its use requires careful and methodical preparation to remove any traces of the caterpillar’s irritant hairs (true setae) and debris (ACNT 1993; Perkins et al. 2016). This practice appears to be restricted to parts of central Australia, with the species being very much avoided throughout northern Australia due to severe itching and swelling induced upon contact with the caterpillar’s hairs (e.g. Jones et al. 2011; Karadada et al. 2011; Roberts et al. 2011; Djorri et al. 2015).

The remedial properties of the bag shelter are mostly attributed to its physical structure, providing an inert protective layer or artificial skin (Barr et al. 1988). The cocoon nests produced by the African wild silkmoth, Anaphe panda (Thaumetopoeinae), are made up of fibroin and sericin with mechanical properties akin to those of silk fibres produced by B. mori (Teshome et al. 2012; Kebede et al. 2014). Whether silkmoth larvae sequester plant-derived bioactive compounds in a manner similar to B. mori awaits further exploration. The host plants of O. lunifer include Acacia, Eucalyptus, Senna and Grevillea species (Floater 1996; Walsh et al. 2014), several of which (e.g. A. aneura, A. impexa, E. intertexta and G. striata) have therapeutic properties associated with the treatment of skin lesions (Peile and Bindon 1997; Lassak and McCarthy 2011) (Table 2). The question remains as to whether the bag shelters of O. lunifer contain sequestered phytochemicals that may enhance the wound healing and/or antiseptic properties of the silken bandages.

**CONCLUSION**

Using Australian Lepidoptera as a case study, we have presented a systematic approach to bioprospecting that integrates traditional knowledge, ecological insight and phytochemistry. A similar strategy can be applied to other insect orders. We hope that our case study of Lepidoptera will encourage the documentation of similar information across the Class. Compared to other traditional cultures across the rest of the world, the medicinal use of insects has not been widely recorded for Australian Aborigines. This may in part be explained by factors associated with Australia’s unpredictable and often harsh environment but is also likely to reflect a rapid loss of Indigenous knowledge following relatively recent European settlement. Particularly, the face-to-face documentation of unpublished Indigenous knowledge is important before it is lost but was beyond the resources available to the present review. Moreover, there is a desperate need for western science to address the dearth of taxonomic and life history information for culturally significant invertebrates. Nevertheless, our work highlights global evidence for the significance, value and importance of better understanding plant-derived bioactive chemicals in insects.

The importance of conserving traditionally and ecologically significant species cannot be over-emphasised, and we stress that wild harvest of plants and insects is not feasible for many of the species discussed. The biology and life history of witchetty grubs, for example, is poorly understood, but some Cossid species are relatively long-lived (2-year larval stage), and their collection often involves partial or complete destruction of the host plant. Sustainable and ethical supplies of insects may therefore require the establishment of commercial production facilities such as those outlined by Rich (2006). Ideally, the commercialisation of any natural products derived from plants or insects would ultimately involve the development of synthetic analogues.

A thorough understanding of insect–plant interactions can help guide, focus and expedite the search for new bioactive compounds. Witchetty grubs exemplify such an integrated approach; linking traditional uses of insects and plants with phytochemistry and the potential sequestration of plant-derived chemicals by insects. Undoubtedly, there is a wealth of existing traditional, ecological and chemical knowledge, which, once connected, could provide many new opportunities for biodiscovery. Importantly, such discoveries remain dependent on the conservation of global biodiversity generally and the sustainable management of vulnerable ecosystems particularly. Our work points to a great potential for basic scientific and ecological investigations, as well as for the development of pharmaceutical or cosmetic industries in collaboration with Indigenous communities.

![Fig. 3. Silken bag shelter constructed by Processionary caterpillars, Ochrogaster lunifer, in Acacia aneura shrub, South Australia. Image courtesy of P.A. Clarke.](image-url)
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