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Drug Discovery Insights from Medicinal Beetles in Traditional Chinese Medicine

Stephen T. Deyrup[1,*], Natalie C. Stagnitti[1], Mackenzie J. Perpetua[1] and Siu Wah Wong-Deyrup[2]

[1]*Department of Chemistry and Biochemistry, Siena College, Loudonville, NY 12309,*
[2]*The RNA Institute and Department of Biological Sciences, University at Albany, State University of New York, Albany, NY 12222, USA*

Abstract

Traditional Chinese medicine (TCM) was the primary source of medical treatment for the people inhabiting East Asia for thousands of years. These ancient practices have incorporated a wide variety of materia medica including plants, animals and minerals. As modern sciences, including natural products chemistry, emerged, there became increasing efforts to explore the chemistry of this materia medica to find molecules responsible for their traditional use. Insects, including beetles have played an important role in TCM. In our survey of texts and review articles on TCM materia medica, we found 48 species of beetles from 34 genera in 14 different families that are used in TCM. This review covers the chemistry known from the beetles used in TCM, or in cases where a species used in these practices has not been chemically studied, we discuss the chemistry of closely related beetles. We also found several documented uses of beetles in Traditional Korean Medicine (TKM), and included them where appropriate. There are 129 chemical constituents of beetles discussed.

Key Words: Beetle, Traditional Chinese Medicine, Traditional Korean Medicine, Coleoptera, Chemical defense, Secondary metabolites

INTRODUCTION

Traditional Chinese Medicine (TCM) is widely used both inside China and beyond its borders. One survey indicated that approximately 20% of Chinese people over 45 years old used TCM, and use of TCM for chronic conditions was even higher (Liu *et al*., 2015). In the United States, it was estimated that over 1 million people used TCM, and that approximately 12% of Americans and 9% of Australians used at least one form of herbal medicine in the prior year (Ernst, 2000). Although traditional Korean medicine (TKM) shares a common origin as TCM, and was heavily influenced by TCM, it started to develop into a separate practice around the early 1600's upon publication of the *Dongeuibogam* (sometimes spelled *Dongui Bogam*) (Cha *et al*., 2007). The use of TKM is still an integral part of the healthcare of the Korean people with over 30,000 practitioners as of 2007, which was an increase from the ten years prior (Cha *et al*., 2007). These traditional medicines have existed for over 2000 years, constantly evolving to be ever more effective. TCM differs from Western medicine by focusing on addressing the underlying issues rather than treating symptoms. There are several guiding philosophies and treatment modalities including acupuncture, moxibustion, and qi gong (Liu and Liu, 2009; Fung and Linn, 2015; National Center for Complementary and Integrative Health, 2019). However, the most relevant form of TCM to the discovery of new chemical entities for drug discovery is the use of materia medica.

In the search for effective ways to treat illness, TCM has accumulated a vast wealth of information on effective materia medica. These components, which are often combined to make treatments, are sometimes referred to in general as herbal medicines even though they can be derived from mineral or animal sources as well as from plants (Yang, 1998; National Administration of Traditional Chinese Medicine, 1999; Liu and Liu, 2009). Animal sources of materia medica are incredibly diverse, ranging from the antlers of deer, to fossilized bones, to snake skin, to scorpions, to human hair (Yang, 1998). The chemical study of arthropods, especially insects, is most compelling for drug discovery when one considers the animal-based medicinal materials. This is due to the fact that they are most likely to be available in large quantities without having major negative implications on their native popula-

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***Corresponding Author**
E-mail: sdeyrup@siena.edu
Tel: +1-518-782-6815, Fax: +1-518-783-2986

Table 1. Beetles used in Traditional Chinese Medicine (TCM) along with their common name, TCM name, traditional use, and chemical class

Beetle used	Common name	TCM name	Traditional use	Chemical class[a]
Bostrichidae			Detoxification, removal of pus/cysts[b]	Aliphatic esters
Lyctus brunneus	Brown powderpost beetle	竹蠹虫		
Buprestidae			Insecticidal, eczema, itching,[b] aphrodisiac[c]	Buprestins
Chalcophora japonica	Flat-headed wood-borer	吉丁虫		
Chrysochroa elegans	Japanese Jewel beetle	吉丁虫		
Carabidae			Stomachache, feverish chills, amenorrhea[c]	1,4-benzoquinones
Pheropsophus jessoensis	Bombardier beetle	行夜		
Cerambycidae			Improve blood circulation,[b,d] pain relief, bruises, inflammation, menstrual pain[b] (Bruises, poison, pain, bleeding,[b] angina pectoris,[b,c] knife wounds[c])	Long-chain ethers, gomadalactones, juvenile hormome III
Anoplophora chinensis	Longhorn beetle (larva)	天牛 (桑蠹虫)		
Apriona germari	Longhorn beetle (larva)	天牛 (桑蠹虫)		
Batocera horsfieldi	White striped longhorn (larva)	天牛 (桑蠹虫)		
Curculionidae			Treat paralysis pain, arthritis[b]	Phenol and aliphatic esters, ketones, and aldehydes
Cyrtotrachelus longimanus	Snout beetle	竹象鼻虫		
Dytiscidae			Improve blood circulation,[d] polyuria, enuresis[e]	Benzoic acid derivatives, steroids
Cybister japonicus	Diving beetle	龙虱, 물방개[g]		
Cybister tripunctatus	Diving beetle	龙虱, 물방개[g]		
Elateridae			Increase muscular strength, malaria[b]	Aliphatic acids
Pleonomus canaliculatus	Click beetle	叩头虫		
Geotrupidae			Reduce bruising, constipation, congestion, remove pus or dead skin, indigestion, nausea, pain, swelling,[b] covulsions, fevers, insanity[c]	Unknown
Phelotrupes laevistriatus	Earth-Boring Dung Beetle	蜣螂		
Gyrinidae			Remove toxins, treat warts,[b] nasal polyps,[c] infected boils[b,c]	Norsesquiterpenoids, aliphatic acids
Gyrinus curtus	Whirligig beetle	豉虫		
Lampyridae			Treat burns,[b] clarify eyesight, cure night blindness[c]	Monoterpenoids
Aquatica lateralis	Firefly	萤火		
Meloidae			Cancer, poison, bruises, constipation, amenorrhea, vitiligo, dog bites, scrofula, as a diuretic, nasal polyps, fungal skin infections, menstrual pain,[b] boils, facial paralysis, STIs,[e] abortions, urinary obstruction[c]	Cantharidin and analogues
Epicauta chinensis	Blister beetle	葛上亭长		
Epicauta gorhami	Blister beetle	葛上亭长		
Lytta caraganae	Blister beetle	芫青		
Lytta chinensis	Blister beetle	芫青		
Lytta suturella	Blister beetle	芫青		
Meloe coarctatus	Oil beetle	地胆		
Mylabris calida	Blister beetle	斑蝥, 반묘[g]		
Mylabris cichorii	Blister beetle	斑蝥, 반묘[g]		
Mylabris phalerata	Blister beetle	斑蝥, 반묘[g]		
Mylabris sidao	Blister beetle	斑蝥, 반묘[g]		
Mylabris speciosa	Blister beetle	斑蝥, 반묘[g]		

tions, there are less ethical concerns over the treatment of insects than with vertebrates, and insects are widely known to produce a wide variety of chemical compounds. This, combined with the fact that they are historically under studied when compared to plants, makes insects an ideal group of taxa for chemical investigations (Dossey, 2010; Dettner, 2011; Seabrooks and Hu, 2017).

Beetles are the most diverse group of insects, of the ~1 million described species of insects, over 400,000 are beetles, and some estimates put the total number of beetle species on the planet at over 5 million (Berenbaum and Eisner, 2008; Yuan *et al*., 2016). They occupy almost every conceivable ecological niche other than that of primary producer. This extreme ecological and behavioral diversity means that beetles are exposed to a wide-range of challenges to which they must overcome, some of which cannot be overcome via physical methods and therefore require chemical or biological approaches, e.g., bacterial infection (Hunt *et al*., 2007; Yuan *et al*., 2016). Beetles can sequester or biosynthesize small molecules to increase fitness, and therefore make excellent candidates to search for novel bioactive chemistry (Eisner, 2003; Eisner *et al*., 2005; Dettner, 2011). Therefore, we de-

Table 1. Continued

Beetle used	Common name	TCM name	Traditional use	Chemical class[a]
Scarabaeidae			Reduce bruising, constipation, congestion, remove pus or dead skin, indigestion, nausea, pain, swelling,[b] covulsions, fevers, insanity[c] (Remove bruises, constipation, relieve pain, remove toxins, reduce menstrual bleeding, gout, tetanus, carbuncle, acute skin infections,[b] feverish chills,[c] liver cirrhosis[e])	Long-chain alcohols, aldehydes, esters, ketones, and lactones, alkaloids, benzoic acid derivatives, branched carboxylic acids, flavonoids, diketopiperazines, β-carbolines, *N*-acetyl dopamine dimers, *N*-acetyl dopamine dimer analogues
Alissonotum impressicolle	Scarab beetle (larva)	蛴螬		
Allomyrina dichotoma	Horned beetle	蜣螂		
Anomala corpulenta	Leaf chafer (larva)	蛴螬		
Anomala cupripes	Leaf chafer (larva)	蛴螬		
Anomala exoleta	Leaf chafer (larva)	蛴螬		
Catharsius molossus	Dung beetle	蜣螂		
Catharsius pithecius	Dung beetle	蜣螂		
Gymnopleurus mopsus	Scarab beetle	蜣螂		
Heliocopris bucephalus	Northeast block chafer	蜣螂		
Holotrichia diomphalia	Chafer (larva)	蛴螬, 굼벵이[g]		
Holotrichia morosa	Chafer (larva)	蛴螬, 굼벵이[g]		
Holotrichia sauteri	Brown chafer (larva)	蛴螬, 굼벵이[g]		
Holotrichia titanis	Chafer (larva)	蛴螬, 굼벵이[g]		
Onitis subopacus	Dung beetle	蜣螂		
Oxycetonia jucunda	Mulberry chafer (larva)	蛴螬		
Pentodon quadridens	Rhinoceros beetle (larva)	蛴螬		
Protaetia brevitarsis	Flower chafer (larva)	蛴螬, 제조[g], 굼벵이[g]		
Protaetia orientalis	Flower chafer (larva)	蛴螬		
Scarabaeus sacer	Sacred scarab beetle	蜣螂		
Trematodes tenebrioides	Scarab (larva)	蛴螬		
Xylotrupes dichotomus	Rhinoceros Beetle (larva)	蜣螂 (蛴螬)		
Staphylinidae			Treat tooth pain, itching,[b] skin infections and ailments,[b,c] remove tattoos,[c] vitiligo	Pederin and analogues
Paederus fuscipes	Rove beetle	青腰虫/花蚁虫		
Tenebrionidae			Cancer,[b] coughs, bone problems, stomach illness, stroke,[f]	1,4-benzoquinones, limone, long-chain alkenes
Ulomoides dermestoides	Darkling beetle	洋虫		

[a]Class of chemicals identified from the beetle or from closely related beetles. See the text for more detail. [b](National Administration of Traditional Chinese Medicine 1999). [c](Namba et al. 1988). [d](Ding et al. 1997). [e](Pemberton 1999). [f](Zhang et al. 2019). [g]TKM name.

cided to explore the known chemistry of beetles used in TCM as a way to demonstrate the value of these resources, as well as to highlight gaps in the current knowledge that warrant additional studies.

To build this article, we first had to make a list of all the beetles known to be used in TCM. To build this list, we relied primarily on six sources (Namba *et al*., 1988; Ding *et al*., 1997; Yang, 1998; National Administration of Traditional Chinese Medicine, 1999; Pemberton, 1999; Zhang *et al*., 2019). We then searched the literature for information on the chemistry of each genus and species of beetle. There were several review articles and books that were particularly helpful in describing the chemistry of beetles that we cite repeatedly throughout the article (Schildknect, 1970; Dettner, 1985, 1987, 2015; Eisner *et al*., 2005; Vuts *et al*., 2014), but mostly we relied upon primary research articles for this aspect of the paper. We organized the paper by taxonomic families of beetles, alphabetically, with one exception. The family Geotrupidae was included with Scarabaeidae because the larva of these groups were used interchangeably and Scarabaeidae is the larger and better known taxonomic group. The scientific names of some of the beetles used in TCM have changed since the publication of the article cited, and in these cases we searched for both the name provided and the currently used nomenclature. Where there were uncertainties about which scientific name for a beetle was currently accepted, we frequently used the Global Biodiversity Information Facility as a guide (GBIF Secretariat, 2020).

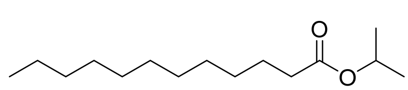
The goal of this article is to link the knowledge of medicinal use of these beetles with what is known of their chemistry (Table 1). While there are great resources available on which beetles have been used most prominently in TCM and there are similarly impressive reviews on the chemistry of beetles, we could not find a reference that systematically connected the two pools of information. This article is intended to not only show us what we know of the chemistry of beetles used in TCM, but also highlight the fact that there is so much additional work to be done in this field. There are many beetles covered in this article that have never been studied chemically, and many of those that have been chemically investigated have not been done at the same life-stage of the organism that is used medicinally. Furthermore, work on the chemical changes that occur during the preparation of the insects for consumption, e.g., drying, decoction, etc., would provide even greater insights into potentially bioactive compounds. We hope that this article can act as a call to action to chemical ecologists and natural products chemists to fill in the gaps in the knowledge exposed herein.

BEETLES USED IN TCM BY FAMILY

Bostrichidae

***Lyctus*:** Bostrichids are small, wood-boring beetles often called powderpost beetles. The only record of use of a Bostrichid in TCM is that of *Lyctus brunneus* (National Administration of Traditional Chinese Medicine, 1999). *Lyctus brunneus* is one of the most economically destructive powderpost beetles, causing damage to wood products into which they bore, leaving small holes and piles of powdery frass in their efforts to consume the starch within the wood (Parkin, 1940; Martin, 1979; Ide *et al*., 2016). In TCM, it is typically the larval stage of *L. brunneus* that is used as a way to detoxify the body and for the removal of pus and cysts, and goes by the name 竹蠹虫 (*Zhú Dù Chóng*) (National Administration of Traditional Chinese Medicine, 1999).

We could not find any chemistry known from *L. brunneus*, but three of constituents of the aggregation pheromone of the closely related species *L. africanus* have been determined (1-3 in Fig. 1) (Kartika *et al*., 2015). Two other species of Bostrichids, *Rhizopertha dominica* and *Prostephanus truncatus*, have also have been found to use esters as aggregation pheromones, but those contained shorter, unsaturated chains (4-5 in Fig. 1) (Francke and Dettner, 2005). It therefore seems likely that *L. brunneus* also uses esters as aggregation pheromones. It should also be mentioned that *L. brunneus* has pygidial glands that, in other species of beetle, produce defensive compounds, but the products of these glands have not been studied in *L. brunneus* (Altson, 1924).



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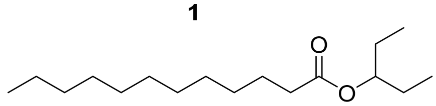

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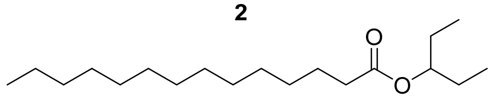

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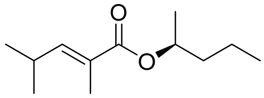

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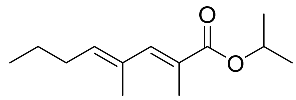

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Fig. 1. Pheromones identified from Bostrichid beetles. Compounds 1-3 were identified from *Lyctus africanus*. Compounds 4 and 5 are examples of pheromones identified from other genera of Bostrichids.

Buprestidae

There are over 15,000 species of beetles in the family Buprestidae, which are often called jewel beetles or metallic wood-boring beetles. They have a world-wide range and many are prized by collectors for their bright metallic colors (Hong *et al*., 2009). Some Buprestids are economically important pests, including the emerald ash borer (*Agrilus planipennis*) which is devastating large populations of ash trees in the United States and Canada (Silk and Ryall, 2015). Two genera of Buprestids, *Chalcophora* and *Chrysochroa*, have been reported to be used in TCM.

***Chalcophora*:** Within the family Buprestidae, the genus *Chalcophora* consists of around 15 species of somewhat large wood-boring beetles, some of which are economically important as forestry pests (Maier and Ivie, 2013). *Chalcophora japonica*, the flat-headed wood-borer, has been used in TCM under the name 吉丁虫 (Jí Dīng Chóng) as an insecticide as well as to treat eczema and itching (National Administration of Traditional Chinese Medicine, 1999).

Although we did not find any evidence of chemical studies on *Chalcophora japonica* in our search, other Buprestids have been investigated. Excellent work by Brown, Moore, and colleagues (Brown *et al*., 1985; Moore and Brown, 1985) not only isolated and described the main defensive chemicals of Buprestids, but did so by surveying a wide variety of jewel beetles from Australia along with a few from Europe and Asia. They elucidated that these “bitter principles” were based upon β-D-glucose with three aromatic acyl groups attached, and called them buprestins A and B (6-7 in Fig. 2). Later work expanded the number of buprestins known and also confirmed their presence in a species of *Chalcophora* (*C. mariana*) (e.g., 8-9 in Fig. 2) (Ryczek *et al*., 2009; Dettner, 2015). The use of *C. japonica* as an insecticide corresponds well with the fact that buprestins were found to be repellant to ants (Moore and Brown, 1985; National Administration of Traditional Chinese Medicine, 1999; Ryczek *et al*., 2009). It would be interesting to test these compounds for anti-inflammatory activity, considering the other uses to which this beetle has been put in TCM.

***Chrysochroa*:** The genus *Chrysochroa* is renowned for its brilliant iridescent colors, and is a major reason why Buprestids in general are called jewel beetles. Members of this genus were literally used in jeweled ornaments in Asia, including in the Silla Dynasty, Korea (Han *et al*., 2012). According to Namba *et al*. (1988), *Chrysochroa elegans* was also called 吉丁虫 (Jí Dīng Chóng) and kept in peoples clothing as an aphrodisiac. It appears that *C. elegans* is a synonym of the species *C. fulgidissima*, however, *C. fulgidissima* may itself be a species complex (Han *et al*., 2012; Kim *et al*., 2014c; GBIF Secretariat, 2019a).

We were unable to find any chemical studies on beetles from the genus *Chrysochroa*, however based on the wide distribution of buprestins as defensive molecules in the Buprestidae, it seems quite likely that these beetles contain this class of molecule (Fig. 2) (Moore and Brown, 1985). A complete mitogenome of *C. fulgidissima* has been sequenced, published, and used in taxonomic studies (Hong *et al*., 2009; Kim *et al*., 2014c). Unsurprisingly, the majority of the scientific studies on *Chrysochroa* spp. has been on their bright coloration and the physical structure of the cuticle that is responsible, along with

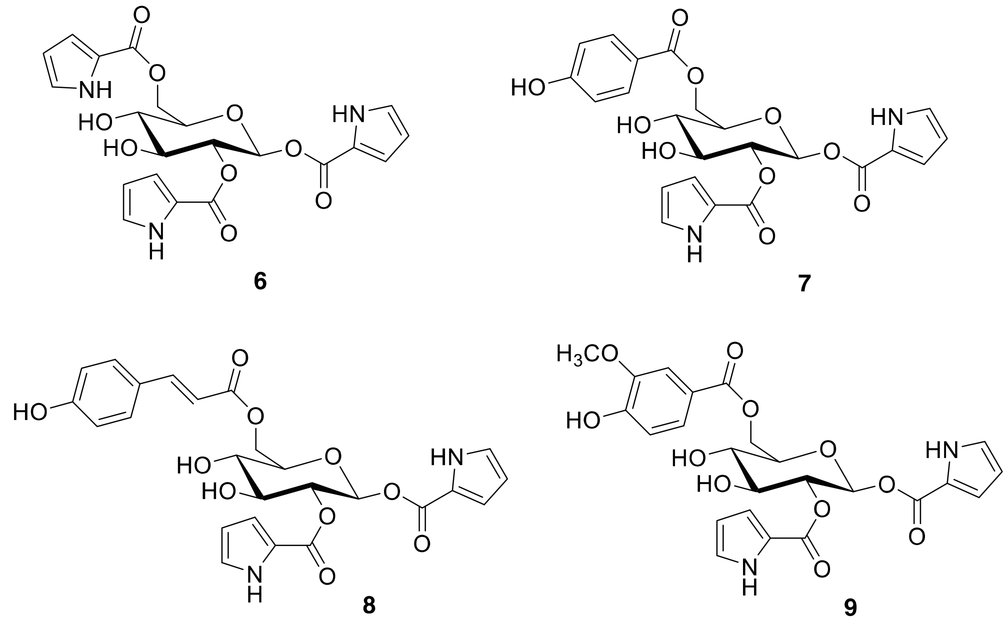


Fig. 2. Representative compounds described from jewel beetles (Coleoptera: Buprestidae). Compounds 6 and 7 are buprestins A and B. Compounds 8 and 9 are buprestins D and G.

attempts to mimic this beautiful feature (Stavenga *et al*., 2011; Yoshioka *et al*., 2012; Tzeng *et al*., 2015).

Carabidae

Carabids are often called ground beetles (not to be confused with *Eupolyphaga sinensis*, a flightless cockroach also sometimes referred to as "ground beetle", 土鳖虫, in TCM) and are predatory rather than herbivorous (Ding *et al*., 1997). In Namba *et al*. (1988), they mention unidentified Carabids called "*Tian Ke Chong*" being used in order to "stimulate mutual love". Different subfamilies of Carabids have different defensive chemistry (10-18 in Fig. 3) including 1,4-benzoquinones from the Brachininae, substituted phenols from the Harpalinae, and simple acids from the Carabinae (Schildknect 1970; Eisner *et al*., 2005; Holliday *et al*., 2012), so without more details on the identification, it is difficult to predict the chemistry of "*Tian Ke Chong*".

***Pheropsophus*:** We could find two sources indicating that the bombardier beetle (Carabidae: Brachininae) *Pheropsophus jessoensis* is used in TCM. This beetle is called 行夜 (*Xíng Yè*) and is used to treat stomachache, feverish chills, and amenorrhea (Namba *et al*., 1988; National Administration of Traditional Chinese Medicine, 1999). Being in the subfamily Brachininae, it most likely contains 1,4-benzoquinones which it uses as a chemical defense (10-11 in Fig. 3) (Schildknect, 1970; Eisner, 2003; Eisner *et al*., 2005). This is quite interesting, because 1,4-benzoquinones are known to exhibit hepatotoxicity (Moore *et al*., 1987; Abernethy *et al*., 2004; Chan *et al*., 2008). Caution should be taken when handling these beetles, because, like other bombardier beetles, *Pheropsophus* spp. propel their chemical defenses as hot (nearly 100°C) liquid mixtures, and there are reports of burns that required medical attention (Schildknect, 1970; Eisner *et al*., 2005; de Oliveira Pardal *et al*., 2016).

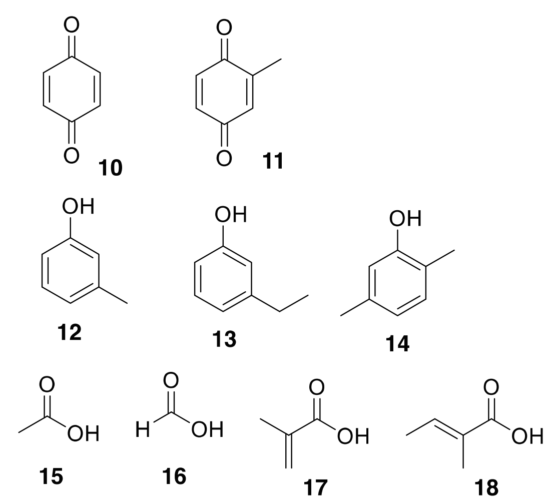


Fig. 3. Chemical defenses identified from Carabid beetles. Compound 10 and 11 are 1,4-benzoquinone and 2-methyl-1,4-benzoquinone identified from members of the subfamily Brachininae. Compounds 12-14 are in substituted phenols identified from members of the subfamily Harpalinae. Compounds 15-18 are examples of some defensive compounds identified from the subfamily Carabinae.

Cerambycidae

The family Cerambycidae, known as longhorn beetles (a.k.a., long-horned beetles or longicorn beetles), is a group of beetles that are well known for having several large, brightly colored species, often with very long antennae. There are over 35,000 species of Cerambycids currently described (Allison *et al*., 2004). Larvae of these beetles bore into living or dead wood, and several species are serious economic pests, with

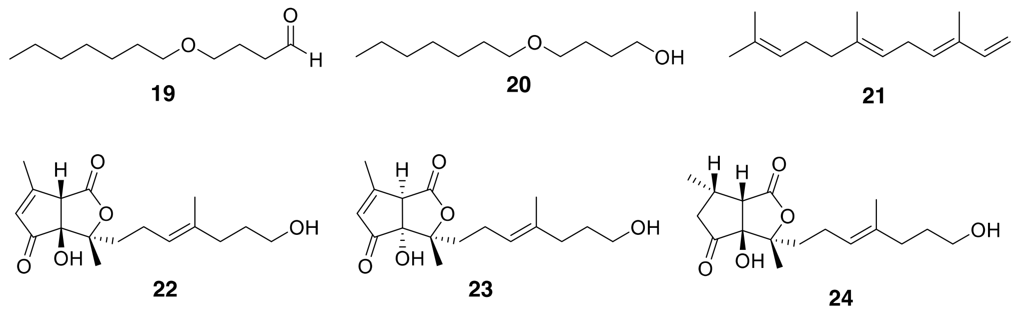


Fig. 4. Pheromones identified from *Anoplophora* spp. Male sex pheromones, 4-(*n*-heptyloxy)-butanal (19), 4-(*n*-heptyloxy)-butan-1-ol (20), and (3*E*,6*E*)-α-farnesene (21). Compounds 22-24 are female sex pheromones gomadalatone A-C (left to right). Several long-chain alkanes, alkenes, and ketones were also identified as female specific sex and trail pheromones, but are not shown here (see text for citations).

potential damage caused in the USA by a single introduced species (*Anoplophora glabripennis*) estimated at $669 billion (Allison *et al*., 2004; Nowak *et al*., 2009).

In addition to the specific Cerambycid genera being used in TCM (see descriptions below) we also found reference to unidentified longhorn beetles being used in TCM. According to Namba *et al*. (1988), the ancient Chinese medicine *Fei Shen Chong* was most likely the adults of Cerambycids and was used to aid during difficult childbirth, while the larval stage was used as 木蠹虫 (*Mù Dù Chóng*) to treat weakness, poor blood circulation, amenorrhea, back pain, anemia, and pain in the upper thorax (epigastrium). Several longhorn beetles in the subfamily Cerambycinae have been shown to secrete defensive chemicals from metasternal glands, however, the three specified genera of longhorn beetles still in use in TCM, *Anoplophora*, *Apriona*, and *Batocera*, are all in the subfamily Lamiinae, for which we could not find reports of defensive secretions (Francke and Dettner, 2005).

The genera *Anoplophora*, *Apriona*, and *Batocera* are still used in TCM in both the larval and adult life stages. The larval stages of beetles in these genera are called 桑蠹虫 (*Sāng Dù Chóng*), and are used to remove poison, remove bruises, reduce pain, decrease bleeding, treat knife wounds, and to ameliorate angina pectoris (Namba *et al*., 1988; National Administration of Traditional Chinese Medicine, 1999). Adults of *Anoplophora chinensis*, *Apriona germarii* (=*Apriona germari*), and *Batocera horsfieldi* are termed 天牛 (*Tiān Niú*), and are used to improve blood circulation, relieve pain (including menstrual pain), reduce bruising, and reduce inflammation (Namba *et al*., 1988; Ding *et al*., 1997; National Administration of Traditional Chinese Medicine, 1999).

***Anoplophora*:** Because some species of *Anoplophora*, including *A. glabripennis*, *A. malasiaca*, and even *A. chinensis* (the species used in TCM) are agricultural and forestry pests, there have been several studies on their chemical signaling, especially pheromones (Allison *et al*., 2004; Nowak *et al*., 2009; Yasui, 2009). Work has been done to elucidate male sex pheromones (Zhang *et al*., 2002; Crook *et al*., 2014; Hansen *et al*., 2015), female sex pheromones (Yasui *et al*., 2003, 2007; Zhang *et al*., 2003; Wickham *et al*., 2012), and female trail pheromones (Hoover *et al*., 2014), which provides insights into some of the chemical constituents of adult *Anoplophora* spp. (19-21 in Fig. 4).

The most interesting of the compounds found in *Anoplophora* are the gomadalactones (22-24 in Fig. 4). These molecules were isolated as part of the female sex pheromone and contain an intriguing oxabicyclo[3.3.0]octane ring-system (Yasui *et al*., 2007). This ring-system is analogous to the one found in the endogenous vasodilator prostaglandins I2, also known as prostacyclin, and when synthesized as epoprostenol (Sitbon and Vonk Noordegraaf, 2017). Synthetic molecules with oxabicyclo[3.3.0]octane rings have also been shown to be vasodilators and platelet aggregation factor antagonists (Akiba *et al*., 1986; Peçanha *et al*., 1998). Therefore, the structures of the gomadalactones intriguingly match some of the functions of the TCM made from *A. chinensis*, namely improving blood circulation.

***Apriona* and *Batocera*:** Both *Apriona germarii* (=*A. germari*) and *Batocera* horsefieldi are in the subfamily Lamiinae, and are used interchangeably with *Apolophora chinensis* in TCM (described above). However, the chemistry of these genera has been less well studied. It has been found that *A. germarii* males produce juvenile hormone III (JHIII) in a male accessory gland which they then transfer to females during copulation (Tian *et al*., 2010). While studies on *Apriona* and *Batocera* chemistry are somewhat sparse, the sex pheromones of several other genera in the Lamiinae have been described (25-30 in Fig. 5) (Hughes *et al*., 2013; Meier *et al*., 2019, 2020). Interestingly, it seems like the absolute configurations of these pheromones can vary based on species (Hughes *et al*., 2016).

Curculionidae

***Cyrtotrachelus*:** Curculionids are the familiar group of beetles commonly called weevils or snout beetles. This family is incredibly diverse with over 62,000 described species so far and estimates of 220,000 extant species (Oberprieler *et al*., 2007). Whole bodies of adult *Cyrtotrachelus longimanus* are used in TCM under the name 竹象鼻虫 (*Zhú Xiàng Bí Chóng*) to treat pain due to paralysis and arthritis, and have also been eaten as a prepared food dish (National Administration of Traditional Chinese Medicine, 1999; Pemberton, 2003). Bamboo borers (*C. longimanus* and *C. buqueti*) are serious pests in commercial bamboo and bamboo shoot production (Li *et al*., 2017; Yang *et al*., 2018). Due to the close relationship of these two species, along with their similar habitats, it is likely that either one may be used as 竹象鼻虫 (*Zhú Xiàng Bí Chóng*).

As with many groups of beetles that are primarily known as agricultural pests, the vast majority of chemical studies on Curculionids have been directed towards pheromones, both

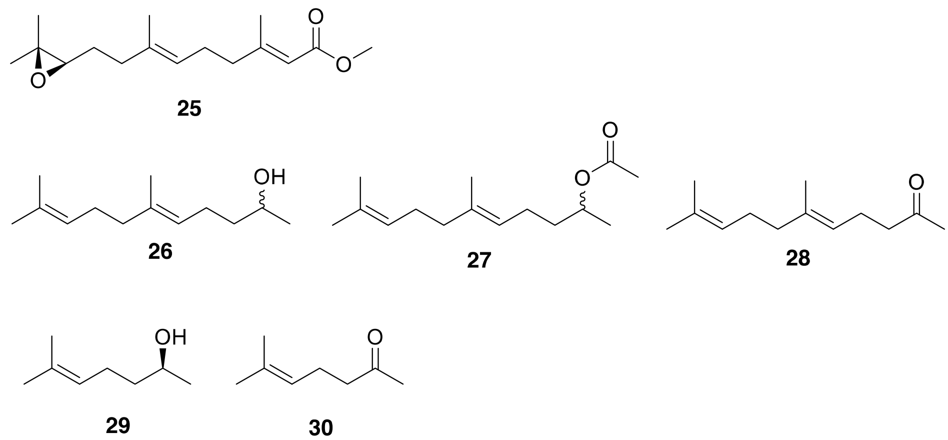


Fig. 5. Compound 25 is juvenile hormone III, which is produced by *Apriona germari* males and transferred to females during copulation. Compounds 26-28 are fuscumol, fuscumol acetate, and geranylacetone, respectively, which are sex pheromones identified from Lamiinae longhorn beetles. Both enantiomers are made by Lamiinae, but they vary by species. (*S*)-Sulcatol (29) and sulcatone (30) are sex pheromones identified from Lamiinae longhorn beetles.

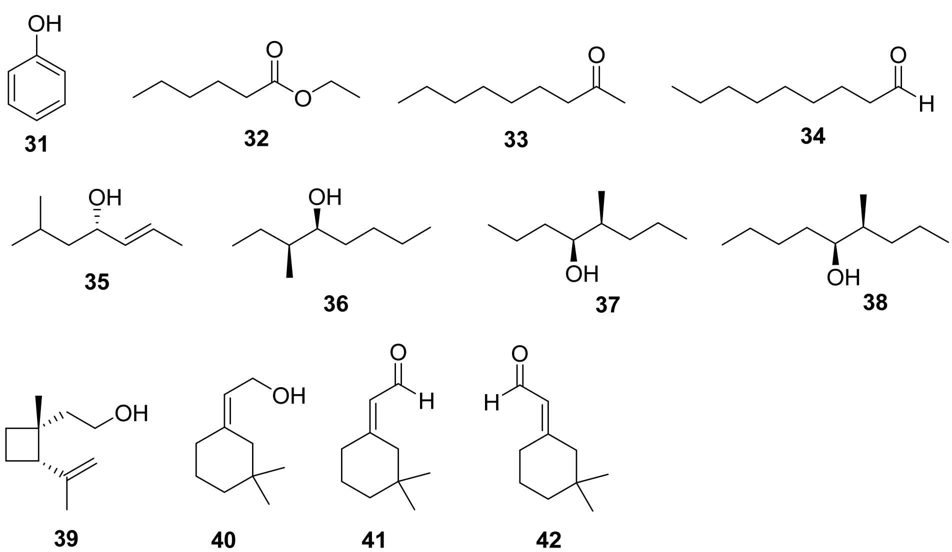


Fig. 6. Pheromones identified from weevils. Compounds 31-34 are pheromones isolated from *Cyrtotrachelus buqueti*. Compounds 35-38 are pheromones isolated from *Rhynchophorus* spp., which are also in the subfamily Dryophthorinae. Compounds 39-42 are pheromones from weevils in the subfamily Curculioninae.

aggregation and sex pheromones, in an effort to aid in control of these species. *Cyrtotrachelus buqueti* has been shown to have produce phenol, ethyl hexanoate, 2-nonanone, nonanal, and methyl pentadecanoate as sex pheromones (31-34 in Fig. 6) (Mang *et al*., 2012). Other compounds have been found from the palm weevils, which are in the same subfamily, Dryophthorinae, but in the genus *Rhynchophorus* (35-38 in Fig. 6) (Hallett *et al*., 1993; Francke and Dettner, 2005). Less closely related weevils, in the subfamily Curculioninae, tend to have cyclic structures in their pheromones (39-42 in Fig. 6) (Hedin *et al*., 1997). There are also indications that some species of weevils sequester chemical defenses from their food plants (Francke and Dettner, 2005). The secretions from the male accessory glands of *C. buqueti* have been shown to have antibacterial activity against Gram-positive bacteria (Liang *et al*., 2016). However, the isolation of phenol from *C. buqueti*, a well-known topical anesthetic, correlates most closely with its use in TCM to treat localized pain due to arthritis or paralysis (Mang *et al*., 2012; Kumar *et al*., 2015).

Dytiscidae

***Cybister*:** The genus *Cybister* consists of diving beetles, many of which are large, that are found worldwide (Miller *et al*., 2007; Michat *et al*., 2017). These beetles inhabit freshwater environments including ponds, lakes, and streams and are predatory in both the larval and adult life-stage (Eisner *et al*., 2005). Several of our sources cited whole insects of either *C. tripunctatus* and/or *C. japonicus* as having been used in

TCM and TKM. The TCM name is 龙虱 (*Long Shī*), the TKM name is 물방개 (*Mul Bang Gae*), and it has been recorded as being used to improve blood circulation and to treat polyuria and enuresis (Ding *et al*., 1997; National Administration of Traditional Chinese Medicine, 1999; Pemberton, 1999). Beetles in the genus *Cybister* have also been substituted, perhaps erroneously, for the more commonly used *Eupolyphaga sinensis* or *Steleophaga plancyi* (土鳖虫) (Hu *et al*., 2004). *Cybister japonicus* is also eaten as a food in parts of China and work on rearing them in artificial environments has been done (Jäch, 2003; Wang *et al*., 2017).

There have been several chemical studies on species within the genus *Cybister*, including on *C. tripunctatus* which have been summarized in several excellent reviews on beetle defensive chemistry (Schildknect, 1970; Dettner, 1987, 2014). It does not appear that *C. japonicus* (=*C. chinensis*) has been investigated for chemical composition, but it has recently been the subject genetic investigation using RNA seq technology (Hwang *et al*., 2018). Beetles in this genus contain a series of simple aromatic compounds as well as steroids, both used as glandular secretions (chemical constituents of *C. tripunctatus*, are shown in 43-49 in Fig. 7) (Schildknect, 1970; Dettner, 1987, 2014). The presence of steroids in these beetles is particularly interesting due to the many extremely potently bioactive steroids used as medicines.

Elateridae

***Pleonomus*:** Members of the family Elateridae are commonly known as click beetles. These beetles are most well-known for their ability to "click" when they rapidly move their prosternum in relation to their mesosternum with the aid of a structural peg and groove system, which allows them to flip themselves with great force relative to their size (Eisner *et al*., 2005). The most prominent Elaterid used in TCM is *Pleonomus canaliculatus*, which is called 叩头虫 (*Kòu Tóu Chóng*) and is used to increase muscular strength, especially in children with underdeveloped limb musculature, and to treat malaria (National Administration of Traditional Chinese Medicine, 1999). However, most work done on *P. canaliculatus* is in relation to controlling the population since it is a serious pest of Chinese winter wheat, referred to as a "wireworm" (Zhang *et al*., 2017).

Although a few genera within the family Elateridae have been chemically studied, we could not find any information on the chemical composition of *P. canaliculatus* or any member of the genus *Pleonomus*. The genus *Pleonomus* resides within the subfamily Dendrometrinae, as does the genus *Limonius* (Etzler and Johnson, 2018). *Limonius* spp. have been found to use simple carboxylic acids as sex pheromones, including hexanoic acid and pentanoic acid (50-51 in Fig. 8) (Francke and Dettner 2005). Other subfamilies within Elateridae have been found to have isoprenoid-derived pheromones (52-53) (Elaterinae) and glandular defensive secretions (Agrypinae) using nitrogen- and sulfur-containing compounds (54-58 in Fig. 8) (Dettner, 1987; Francke and Dettner, 2005; Kundrata *et al*., 2018).

Gyrinidae

***Gyrinus*:** Whirligig beetles, members of the family Gyrinidae, are aquatic beetles often seen in swarms on freshwater. They tend to move in tight circles or gyrate on the surfaces of water, this behavior is the basis for their common name (Eisner *et al*., 2005). Beetles in the genus *Gyrinus* are used in TCM under the name 豉虫 (*Chǐ Chóng*). References specifically cite *Gyrinus curtus* as the species primarily used to treat nasal polyps and infected boils (Namba *et al*., 1988; National Administration of Traditional Chinese Medicine, 1999). It also seems likely that *G. japonicus* and larger species within the genus *Dineutus* may also be used occasionally in addition to *G. curtus* (Namba *et al*., 1988; Meyer-Rochow, 2017).

Although we could not find any chemical studies on *G. cur-*

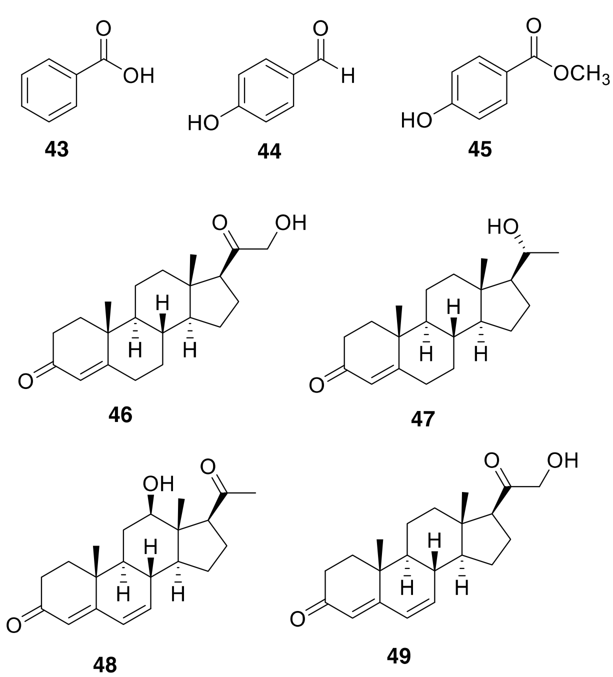


Fig. 7. Chemical constituents of *Cybister tripunctatus*. Compounds 43-45 are benzoic acid, 4-hydroxybenzaldehyde, methyl 4-hydroxybenzoate. Compounds 46 and 47 are 11-deoxycorticosterone, and 20β-hydroxypregn-4-ene-3-one. Compounds 48 and 49 are cybisterol, and 21-hydroxypregna-4,6-diene-3,20-dione.

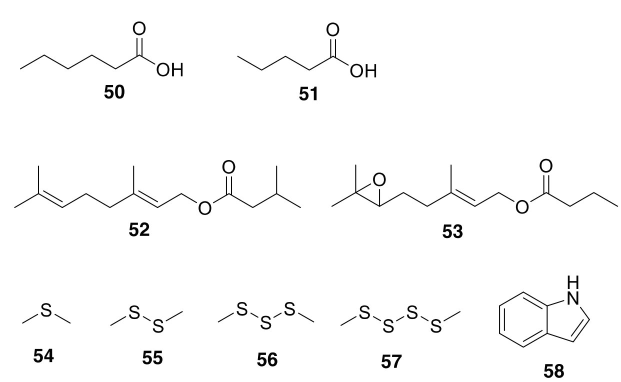


Fig. 8. Compounds identified from Elaterid beetles. Compounds 50 and 51 are hexanoic acid and pentanoic acid, identified from members of the subfamily Dendrometrinae. Compounds 52 and 53 are examples of pheromones identified from members of the subfamily Elaterinae (absolute configuration of 53 is unknown). Compounds 54-58 are examples of some defensive compounds identified from the subfamily Agrypinae.

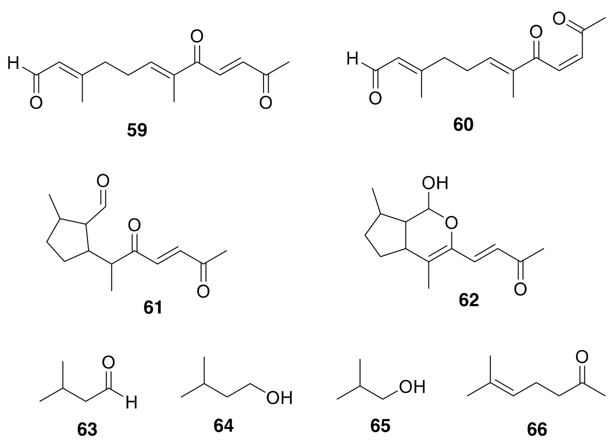


Fig. 9. Chemical constituents of *Gyrinus* spp. Compounds 59 and 60 are gyrinidal, and isogyrinidal. Compounds 61 and 62 are gyrinidione, and gyrinidone (relative and absolute configuration not fully described in the literature). Compounds 63-66 are 3-methylbutanal, 3-methyl-1-butanol, 2-methyl-1-propanol, 6-methyl-5-hepten-2-one.

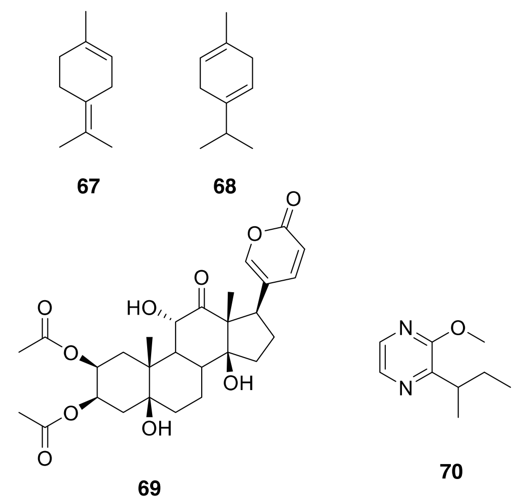


Fig. 10. Representative defensive compounds from fireflies (Coleoptera: Lampyridae). Compounds 67 and 68 are δ-terpinene, and γ-terpinene. Compounds 69 and 70 are lucibufagin C, and 2-methoxy-3-(1-methylpropyl) pyrazine (absolute configuration of 70 was not described in the literature).

tus, there have been several investigations into the chemical defenses and chemical signaling of other *Gyrinus* species. *Gyrinus* spp. use a series of norsequiterpenoids as their primary chemical defenses, including gyrinidal (59-62 in Fig. 9) (Meinwald *et al*., 1972; Miller *et al*., 1975). Based on the widespread presence of the same type of chemical defenses within *Gyrinus*, and even in the related genus *Dineutus*, it seems likely that *G. curtus* also contains this class of molecule (Dettner, 1985, 2019). Additional studies have shown that *Gyrinus* and *Dineutus* species release small volatile molecules (63-66 in Fig. 9) as well that play a role in intraspecific communication and chemical defense (Ivarsson *et al*., 1996; Karlsson *et al*., 1999; Härlin, 2005). However, most interestingly, it has been shown that the secretion of the pygidial glands (which contain the aforementioned norsesquiterpenoids) have antibacterial activity against *E. coli* (Kovac and Maschwitz, 1990), which corresponds intriguingly to the use of these beetles to treat infected boils (Namba *et al*., 1988).

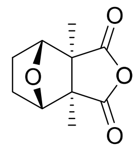
Lampyridae

Aquatica: Beetles in the family Lampyridae are known as fireflies and are famous for their beautiful displays of bioluminescence. There are over 2000 described species and all of them emit light in at least one life-stage (Bessho-Uehara and Oba, 2017; Maeda *et al*., 2017). Although there are around 100 genera of fireflies, we could only find reference to one species as being used in TCM, which is *Luciola vitticollis* (Namba *et al*., 1988; Yang, 1998; National Administration of Traditional Chinese Medicine, 1999). However, it appears that this species has been reclassified to now be called *Aquatica lateralis*, although it is still often referred to as *Luciola lateralis* in the literature (Fu *et al*., 2010). When used in TCM, *A. lateralis* is called 萤火 (*Yíng Huǒ*) (or occasionally *Ye Guang*), and is used to clarify eyesight, cure night blindness, and treat wounds and burns caused by fire (Namba *et al*., 1988; Yang, 1998; National Administration of Traditional Chinese Medicine, 1999).

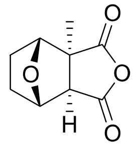
Several species of fireflies from different genera have been studied for their chemical defenses and have been found to contain steroidal compounds called lucibufagins that are similar in structure to the bufadienolides found in toads that are used in TCM (69 in Fig. 10) (Eisner *et al*., 1978, 1997; Tyler *et al*., 2008; Smedley *et al*., 2017). However, recent work was unable to show evidence of lucibufagin presence in *A. lateralis* (Fallon *et al*., 2018). A study on the related firefly (also in the subfamily Luciolinae) *Luciola leii* demonstrated that larvae have glands that produce the monoterpenoids δ-terpinene and γ-terpinene (67-68 in Fig. 10) as defensive substances (Fu *et al*., 2007). Another study showed that some firefly species produce pyrazine compounds (70 in Fig. 10) as an olfactory aposematic signal (Vencl *et al*., 2016). There was also work on the cuticular hydrocarbons of a *Luciola* species (Shibue *et al*., 2004), but most of the chemical work on this genus have related to their bioluminescence, primarily interested in luciferin and luciferase (Oba *et al*., 2010; Bessho-Uehara and Oba, 2017). *Aquatica lateralis* is one of the few species of firefly that has been raised in large numbers in the lab (Noh *et al*., 1990; Kim *et al*., 2014a). Although their chemistry remains somewhat mysterious, a complete mitochondrial genome and a nuclear genome of *A. lateralis* have now been published (Maeda *et al*., 2017; Fallon *et al*., 2018).

Meloidae

There are over 3,000 described species of beetles in the family Meloidae, which are called blister beetles. Their common name derives from the fact that most beetles in this family produce the powerful vesicant (blistering agent) cantharidin (Eisner *et al*., 2005). This group of beetles is probably the most widely known and used beetle in traditional medicines, not only being used in traditional East Asian medicine, but it has also been described as a medicine in ancient Greek texts and in Europe in general, where some species were called "Spanish fly" and used as an aphrodisiac (Young, 1984; Wang, 1989). We found evidence that four genera of Meloids are



71



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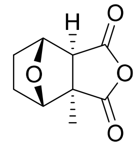


73

Fig. 11. Compounds likely to be present in most Meloidae, including *Epicauta*, *Lytta*, *Meloe*, and *Mylabris*. Compound 71 is cantharidin, compounds 72 and 73 are *R*-(+)-palasonin, and *S*-(-)-palasonin.

used in TCM, those being *Epicauta*, *Lytta*, *Meloe*, and *Mylabris*.

***Epicauta*:** Within the genus *Epicauta*, we were able to find references for the use of two species in TCM. *Epicauta gorhami* and *E. chinensis* are both referred to as 葛上亭长 (*Gě Shàng Tíng Zhǎng*). These beetles are used to treat poison, bruises, and constipation, as well as to induce abortions and clear obstructed urinary passages (Namba *et al*., 1988; National Administration of Traditional Chinese Medicine, 1999).

Blister beetles in the genus *Epicauta*, like most beetles in the family Meloidae, contain the potently bioactive and toxic terpenoid cantharidin (71 in Fig. 11) (Walter and Cole, 1967; Carrel *et al*., 1986). Due to its original use as an aphrodisiac, along with subsequent discovery of anticancer activity, there have been numerous studies on the bioactivity and toxicity of cantharidin and its analogs, including several high-quality review articles and book chapters including Schmitz 1989; Karras *et al*., 1996; Liu and Chen, 2009; Dettner, 2011; Deng *et al*., 2013; Ghoneim, 2013; Puerto Galvis *et al*., 2013. Cantharidin is used in western medicine as a treatment for various skin diseases, including molluscum contagiosum and verruca vulgaris, due to its strong vesicant action (Torbeck *et al*., 2014). Cantharidin is extremely toxic to humans and livestock when ingested and can cause death due to hemorrhage of the gastrointestinal and urinary tracts, among other dangerous symptoms (Schmitz, 1989; Karras *et al*., 1996). Recently, there have been several studies investigating the biosynthetic genes and tissues responsible for cantharidin production in *Epicauta* (Jiang *et al*., 2017a, 2017b, 2019).

Based on the wide range of Meloids that have been shown to produce both enantiomers of palasonin (demethylcantharidin, 72-73 in Fig. 11), these molecules are also likely to occur in *Epicauta* (Fietz *et al*., 2002; Nikbakhtzadeh and Tirgari, 2002; Nikbakhtzadeh and Ebrahimi, 2007; Mebs *et al*., 2009). Although it is unusual to find mixtures of enantiomers formed biosynthetically, in this case it seems plausible since it is believed that cantharidin, which is achiral, has one of two methyl groups removed via oxidative decarboxylation to form the chiral product, palasonin (Fietz *et al*., 2002).

***Lytta*:** Our sources specified three blister beetles from the genus *Lytta* used in TCM, *L. caraganae*, *L. chinensis*, and *L. suturella*. These three species are used interchangeably under the name 芫青 (*Yuán Jīng*) as a diuretic and to treat bruises, poison, scrofula, bites from rabid dogs, infections, and to induce abortions (Namba *et al*., 1988; National Administration of Traditional Chinese Medicine, 1999). The genus *Lytta* is closely related to *Epicauta*, and it appears that some species are even synonymous (*Lytta chinensis*=*Epicauta sibirica*) (Pan and Ren, 2018). Being Meloids, these beetles contain cantharidin. In fact, cantharidin was first isolated from beetles in this genus in 1810 (Young, 1984). It is likely that *Lytta* spp. also contain palasonin due to its widespread distribution in the Meloidae.

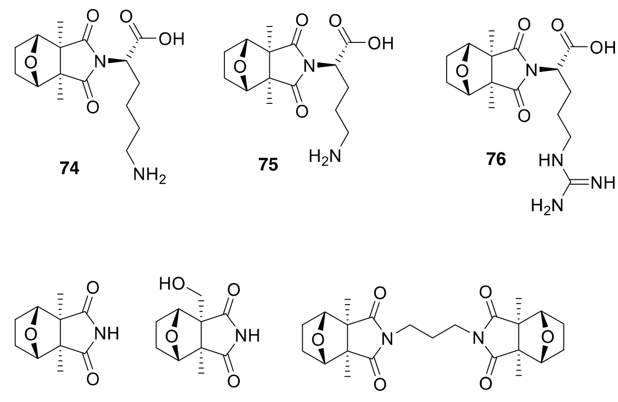
***Meloe*:** Beetles in the genus *Meloe*, in addition to being generalized as blister beetles because they are in the family Meloidae, are also sometimes called oil beetles. *Meloe coarctatus* is used in TCM under the name 地胆 (*Dì Dǎn*), and is used to remove poison, bruises, boils, warts, and necrotic tissue, as well as to increase liver function, treat scrofula, clear bowel obstruction, reduce feverish colds, and induce abortions (Namba *et al*., 1988; National Administration of Traditional Chinese Medicine, 1999). As with *Epicauta* and *Lytta*, beetles in the genus *Meloe* contain cantharidin (Young, 1984), and are likely to contain palasonin.

***Mylabris*:** Of all of the genera of blister beetles (Meloidae) used in TCM, *Mylabris* has been studied the most intensely. We found references for five species of *Mylabris* used in TCM. The most common species used is *Mylabris phalerata*, but *M. calida*, *M. cichorii*, *M. sidao*, and *M. speciosa* are also used (Namba *et al*., 1988; Jiang, 1990; Ding *et al*., 1997; Yang, 1998; National Administration of Traditional Chinese Medicine, 1999; Pemberton, 1999; Zhang *et al*., 2019). The TKM name for *Mylabris* is 반묘 (*Ban Myo*) and it is used to treat skin diseases including boils, fungal infection, and paralysis due to stroke, as well as swelling and lymphangitis, rabies, cancer, gonorrhea, and syphilis (Pemberton, 1999). The TCM name for *Mylabris* spp. is 斑蝥 (*Bān Máo*), and it is used to treat a long list of disorders including: infectious fevers, scrofula, boils, necrotic tissue, bladder stones, baldness, bruises, urinary blockage, to induce abortions, and, most famously, to fight several forms of cancer (Namba *et al*., 1988; Jiang, 1990; Ding *et al*., 1997; National Administration of Traditional Chinese Medicine, 1999; Zhang *et al*., 2019). Use of *Mylabris* spp. in TCM dates back over 2000 years (Wang, 1989). There is some confusion in the literature about the taxonomy of *Mylabris* and several papers use the genus name *Hycleus* for some *Mylabris* species, but it appears that *Mylabris* is a currently accepted genus (Bologna and Pinto, 2002).

The chemistry of *Mylabris* spp. has been the subject of several studies. Interestingly, in addition to cantharidin and palasonin, there have been additional cantharidin analogs, known as cantharimides and cantharidinimides found in this beetle (74-79 in Fig. 12) (Nakatani *et al*., 2004; Nikbakhtzadeh and Ebrahimi, 2007; Dettner, 2011; Zeng *et al*., 2020). The most recent of these studies used a very sensitive UPLC-MS technique to propose the structures of 34 chemical constituents of *M. phalerata*, the majority of which were cantharidinimides (Zeng *et al*., 2020).

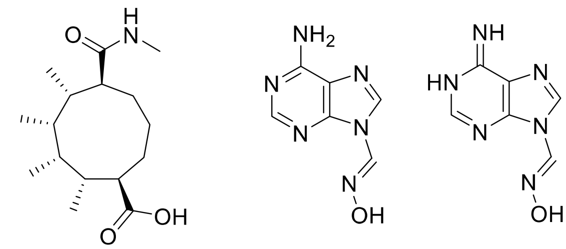
Scarabaeidae and Geotrupidae

The scarab beetles, members of the family Scarabaeidae, are a large and diverse group with over 2,000 genera and 25,000 species. In addition to the beetles commonly known as



74 75 76 77 78 79

Fig. 12. Compounds 74-79 are examples of cantharidin analogs identified from *Mylabris phalerata*.



80 81 82

Fig. 13. Compounds 80-82 are identified from adult *Allomyrina dichotoma*.

scarabs, many dung beetles, chafers, and rhinoceros beetles also belong in this group. Although this is a well-known group of beetles, not many chemical defenses have been described from scarabs (Eisner *et al*., 2005). There have been numerous studies on the pheromones of scarabs, especially on pest species (Leal, 1998; Francke and Dettner, 2005; Vuts *et al*., 2014, and references therein). The earth-boring dung beetles, family Geotrupidae, are a smaller group, with only around 350 described species (Cunha *et al*., 2011). We have included the family Geotrupidae in our discussion of the Scarabaeidae because beetles from these families are called the same name in TCM and are used interchangeably as the same medicine to perform the same function (Namba *et al*., 1988; Yang, 1998; National Administration of Traditional Chinese Medicine, 1999).

Beetles in the family Scarabaeidae along with those in the Geotrupidae are used in both the adult and larval form in TCM, but the larval stage is primarily used in TKM. In TKM, the larval stages of scarabs are called 굼벵이 (*Kum Bang Yi*). It is used frequently (70% of TKM clinics surveyed had prescribed this medicine) to treat cirrhosis of the liver (Pemberton, 1999). Scarab larvae are called 蛴螬 (*Qí Cáo*) in TCM and are used to reduce bruising, remove toxins, reduce menstrual bleeding, treat constipation, relieve pain, and to treat gout, tetanus, infected boils, feverish chills and acute skin infections (Namba and Inagaki, 1984; Namba *et al*., 1988; Ding *et al*., 1997; Yang, 1998; National Administration of Traditional Chinese Medicine 1999; Zhang *et al*., 2019). Larvae from several subfamilies, including the Cetoniinae, Dynastinae, Melolonthinae, Rutelinae are still used as *Qí Cáo* in Hong Kong and China (Namba and Inagaki, 1984). Adult scarab beetles and Geotrupids are called 蜣螂 (*Qiāng Láng*) in TCM and are used to treat convulsions, feverish chills, adult insanity, to reduce bruising, relieve constipation, ameliorate congestion, remove pus, remove dead skin, treat indigestion, alleviate nausea, and to reduce pain and swelling (Namba *et al*., 1988; Ding *et al*., 1997; Yang, 1998; National Administration of Traditional Chinese Medicine, 1999; Zhang *et al*., 2019).

***Alissonotum*:** We could find evidence that the larvae of one species from the genus *Alissonotum*, *A. impressicolle*, has been used in TCM as *Qí Cáo* (National Administration of Traditional Chinese Medicine, 1999). This species is known to be a pest on Chinese sugarcane, yet we still could not find any chemical studies for this genus (Liu *et al*., 1985). Chemical studies on other members of the subfamily Dynastinae may be informative (e.g., Allomyrina, below).

***Allomyrina*:** The genus *Allomyrina* is in the subfamily Dynastinae, which includes many of the rhinoceros beetles (Bouchard *et al*., 2011). The larvae of *A. dichotoma* have been widely used as *kumbangi* in TKM and *Qí Cáo* in TCM (see description and references above). Due to its widespread use in TCM and TKM, *A. dichotoma* extracts have been studied for bioactivity and chemical constituents. Even though *A. dichotoma* was determined to be non-toxic up to doses of 2.5 g/kg in rats (Noh *et al*., 2015), various forms and extracts were found to contain antibacterial proteins (Miyanoshita *et al*., 1996; Sagisaka *et al*., 2001), to exhibit anti-obesity effects (Yoon *et al*., 2015), and be antioxidant in nature (Suh *et al*., 2010). The fatty acid composition of *A. dichotoma* was described (Youn *et al*., 2012), however, what most likely sets *Allomyrina* apart from other scarabs was the discovery of three new alkaloids from adult *A. dichotoma* with moderate antibacterial activity (80-82 in Fig. 13) (Niu *et al*., 2016). The finding that *A. dichotoma* has at least two types of antibacterial substances (proteins and alkaloids) corresponds intriguingly with its use in TCM to treat infections.

***Anomala*:** The subfamily Rutelinae are called metallic leaf chafers, and includes the one of the most diverse genera (>1,000 species) in the animal kingdom, *Anomala* (Jameson, 1997). There are three species in the genus *Anomala* that have larvae used as *Qí Cáo* in TCM, *A. corpulenta*, *A. cupripes*, and *A. exoleta* (Namba *et al*., 1988; Ding *et al*., 1997; National Administration of Traditional Chinese Medicine, 1999). Although we could not find studies on the chemistry of the species of *Anomala* used in TCM, there has been a lot of work done revealing the pheromones of other *Anomala* spp. (83-90 in Fig. 14) (Leal, 1998; Francke and Dettner, 2005; Vuts *et al*., 2014, and references therein).

***Catharsius*:** The genus *Catharsius* is a group of scarabs consisting mostly of dung beetles in the subfamily Scarabaeinae. Two species in this genus, *C. molossus* and *C. pithecius* are used in TCM as *Qiāng Láng* (Namba *et al*., 1988; Yang, 1998; National Administration of Traditional Chinese Medicine, 1999; Zhang *et al*., 2019). In addition to the uses of *Qiāng Láng* described above, *C. molossus* has also been used to treat enlarged prostate (Zhao *et al*., 2006; Jiang *et al*., 2012).

Due to its use in TCM, there have been some studies on the chemistry of *Catharsius molossus*. The structure and charac-

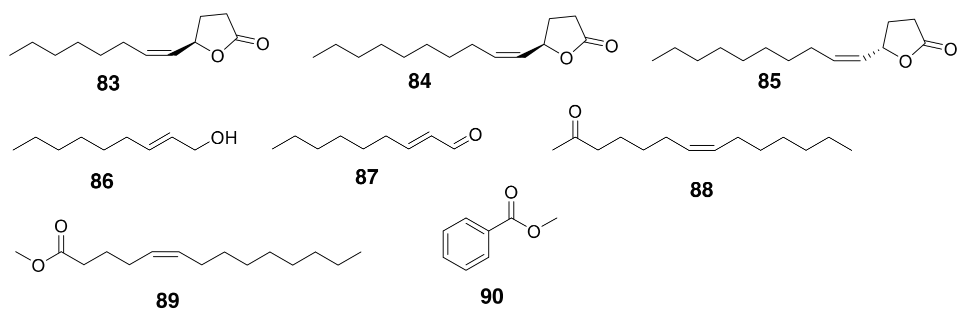


Fig. 14. Pheromones identified from *Anomala* spp. Compounds 83-85 are (*R*)-buibuilactone, (*R*)-japonilure, (*S*)-japonilure. Compounds 86-88 are (*E*)-2-nonen-1-ol, (*E*)-2-nonenal, (*Z*)-7-tetradecen-2-one. Compounds 89 and 90 are methyl (*Z*)-5-tetradecenoate and methyl benzoate.

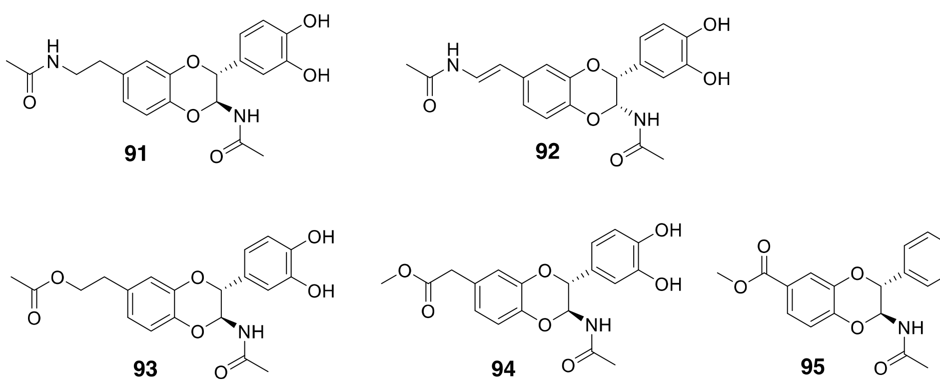


Fig. 15. Compounds identified from *Catharsius molossus*. Compounds 91 and 92 are *N*-acetyldopamine dimers. Compounds 93-95 are *N*-acetyldopamine dimer derivatives.

teristics of melanin (Xin *et al*., 2015) and chitosan (Ma *et al*., 2015) isolated from *C. molossus* have been investigated. A protein with fibrinolytic activity was also isolated from this beetle (Ahn *et al*., 2003). A chemical study of *C. molossus* identified *N*-acetyldopamine dimers and derivatives (91-95 in Fig. 15), similar to what was found in *Protaetia* (and other insects) (Lu *et al*., 2015). The finding of *N*-acetyldopamine dimers and derivatives in *C. molossus*, which are similar in structure to compounds with demonstrated anti-inflammatory activity (Xu *et al*., 2006; Yan *et al*., 2015), corresponds well with its use to treat enlarged prostates and the use of it as *Qiāng Láng* to reduce pain and swelling.

***Gymnopleurus*:** The genus *Gymnopleurus* consists of dung beetles, including *G. mopsus*, a dung-rolling beetle found in Mongolia, Northern China, and the Korean peninsula that is used in TCM as *Qiāng Láng* (Namba *et al*., 1988; Kang *et al*., 2018). Although we could not find any bioactivity or chemical constituent studies on any species of *Gymnopleurus*, they are in the subfamily Scarabaeinae, so they may contain similar compounds to those from *Catharsisus* (91-95 in Fig. 15). Additionally, several pheromones have been identified from dung beetles in the genus *Kheper* (96-99 in Fig. 16), which is also in the Scarabaeinae, so there could be compounds of this type present in *G. mopsus* (Francke and Dettner, 2005).

***Heliocopris*:** Dung beetles in the genus *Heliocopris* are also in the subfamily Scarabaeinae. These beetles have been eaten as food in some regions, and *H. bucephalus* has been used as *Qiāng Láng* in TCM, and to treat diarrhea in Laos (Namba *et al*., 1988; Ratcliffe, 2006). We could not find any chemical or bioactivity data for *H. bucephalus*, or any other members of this genus, but they may have similar chemistry to other members of the Scarabaeinae (91-95 in Fig. 15 and 96-99 in Fig. 16).

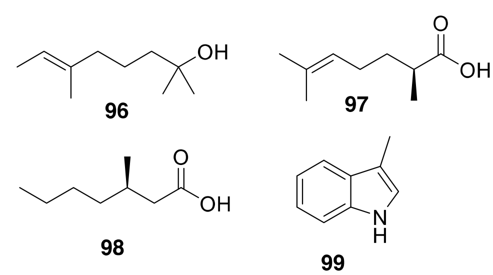


Fig. 16. Compounds 96-99 are pheromones identified from dung beetles in the genus *Kheper*, subfamily Scarabaeinae.

***Holotrichia*:** There are over 300 species in the genus *Holotrichia*, which are scarabs in the subfamily Melolonthinae (Pathania *et al*., 2016). Some members of this genus are referred to by the non-specific term “white grub” and can be serious economic pests on a variety of crops (Wang *et al*., 2019a). We found records of six species of *Holotrichia* used as *Qí Cáo* in TCM, *H. diomphalia*, *H. parallela* (=*H. morosa*), *H. oblita* (cited as *H. obrita*), *H. sauteri*, *H. sinensis*, and *H. titanis* (Namba *et al*., 1988; Ding *et al*., 1997; Yang, 1998; National Administration of Traditional Chinese Medicine, 1999). Several papers also mention the use of *H. diomphalia* in TKM, but do not provide a Korean name, and it is likely that these also fall under the term 굼벵이 (*Kum Bang Yi*) (scarab larvae, see description above under Scarabaeidae and Geotrupidae) (Kang *et al*., 2002; Oh *et al*., 2003). A number of studies have shown *Holotrichia* larvae or their extracts to have bioactivities using *in vitro* and *in vivo* assays including immunomodulatory (Kang *et al*., 2002), hepatoprotective (Oh *et al*., 2003), antifungal (Dong *et al*., 2008), antioxidant (Liu *et al*., 2012), anticancer (Song *et al*., 2014), anticoagulant (Xu *et al*., 2016), and anti-asthma (Hong *et al*., 2019). Additionally, antifungal and antibacterial proteins have been isolated from *H. diomphalia* (Lee *et al*., 1994, 1995a, 1995b).

Due to the pest status of some *Holotrichia* species, along with their usage in TCM and TKM, there have been studies on the chemical constituents of these beetles. The sex pheromones of some species have been elucidated (Leal, 1998; Francke and Dettner, 2005; Vuts *et al*., 2014, and references therein), as have some chemical constituents of these beetles (100-105 in Fig. 17) (Dong *et al*., 2011; Liu *et al*., 2012; Wang *et al*., 2012). Many of the isolated compounds are phenolic, which corresponds well with the antioxidant findings, although the flavonoids are likely to be obtained from the diet and could change upon feeding on a different substrate (100-105 in Fig. 17) (Liu *et al*., 2012; Wang *et al*., 2012). The hepatoprotective effects of the extracts, along with the antioxidant activity corresponds well to the use of these scarab larvae to treat cirrhosis in TKM, while the antibacterial proteins correlate well with the use of these larvae in TCM to treat infections. It should be noted, however, that Ding *et al*. (1997) mention that beetles in the genus *Holotrichia* are toxic and caution should be used in their application.

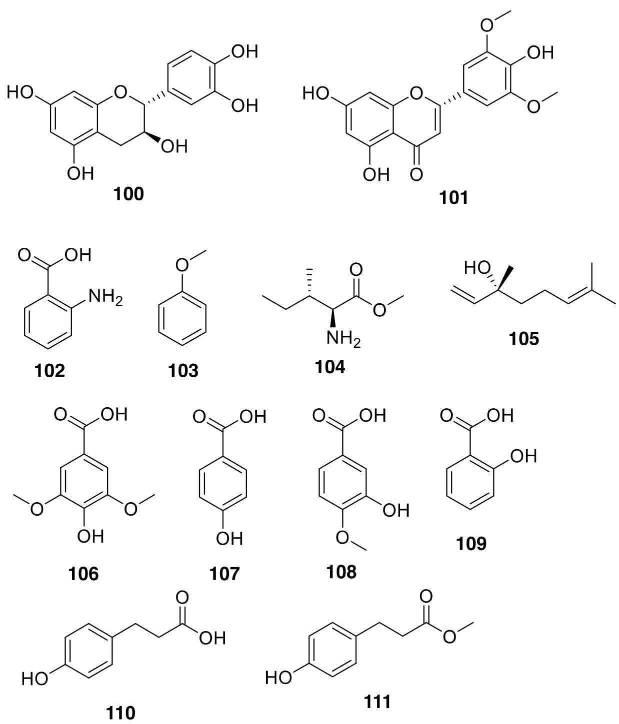


Fig. 17. Compounds reported from *Holotrichia* spp. Compounds 100 and 101 are flavonoids catechin and tricin. Compounds 102-105 are pheromones identified from *Holotrichia* spp. Compounds 106-111 are phenolic compounds from *H. diomphalia*.

***Onitis*:** The genus *Onitis* is in the subfamily Scarabaeinae and consists of dung beetles. *Onitis subopacus* has been used as *Qiāng Láng* in TCM (Namba *et al*., 1988). It is notable that beetles in this genus have been eaten as a food, so are unlikely to have significant toxicity (Ratcliffe, 2006). Some species of *Onitis* have exocrine glands that likely produce pheromones, however the structures of these compounds have not been elucidated (Houston, 1986). Other compounds from dung beetles in the Scarabaeinae were discussed earlier (91-95 in Fig. 15 and 96-99 in Fig. 16).

***Oxycetonia*:** The smaller green flower chafer, *Oxycetonia jucunda*, is the only member of the species *Oxycetonia* that we could find references for as being used in TCM as *Qí Cáo* (Namba *et al*., 1988). This beetle is known to visit citrus flowers, but is not a major pest (Nishino *et al*., 1970). Little is known about the chemistry of beetles in the genus *Oxycetonia*. They do seem to be attracted to floral scented lure traps, but not to pheromones of the Japanese beetle, *Popillia japonica* (Klein and Edwards, 1989; Leal, 1998; Vuts *et al*., 2014).

***Pentodon*:** The genus *Pentodon* is a relatively small group of scarabs with only 14 species and is in the subfamily Dynastinae (Jang and Kim, 2019). One species has been cited as being used in TCM as *Qí Cáo*, *Pentodon quadridens* (=*Pentodon patruelis*) (Namba *et al*., 1988; National Administration of Traditional Chinese Medicine, 1999). Even though *P. idiota* is a pest species on turfgrass, we could not find any chemical studies on members of this genus (Hosseini *et al*., 2019). There could be some clues of general chemical types based on analysis of the chemistry from other genera in the same subfamily (Dynastinae), e.g., *Allomyrina* (80-82 in Fig. 13).

***Phelotrupes*:** The genus *Phelotrupes* is currently regarded to be in the family Geotrupidae, the earth-boring dung beetles (Cunha *et al*., 2011). Three references indicated that *Phelotrupes laevistriatus* (cited as *Geotrupes laevistriatus*) is used in TCM as *Qiāng Láng* (Namba *et al*., 1988; Yang, 1998; National Administration of Traditional Chinese Medicine, 1999). We could not find any chemical or bioactivity studies on *Phelotrupes*. It has been noted that other Geotrupids excrete a red fluid when disturbed, so the chemical constituents of the Geotrupidae definitely warrant further examination (Cunha *et al*., 2011).

***Protaetia*:** The genus *Protaetia* is in the subfamily Cetoniinae and are often referred to as flower-chafers. We found evidence that the larval stage of two species were used in TCM as *Qí Cáo*, *P. brevitarsis*, and *P. orientalis* (Namba and Inagaki 1984; Namba *et al*., 1988). Additionally, *P. brevitarsis* is used in TKM, either called 제조 (*Je Jo*), or used as 굼벵이 (*Kum Bang Yi*) to treat liver problems and cancer, and has been approved as a food ingredient by the Korean Ministry of Food and Drug Safety (Yoo *et al*., 2007; Wang *et al*., 2019b). Various bioactivities of *P. brevitarsis* and *P. orientalis* larvae and extracts have been described, including hepatoprotective (Kang *et al*., 2001; Hwang *et al*., 2005; Chon *et al*., 2012; Lee *et al*., 2014), anticancer (Yoo *et al*., 2007; Lee *et al*., 2014), antioxidant (Park *et al*., 2012; Suh and Kang, 2012; Lee *et al*., 2017a), anti-inflammatory (Sung *et al*., 2016; Lee *et al*., 2019), and antithrombotic (Lee *et al*., 2017c). Antibacterial and antifungal peptides have also been isolated from *P. brevitarsis* (Park *et al*., 1994; Yoon *et al*., 2003; Hwang *et al*., 2008). A complete mitochondrial genome and nuclear genome of *P. brevitarsis* have been published (Kim *et al*., 2014b; Wang *et al*., 2019b).

There have been several chemical studies on *P. brevitarsis*, primarily due to its use in traditional medicines. The fatty-acid and volatile constituents of *P. brevitarsis* have been published, as has the purported anticancer activity of some of the fatty acids (namely, palmitic acid, oleic acid, and stearic acid) (Yoo *et al*., 2007; Yeo *et al*., 2013). A detailed investigation of the chemical constituents of *P. brevitarsis* identified 16 compounds (112-123 in Fig. 18) (Lee *et al*., 2017b). Several of the classes of compounds identified from this scarab have shown potent bioactivity, perhaps the most exciting of which are the β-carboline-type structures, which are very similar to antidepressant drug candidates (Ferraz *et al*., 2019) and the *N*-acetyldopamine dimers which are similar to some reported to have anti-inflammatory activity (including COX-2 inhibition), which matches the use of *Qí Cáo* for pain relief (Xu *et al*., 2006; Yan *et al*., 2015).

***Scarabaeus*:** Dung beetles in the genus *Scarabaeus* may be the famous scarabs depicted in ancient Egyptian artwork. Beetles in this genus have been eaten by people throughout their range, as well as used in traditional medicines (Ratcliffe, 2006). Most relevant to this work, however, is that *S. sacer* was noted as being used as *Qiāng Láng* in TCM (National Administration of Traditional Chinese Medicine, 1999). We could not find any in-depth studies of the chemical properties of *S. sacer*, but chitosan isolated from this beetle has recently been tested for and displayed anticancer activity (Wahid *et al*., 2018). There has also been work on the cuticular hydrocarbon profile of *S. sacer*, as well as indication that they have sternal glands that likely produce organic compounds, but no specific compounds have been elucidated (Niogret *et al*., 2006, 2018).

***Trematodes*:** The genus *Trematodes* is in the subfamily Melolonthinae, similar to *Holotrichia*. It was reported in Namba *et al*. (1988) that *T. tenebrioides* is used as *Qí Cáo* in TCM. Although *T. tenebrioides* is one of the most common scarabs in Inner Mongolia (Liu and Wu, 2004), we could find no information on the chemistry of this genus. They may have similar compounds as *Holotrichia* since they are in the same subfamily (100-111 in Fig. 17).

***Xylotrupes*:** The genus *Xylotrupes* is in the subfamily Dynastinae, and are therefore rhinoceros beetles. Even though we found sources indicating that *X. dichotomus* was used in TCM as both *Qí Cáo* (in the larval stage) and *Qiāng Láng* (in the adult stage), we could not find any studies on the chemistry of this beetle (Namba and Inagaki, 1984; Namba *et al*., 1988; National Administration of Traditional Chinese Medicine, 1999). Considering that it is in the same subfamily as *Allomyrina*, it would be interesting to see if it had similar chem-

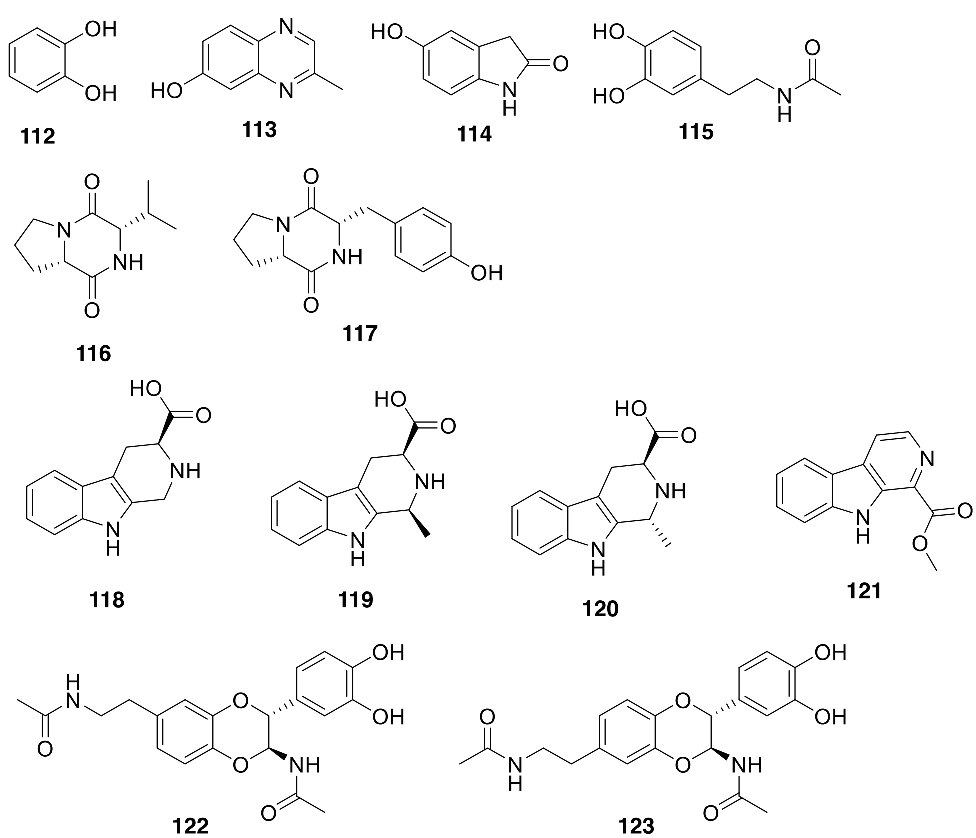


Fig. 18. Representative compounds reported from *Protaetia brevitarsis*. Compounds 112-115 are simple aromatic compounds. Compounds 116 and 117 are diketopiperazines. Compounds 118-121 are β-carbolines. Compounds 122 and 123 are *N*-acetyldopamine dimers.

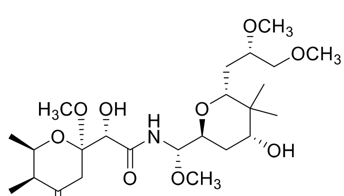
istry (80-82 in Fig. 13).

Staphylinidae

Paederus**:** The Staphylinidae, or rove beetles, are a large group (~1,500 genera and 25,000 species) of predacious beetles that have long, narrow bodies that when combined with their short elytra often leave large portions of their abdomen exposed (Eisner *et al*., 2005). The fact that so much of the abdomen is physically unprotected has led to the assumption, and later support of this hypothesis, that most species have some sort of chemical defense (Dettner, 1987, 2015; Eisner *et al*., 2005). We have found one species of Staphylinid used in traditional Chinese and traditional Korean medicine, *Paederus fuscipes*, although it is sometimes listed as the synonymous names *P. densipennis* or *P. idae* (GBIF Secretariat, 2019b). In TCM it is called 青腰虫, *Qīng Yāo Chóng* (although one source called it 花蚁虫, *Huā Yǐ Chóng*) and is used to remove tattoos, and treat skin ailments including infected boils, nasal polyps, and ringworm (Frank and Kanamitsu, 1987; Namba *et al*., 1988; National Administration of Traditional Chinese Medicine, 1999). We were unable to find the Korean name for this insect, but it has been traditionally used to treat vitiligo (You *et al*., 2003).

Beetles in the genus *Paederus* have been studied intensively due to their role in causing outbreaks of severe dermatitis called Paederus dermatitis or dermatitis linearis. Swarms of *Paederus* spp. occasionally occur, especially when they are attracted to bright lights at night near agricultural areas, and can cause many cases of acute skin and eye damage (Huang *et al*., 2009; Bong *et al*., 2015; Prasher *et al*., 2017). There have been several excellent reviews relating to *Paederus* spp. including on the natural history and medical importance (Frank and Kanamitsu, 1987), outbreaks of Paederus dermatitis (Bong *et al*., 2015), chemical defenses (Dettner, 2011, 2015), and chemistry and biological activity (Narquizian and Kocienski, 2000; Mosey and Floreancig, 2012). Three compounds have been identified from *P. fuscipes*: pederin, pseudopederin, and pederone (Fig. 19) (Dettner, 2011, 2015).

Pederin (124 in Fig. 19) was found to be the causative agent in Paederus dermatitis, and displayed extraordinary cytotoxicity, being one of the most potent cytotoxic natural compounds. It has been said that it is over 15 times more toxic than cobra venom (Frank and Kanamitsu, 1987). When applied to skin it causes painful burn-like wounds and blistering which can take one to three weeks to heal. After healing, the skin sometimes shows hyperpigmentation, which along with the complete renewal of the underlying skin, would explain the traditional use to remove tattoos, treat skin infections, and vitiligo (Frank and Kanamitsu, 1987; You *et al*., 2003; Huang *et al*., 2009). It has been found that female *Paederus* spp. contain up to ten times more pederin than males (Kellner and Dettner, 1995), and that this compound is biosynthesized by symbiotic bacteria, probably *Pseudomonas* (Dettner, 2011; Mosey and Floreancig, 2012, and references therein). The mode of action of pederin has been determined to be the inhibition of protein synthesis by binding to the ribosome (Narquizian and Kocienski, 2000, and references therein). Pederin and analogs (124-126) have been investigated for possible use as anticancer agents, but unfortunately they tend to kill cells indiscriminately and are not specific to cancer cells (Narquizian and Kocienski, 2000; Dettner, 2011; Mosey and Floreancig, 2012; Schleissner *et al*., 2017).



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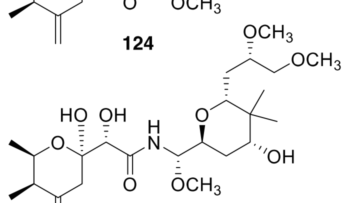

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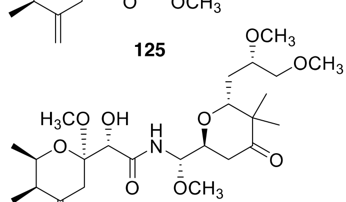

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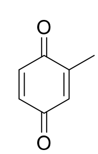
Fig. 19. Compounds identified from *Paederus fuscipes*. Compounds 124-126 are pederin, pseudopederin, pederone.

Tenebrionidae

Ulomoides**:** The family Tenebrionidae, commonly called darkling beetles, include approximately 1,700 genera and 18,000 species. They are notable for the fact that they are predominantly protected by chemicals produced in large glands (Eisner *et al*., 2005). We could only find mention of one species of Tenebrionid used in TCM, *Martianus dermestoides*, which is called 洋虫 (*Yáng Chóng*) (Ding *et al*., 1997; Zhang *et al*., 2019). However, upon further investigation, it became apparent that this species is now classified as *Ulomoides dermestoides* (Gustavo *et al*., 2002). In TCM, *U. dermestoides* is used as a tonic, to treat coughing, stomach illness, bone problems, stroke, and, most notably, cancer (Ding *et al*., 1997; National Administration of Traditional Chinese Medicine, 1999; Zhang *et al*., 2019).

Consistent with earlier studies of other Tenebrionids, the chemical constituents of the defensive secretions of *U. dermestoides* were determined to contain 1,4-benzoquinones, and long-chain 1-alkenes (11, 127-129 in Fig. 20) along with



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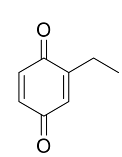

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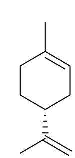

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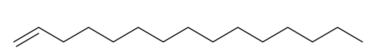

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Fig. 20. Compounds 11 and 127-129 are major compounds identified from the defensive secretions of *Ulomoides dermestoides*.

other, minor constituents, including limonene (Eisner *et al*., 2005; Francke and Dettner, 2005; Villaverde *et al*., 2009; Martins *et al*., 2010). Tests of extracts from *U. dermestoides* and closely related species, along with some of the individual compounds that make up the defensive secretions, have shown a wide-range of bioactivities, including cytotoxicity (Crespo *et al*., 2011), anti-diabetes (Jasso-Villagomez *et al*., 2018), anti-senility (Yan *et al*., 2009), anticoagulatory (Wu *et al*., 1996), and anti-asthma/anti-inflammatory (Wahrendorf and Wink, 2006; Santos *et al*., 2010). These results should be tempered, however, by the reminder that 1,4-benzoquinones are known to be hepatotoxic (Moore *et al*., 1987; Abernethy *et al*., 2004; Chan *et al*., 2008).

The use of *U. dermestoides* as a folk medicine has exploded worldwide in recent years, especially in Latin America, where this species does not occur naturally, but has been introduced (Gustavo *et al*., 2002). This beetle has many common names in its usage outside of the structure of TCM, including "peanut beetle", "Chinese beetle", "Chinese weevil" (even though it has no protruding rostrum and is therefore easily identifiable as not being a weevil), "asthma beetle", and most notoriously, "cancer beetle". It should be noted that the widespread use of *U. dermestoides* without the care, knowledge, and experience of a TCM practitioner can cause severe side effects including eosinophilic pneumonia, palpable purpura, and colitis (Natt *et al*., 2014; Martínez-Rodríguez *et al*., 2015; Saldarriaga Rivera *et al*., 2017).

DISCUSSION AND CONCLUSIONS

We were able to find evidence of 48 species of beetles from 34 genera in 14 different families that are used in TCM. The fact that so many species of beetles are used in TCM would likely surprise most TCM researchers and practitioners, even though this pales in comparison to the number of plant species used in TCM (>2,400) (Dai *et al*., 2016). Beetles are used for treatment of such critical diseases as cancer, stroke, heart disease, and bacterial infection. These are heavily researched areas that are still in dire need of additional therapeutics, and the beetles used in TCM may be a good resource to study for new lead compounds.

It should be noted that the beetles used in TCM were carefully selected over hundreds to thousands of years based, at least in part, by outcomes of patients. This selection is made clear when one compares and contrasts the taxa used by practitioners versus those not used. Several families of beetles bearing compounds with potent bioactivity (and even toxicity) are used including the Meloidae, the Tenebrionidae, and the Staphylinidae. However, other families that are known to have potent and/or high concentrations of bioactive molecules are not represented in TCM use, including the Chrysomelidae, Coccinellidae, Lycidae, and Silphidae (Dettner, 1987; Eisner *et al*., 2005). It seems fair to assume that these unrepresented families of beetles were the subjects of experimentation at least once over the >2,000-year history of TCM, but were discarded for lack of efficacy, presence of side effects, difficulty accumulating significant sources, or some other problem. This does not mean that these taxa are chemically uninteresting. However, it does emphasize that when searching for new potential drug leads, one should start with taxa that have been selected for through the long traditions of TCM.

The depth to which the beetles used in TCM have been chemically investigated varies widely. For instance, blister beetles, especially those in the genus *Mylabris* which are used to treat cancer, have been studied in detail yielding primarily cantharidin, palasonin, and cantharidinimides (Nakatani *et al*., 2004; Nikbakhtzadeh and Ebrahimi, 2007; Zeng *et al*., 2020). These structures and related analogs have been tested and showed potent anti-cancer activity (although toxicity remains problematic) (Liu and Chen, 2009; Dettner, 2011; Puerto Galvis *et al*., 2013). However, the in-depth studies on *Mylabris* and its chemical constituents serves as "the exception that proves the rule", highlighting how few of these medicinal beetles have been intensively investigated.

There is a spectrum of how well beetles used in TCM have been studied, ranging from the aforementioned *Mylabris* example to no chemical studies at all. There are beetles that have known chemistry, and the bioactivities of those molecules matches the TCM use, yet these molecules have not been subjected to rigorous medicinal chemistry work to determine feasibility of progressing to preclinical trials. A good example of this is the genus *Gyrinus*, which produces norsesquiterpenoids including gyrinidal, which have been shown to have antibacterial activity and are used in TCM to treat infected boils. There are also beetles that have known chemistry, yet these molecules have not been tested to see if they demonstrate the bioactivity which has been attributed to the beetle. Good examples of these are the buprestins from *Chalcophora*, the gomadalactones from *Anoplophora*, steroids from *Cybister*, β-carbolines from *Protaetia*, and *N*-acetyldopamine dimers from *Catharsius*. Some beetles, like *Lyctus brunneus*, are known to have glands that likely produce organic molecules, but the constituents of these glands have not been elucidated. Finally, there are some groups for which we could find no chemical studies even though they are used in TCM, including *Pleonomus* and *Phelotrupes*. Therefore, there is plenty of work to be done on beetles used in TCM for scientists ranging from natural products chemists to medicinal chemists to molecular biologists and pharmaceutical scientists.

Many of the beetles that have been chemically studied have only been investigated for pheromone content, which is incredibly valuable, especially for biocontrol work, but tends to focus heavily on volatile and/or cuticular compounds and could overlook non-volatile and more polar compounds. Further work on these taxa should use methodologies such as LC-MS and 2D NMR spectroscopy, in addition to GC-MS, to elucidate the presence of non-volatile molecules. Additionally, studies on the chemical constituents of bacterial and fungal endosymbionts of medicinal beetles could also be extremely valuable, and are underrepresented in the literature when compared to work on endophytic bacteria and fungi (Dettner, 2011, 2015).

Beetles are the most diverse group of insects, and insects are the most numerous group of macroscopic organisms (Berenbaum and Eisner, 2008; Yuan *et al*., 2016). We know that beetles are capable of biosynthesis and/or sequestration of potently bioactive compounds from a number of biosynthetic origins. The chemical prospecting of beetles is therefore likely to yield multitudes of new compounds with exciting biological activities (Dossey, 2010; Dettner, 2011; Seabrooks and Hu, 2017). What is more, the use of beetles in TCM gives us an obvious path towards new chemical entities with potential as lead compounds for therapeutic agents. Study of these insects not only provides the possibility of finding new drugs, but also has the additional benefit of providing insights into millennia-old cultural and medical practices. It is the goal of this paper to not only act as a valuable resource in connecting the ethnopharmacological data on which beetles are used in TCM with the chemical data of what compounds these beetles contain, but also to incite the scientific community into action to fill in the gaps in the knowledge herein exposed.

CONFLICT OF INTEREST

The authors declare no competing interest.

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