Drug Discovery Insights from Medicinal Beetles in Traditional Chinese Medicine

Stephen T. Deyrup1,*, Natalie C. Stagnitti1, Mackenzie J. Perpetua1 and Siu Wah Wong-Deyrup2

1Department of Chemistry and Biochemistry, Siena College, Loudonville, NY 12309,
2The 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.

Keywords: Beetle, Traditional Chinese Medicine, Traditional Korean Medicine, Coleoptera, Chemical defense, Secondary metabolites
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*               |
|-----------------|-------------|------------------------|---------------------------------------------------------------------------------|------------------------------|
| Buprestidae     | Lycus brunneus | Brown powderpost beetle | Detoxification, removal of pus/cysts<sup>b</sup>                                | Aliphatic esters             |
| Cantharidae     | Chalcopephora japonica | Flat-headed wood-borer | Insecticidal, eczema, itching.<sup>a</sup> aphrodisiac<sup>c</sup>               | Buprestins                   |
| Carabidae       | Chrysophroa elegans | Japanese Jewel beetle  | Improve blood circulation,<sup>b</sup>,<sup>d</sup> pain relief, bruises, inflammation, menstrual pain<sup>a</sup> (Bruises, poison, pain, bleeding,<sup>b</sup> angina pectoris,)<sup>d</sup> knife wounds<sup>d</sup>) | Long-chain ethers, gomadalaractones, juvenile hormone III |
| Cerambycidae    | Phorosopus jessoensis | Bombardier beetle      | Treat paralysis pain, arthritis<sup>b</sup>                                      | Phenol and aliphatic esters, ketones, and aldehydes |
| Curculionidae   | Cytotrichelus longimanus | Snout beetle           | Improve blood circulation,<sup>a</sup> polyuria, enuresis<sup>a</sup>              | Benzoic acid derivatives, steroids |
| Dytiscidae      | Cybister japonicus | Diving beetle          | Increase muscular strength, malaria<sup>a</sup>                                  | Aliphatic acids              |
| Elateridae      | Ptyonos canaliculatus | Click beetle           | Reduce bruising, constipation, congestion, remove pus or dead skin, indigestion, nausea, pain, swelling,<sup>b</sup> convulsions, fevers, insanity<sup>b</sup> | Unknown                     |
| Geotrupidae     | Phelotrupus laevistriatus | Earth-Boring Dung Beetle | Remove toxins, treat warts,<sup>c</sup> nasal polyps,<sup>c</sup> infected boils,<sup>a</sup> | Norsesquiterpenoids, aliphatic acids |
| Gyrinidae       | Gyrius curtus | Whirligig beetle       | Remove toxins, treat warts,<sup>c</sup> nasal polyps,<sup>c</sup> infected boils,<sup>a</sup> | Norsesquiterpenoids, aliphatic acids |
| Lampyridae      | Aquatica lateralis | Firefly                | Treat burns,<sup>b</sup> clarify eyesight, cure night blindness<sup>e</sup>         | Monoterpenoids               |
| Meloidae        | Epicauta chinensis | Blister beetle         | Cancer, poison, bruises, constipation, amenorrhea, vitiligo, dog bites, scrofula, as a diuretic, nasal polyps, fungal skin infections, menstrual pain,<sup>b</sup> boils, facial paralysis, STIs,<sup>e</sup> abortions, urinary obstruction<sup>d</sup> | Cantharidin and analogues |
| Mylabris calida | Blister beetle | 斑蝥, 疥疮, 刀伤<sup>a</sup> |
| Mylabris cichorii | Blister beetle | 斑蝥, 疥疮, 刀伤<sup>a</sup> |
| Mylabris phalerata | Blister beetle | 斑蝥, 疥疮, 刀伤<sup>a</sup> |
| Mylabris sidao | Blister beetle | 斑蝥, 疥疮, 刀伤<sup>a</sup> |
| Mylabris speciosa | Blister beetle | 斑蝥, 疥疮, 刀伤<sup>a</sup> |

The use of insects in Traditional Chinese Medicine (TCM) is based on the belief that they are able to produce a wide variety of chemical compounds that can be used to treat various ailments. This is supported by the fact that beetles, in particular, are known for their ability to sequester or biosynthesize small molecules that can increase fitness and thereby make excellent candidates for research into novel bioactive chemistry. However, 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.
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 review that systematically connected the known use of these beetles with what is known of their chemistry, and in these cases we searched for some of the beetles used in TCM that have never been studied chemically, 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 to use, we frequently used the name provided and the currently used nomenclature.

Table 1. Continued

| Beetle used | Common name | TCM name | Traditional use | Chemical class* |
|-------------|-------------|----------|-----------------|-----------------|
| **Scarabaeidae** | *Alisnonotum impressicolle* | Scarab beetle (larva) | 婊嫖 | Reduce bruising, constipation, constipation, remove pus or dead skin, indigestion, nausea, pain, swelling, | Long-chain alcohols, aldehydes, esters, ketones, and lactones, alkaloids, branched, carboxylic acid derivatives, flavonoids, diketopiperazines, β-carbolines, N-acetyl dopamine, dimers, N-acetyl dopamine analogues |
| | *Allomyrina dichotoma* | Horned beetle | 婊嫖, 금병이 | | |
| | *Anomala corporulenta* | Leaf chafer (larva) | 婊嫖 | | |
| | *Anomala cupripes* | Leaf chafer (larva) | 婊嫖 | | |
| | *Anomala exoleta* | Leaf chafer (larva) | 婊嫖 | | |
| | *Catharsius molossus* | Dung beetle | 婊嫖 | | |
| | *Catharsius pithecus* | Dung beetle | 婊嫖 | | |
| | *Gymnopleurus mopus* | Scarab beetle | 婊嫖 | | |
| | *Heliocopris bucephalus* | Northeast block chafer | 婊嫖 | | |
| | *Holotrichia bicornis* | Chafer (larva) | 婊嫖, 금병이 | | |
| | *Holotrichia morosa* | Chafer (larva) | 婊嫖, 금병이 | | |
| | *Holotrichia sauteri* | Brown chafer (larva) | 婊嫖, 금병이 | | |
| | *Holotrichia titanis* | Chafer (larva) | 婊嫖, 금병이 | | |
| | *Onitis subopacus* | Dung beetle | 婊嫖 | | |
| | *Oxycetonia jucunda* | Mulberry chafer (larva) | 婊嫖 | | |
| | *Protaphtha breviviridis* | Flower chafer (larva) | 婊嫖 | | |
| | *Protaetia orientalis* | Flower chafer (larva) | 婊嫖 | | |
| | *Scaraebaeus acher* | Sacred scarab beetle | 婊嫖 | | |
| | *Trematodes tenebroides* | Scarab (larva) | 婊嫖 | | |
| | *Xylotrupes dichotomus* | Rhinoceros Beetle (larva) | 婊嫖 | | |
| **Staphylinidae** | *Paederus fuscipes* | Rove beetle | 青腰虫/花蚊虫 | Treat tooth pain, itching, skin infections and ailments, remove tattoos, vitiligo | Pederin and analogues |
| | *Staphylinus similis* | Darkling beetle | 洋虫 | Cancer, coughs, bone problems, stomach illness, stroke, | 1,4-benzoquinones, limones, long-chain alkenes |

*Class of chemicals identified from the beetle or from closely related beetles. See the text for more detail. *(Namba et al. 1988). *(Ding and et al. 1997). *(Pemberton 1999). *(Zhang et al. 2019). *(National Administration of Traditional Chinese Medicine 1999). *(www.biomolther.org)
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; Martín, 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 Chón) (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, *Rhizophora dominica* and *Prostephanus truncatus*, have also 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).

**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 Buprestis 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 Buprestis, *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 Buprestis, 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 Buprestis in general are called jewel beetles. Members of this genus were literally used in jeweled ornaments in Asia, including China (National Administration of Traditional Chinese Medicine, 1999). Two other species of Buprestis, *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
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).

**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
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 refer to unidentified longhorn beetles being used in TCM. According to Namba *et al*., (1998), 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 (epigastrum). Several longhorn beetles in the subfamily Cerambicinae have been shown to secrete defensive chemicals from metathoracic 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 termed 天牛 (*Tián 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; Pecanha *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 germari* (= *A. germari*) and *Batocera* horsefieldi are in the subfamily Lamiinae, and are used interchangeably with *Aplophora chinensis* in TCM (described above). However, the chemistry of these genera has been less well studied. It has been found that *A. germari* 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 Bǐ 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. buquei*) 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 Bǐ 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...
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 Shi), 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 chemically studied, 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 (Schildknecht, 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) (Schildknecht, 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 (Kōu Tō Chōng) 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 (Agrypineae) 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 止跌 (Chí Chōng). 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 Dinuteus 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-
Gyrinus spp. use a series of norsequiterpenoids as their primary chemical defenses, including gynirindal (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 as 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 norsequiterpenoids) 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 vititollis (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 (Ying Hu) (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 aposmatic 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 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 aposmatic 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).

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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 (Ge 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 Ebframih, 2007; Mels 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 蚶青 (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 sibica) (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 Dān), 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 TCM 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, rashes, cancer, gonorrhea, and syphilis (Pemberton, 1999). The TCM name for *Mylabris* spp. is 璽盤 (Bàn 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 *Hyleus* 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 cantharidin-2,3-imides 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...
scarab larvae are called 埼螬 (Qí Cáo) in TCM and are used to treat convulsions, feverish chills, adult insanity, to reduce pain and swelling (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 小金虫 (Kum Bang Yi) (Pemberton, 1999). Scarab larvae are called 埼螬 (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 堆蜣 (Qi Cao) in TKM 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 Qi Cao (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., Alomyrina, below).

Alomyrina: The genus Alomyrina 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 Qi Cao 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., 2012), however, what most likely sets Alomyrina 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 Qi Cao in TCM, A. corporula, 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 Quang Lăng (Namba et al., 1988; Yang, 1998; National Administration of Traditional Chinese Medicine, 1999; Zhang et al., 2019). In addition to the uses of Quang Lăng 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-
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 Qiānɡ Lánɡ 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 Qiānɡ Lánɡ (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 Catharsius (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 Qiānɡ Lánɡ 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).

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 Qi Cão in TCM, H. diomphalia, H. parallela (=H. morosa), H. oblitra (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 굽벵이 (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), anti-fungal (Dong et al., 2008), antioxidant (Liu et al., 2012), anti-cancer (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.

**Onitis:** The genus Onitis is in the subfamily Scarabaeinae and consists of dung beetles. Onitis subopacus has been used as Qiang Làng 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 Qi Cão (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 Qi Cão. Pentodon quadridentis (=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 Qiang Làng (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 Qi Cão, 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 굽벵이 (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 Qi 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 Qi Ān 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 Qi 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 Qi Cáo (in the larval stage) and Qi Ān (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-
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 Chónɡ* (although one source called it 花腰虫, *Huā Yāo Chónɡ*) 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 Kocienksi, 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 Kocienksi, 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 Kocienksi, 2000; Dettner, 2011; Mosey and Floreancig, 2012; Schleissner et al., 2017).

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 (*Yán ɡōng*) (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...
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 \textit{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), anti-coagulant (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 \textit{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 \textit{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).

\textbf{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 \textit{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 \textit{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 \textit{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 \textit{Gyrinus}, which produces norsesquiterpenoids including glyridinal, 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 \textit{Chalcophora}, the bomadalactones from \textit{Anoplophora}, steroids from \textit{Cybister}, \textit{β}-carbolines from \textit{Protaetia}, and \textit{N}-acetyldopamine dimers from \textit{Catharsius}. Some beetles, like \textit{Lycus bruneus}, 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 \textit{Pleonomus} and \textit{Phletotrupes}. 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 endosymbiants 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 (Dossay, 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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Peçanha, E. P., Fragas, C. A. M., De Sant Anna, C. M. R., De Miranda,
