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Review

Cantharidin Toxicosis to Animal and Human in the World: A Review

Dr. Karem Ghoneim

Faculty of Science, Al-Azhar University, Cairo, Egypt

Email: kar_ghoneim@yahoo.com

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Abstract

In the order Coleoptera, cantharidin is produced by two families, Meloidae (true blister beetles) and Oedemeridae (false blister beetles). Cantharidin is of veterinary and medical importance, since it is super toxic to animals and humans. The present work was conducted aiming to review the cantharidin investigation and cantharidin toxicosis to animals including pathology, symptomatology, preventive measures and curative treatments. Although cantharidin toxicosis in animals had been widely documented, the literature reports on birds are still limited. A comprehensive discussion of the human cantharidiasis had been provided stressing on the most reported cases in the world, pathological effects, clinical symptoms, mode of action, preventive measures and curative treatments.

Key words: Cantharidiasis, toxicity, Meloidae (true blister beetles), Oedemeridae (false blister beetles) and Staphylinidae (rove beetles)

INTRODUCTION

The order Coleoptera (Insecta) constitutes almost 25% of all known life-forms (Powell, 2009). The order includes more species than any other insect order and about 40% of all described insect species are beetles and new species are discovered frequently (Hammond, 1992). The total number of beetle species is approximately one million (Chapman, 2009). In Coleoptera, only Meloidae (true blister beetles), Oedemeridae (false blister beetles) and Staphylinidae (rove beetles) release vesicant chemicals, the first two release cantharidin and the latter releases paederin (Gnanaraj et al., 2007). The main function of cantharidin in these beetles is to preserve their eggs from predators beside some other functions (Frenzel and Dettner, 1994; Hemp et al., 1999; Day et al., 2001; Capinera, 2008; Mullen and Durden, 2009).

Family Meloidae is virtually cosmopolitan but absent only from New Zealand, Antarctica and most Polynesian islands (Bologna, 1991; Dettner et al., 1997; Arnett et al., 2002; Bologna and Pinto, 2002; Bologna et al., 2008). They primarily occur in temperate steeply and arid regions, and in sub-tropical and tropical savannas or other open habitats (Bologna and Di Giulio, 2011). As reported some years ago, Meloidae contains more than 3000 species in 120 genera (Bologna, 1991a, b). Different biological aspects of this family had been reviewed by Ghoneim (2013 a) as well as various agronomic and biodiversity impacts of these beetles had been reviewed by Ghoneim (2013 b). These beetles are commonly known as "oil beetles" because they release yellow oily droplets of haemolymph from their leg joints (and may be from the antennal joints) when disturbed. This exudation contains toxic material "cantharidin' or "cantharid" (derived from the Greek word 'Kantharos') which acts naturally as an aphrodisiac for adult males and females (for review, see Ghoneim, 2013 c). It is well established that in many species, females possess but cannot produce cantharidin (Sierra et al., 1976; Holz et al., 1994). Adult females acquire it from adult males through frequent copulation and it passes thence to eggs for chemical protection, as previously mentioned (Schmidt, 2002, Nikbakhtzadeh et al., 2007). It is surprising that the larvae manufacture and accumulate cantharidin as they feed and grow in size. The quantitative analysis of cantharidin in the blister beetle larvae had been carried out (Haskins et al., 1987). The first five larval instars of the ebony margined blister beetle *Epicauta funebris* Horn were found to produce cantharidin and when

disturbed they exude it, as a defensive agent, in a milky oral fluid, not in haemolymph which adult beetles reflexively discharge (Carrel et al., 1993).

Oedemeridae (false blister beetles) is a family of worldwide distribution. It consists of about 1500 species in 100 genera, mostly associated with rotting wood as larvae, though adults are quite common on flowers (Vazquez-Albalate, 2002). They derive their common name not only from their superficial resemblance to some species of Meloidae but also because many species possess the blistering agent cantharidin. Although they are commonly known as false blister beetles, some recent authors have coined the name pollen-feeding beetles (Vazquez-Albalate, 2002). The available literature contains several reported works on the distribution and systematic of the family Oedemeridae in the Old World regions and countries, such as Russia (Nikitskyn, 1996), southeastern China (Švihla, 2009), Japan and Taiwan (Mizota, 1999), Korea (Yoo et al., 2008), Iran (Abtahi et al., 2012), southern Africa (Vazquez-Albalate, 1996, 2004 a), tropical Africa (Vazquez-Albalate, 2004 b), Socotra Archipelago (in the northwest Indian Ocean)(Švihla, 2012), Iberian peninsula (Lencina et al., 2008), eastern Mediterranean region (Švihla, 2006a), Greece (Brustel and Kakiopoulos, 2009), Latvia (Barševskis, 2009), Bulgaria and Turkey (Švihla, 2006b; Sivilov, 2012), Sweden (Hojer, 2008), and some other regions (Švihla, 1986, 1997, 2004, 2011). With regard to the distribution and systematics of this family in the New World, many published works had been available in the literature such as Campbell (1991), Kriska (2002), Majka and Langor (2011), Webster et al. (2012) for Canada; (Blackwelder (1945), Lawrence and Newton (1995) and Patrice et al. (2011) for Central America and South America; Paula (1975) for New Zealand; and Arnett (1961) for some other regions and countries.

Cantharidin is one among the most widely known insect natural products (Dettner, 1997; McCormick and Carrel, 1987). It usually attracted a great attention of many investigators and research institutions because of its toxicosis on man and painful or fatal diseases for horses and other livestock. Many reports on different aspects of veterinary and medical impacts and uses of cantharidin are available in the literature (MacKay and Wollenman, 1981; Beasley et al., 1983; Kinney et al., 1998; Sandroni, 2001; Ho et al., 2001; Sandroni, 2001; Al-Basheer et al., 2002; Gottesman et al., 2002; McCluskey et al., 2002; Schmidt, 2002; Nikbakhtzadeh and Tirgari, 2002; Bhattacharjee and Brodell, 2003; An et al., 2004; Nikbakhtzadeh and Ebrahim, 2007; Zheng et al., 2008; Mebs et al., 2009; Al-Benali et al., 2010; Nikbakhtzadeh et al., 2012).

The present work aims to review the cantharidin in nature, functions, isolation and determination in blister beetles, as well as the cantharidin-related compounds. Also, its concerned with the cantharidin in veterinary medicine and human cantharidiasis.

1. Cantharidin under investigation

1.1 Cantharidin in nature

Cantharidin (haemolymph exudation through leg joints or/and antennal pores) is among the most widely known insect natural products (Dettner, 1997) and primarily found in the true blister beetles, Meloidae, and secondarily in false blister beetles, Oedemeridae (Arnett et al., 2002; Prestwitch and Blomquist, 1987). It was discovered in haemolymph and gonads of the blister beetle, commonly known as Spanish fly *Lytta vesicatoria* (Linnaeus), in quantity larger than any other member of blister beetles (Bohac and Winkler, 1964). It is one of the oldest-known toxins from insects (Eisner et al., 1990) and has been known to humans for more than 2000 years due to its physiological activities such as blistering (McCormick and Carrel, 1987; Wang, 1989; Pemberton, 1999). Also, it is highly toxic to a wide variety of animals, including birds, amphibians and mammals (Dettner, 1997).

The function and intrinsic role of cantharidin in the courtship behaviour of family Meloidae has never been fully established. It was suggested that cantharidin might be used by female when selecting a mate at close range (McCormick and Carrel, 1987). Pinto (1974, 1975) was, in fact, the first to consider male cuticular pores on antennae which are being involved in the courtship behaviour of species from the genera *Linsleya* and *Tegrodera*. As pointed out in the iron cross blister beetle *Tegrodera aloga* Skinner, individual males donated a large cantharidin-containing spermatophore to their mates, and body size was correlated with the size of the cantharidin-producing accessory glands (Alcock and Hadley, 1987). For some details, adult males of the blister beetle manufacture quantities of cantharidin larger than those of adult females who compensate it by receiving some quantities from their mates during mating as a nuptial or copulatory gift (Pemberton, 1999; Nikbakhzadeh, 2004). Thus, cantharidin production varies widely depending not only on the species but also on the sex, time of year and food source (Dettner et al., 1997). The transferring mechanism of some quantity of cantharidin from adult male into the genitalia of female, as a nuptial gift for mating, was clarified by Nikbakhzadeh et al. (2007).

Meloid beetles have been attacked by some insects and other natural enemies. It was reported that some blister beetles such as *Meloe* spp. are attacked by *Pedilus* (Coleoptera: Pedilidae) (LeSage and Bousquet, 1983) and/or by

some species of Miridae (Heteroptera) (Pinto, 1978). Also, the dark blister beetle *Epicauta murina* (LeConte) and E. *fabricii* are attacked by the fire-coloured beetle *Pedilus lugubris* Say (Williams and Young, 1999). When attacked or disturbed, adults of blister beetles release haemolymph droplets in so called "reflex bleeding". The highly toxic material, "cantharidin" in the haemolymph, is a well defensive reaction against the aggressive creatures. As reviewed by Ghoneim (2013 C), cantharidin is considered responsible for the repellent properties of meloid haemolymph against a wide variety of predators. Although cantharidin serves these beetles effectively in defense against ants and carabid beetles (Carrel and Eisner, 1974), some enemies are undeterred by cantharidin. Among these are frogs, which apparently consume meloids with impunity (Korschgen and Moyle, 1955; Kelling et al., 1990). Acquired cantharidin could convey a protective advantage on frogs *vis â vis* any number of natural enemies, and it could also make frogs poisonous to humans (Eisner et al., 1990). As pointed out by numerous authors (Carrel et al., 1973; Sierra et al., 1976; Carrel et al., 1993; Arnett et al., 2002), adult female of blister beetle uses her own cantharidin and transferred cantharidin for herself and also to cover or coat her eggs for protecting them against the potential predators.

1.2 The cantharidphilous insects

Generally, autogenous producers of cantharidin occur exclusively within the coleopteran families of Meloidae (Dixon et al., 1963; Capinera et al., 1985; Blodgett et al., 1991; Carrel et al., 1993; Dettner, 1997; Hemp et al., 1999 a; b) and Oedemeridae (Carrel et al., 1986 a, b; Nicholis et al., 1990; Samlaska et al., 1992; Holz et al., 1994; Frenzel and Dettner, 1994) in which it occurs in the haemolymph and other tissues (Carrel and Eisner, 1974; Young, 1984; Bologna, 1991a, b; Dettner et al., 1997). A considerable number of insects, so-called cantharidphilous (unable to synthesize cantharidin *de novo*), are attracted over distances towards the natural sources of cantharidin or even the synthetic compound (Holz et al, 1994; Eisner et al., 1996a; Frank and Dettner, 2001). They feed on it without any obvious ill-effects (Hemp and Dettner, 2001) and presumably utilize the compound against their natural enemies (Dettner, 1997). A few studies have by-far quantified cantharidin of the cantharidphilous insects, whereas most reports have been concentrated on the identification, distribution, morphology and behaviour of this group of insects (Frenzel and Dettner, 1994; Holz et al., 1994; Eisner et al., 1996 a, b).

More knowledge about the function of cantharidin in biology of the cantharidphilous insects was summarized (Hemp et al., 1999). Six families of beetles (Coleoptera) are known to be cantharidphilous (Hemp and Dettner, 2001). A study on the chemical ecology of the fire-colored beetle *Neopyrochroa flabellata* (Pyrochroidae) showed that males use cantharidin both to entice prospective mates and as a mid-copulatory gift (Norton, 2002). Tiny amounts of cantharidin- far below the average content for Meloidae- were detected in some coleopterans such as the orange beetle *Cantharis livida* Linnaeus (Cantharidae), *Gastrophysa polygoni* Linnaeus (Chrysomelidae), malachite beetle *Malachius bipustulatus* Linnaeus (Melyridae) and capricorn beetle *Certallum ebulinum* (Linnaeus) (Cerambycidae) in Iran (Nikbakhtzadeh, 2009). In some cases, the fungus beetles (Endomychidae) may actively seek out alternative defensive compounds not internally produced or externally acquired from their primary hosts (Dettner, 1997; Hemp and Dettner 2001; Price and Young, 2007; Shockley et al., 2009). In China, cantharidin was detected in some insects which systematically belong to the family Fulgoridae (Homoptera) (Zhang et al., 2009). The hemipterous insect *Huechys sanguinea* (De Geer) (Hemiptera: Cicadidae) was reported in some Chinese authorities to contain cantharidin but the analytical results indicate that this species does not contain cantharidin (Feng et al., 1988), which finding was confirmed later (Li et al., 2007). For more information about cantharidphily in insects, see: Young (1984), Frenzel et al. (1992), Hemp et al. (1999a, b), Nardi and Bologna (2000), Shockley et al. (2009).

1.3 Cantharidin biosynthesis, detection and isolation

Although the cantharidin biosynthesis in the blister beetles had been studied by some researchers (McCormick et al., 1986; Carrel et al., 1987, 1988, 1990, 1993), it was a debatable issue along several decades ago and the mechanism *in vivo* was not completely understood. However, it is quite sure that it implicates reactions with as first compound a terpenic alcohol. A proof can be given with mass spectroscopy using the ^{14}C, ^{3}H, ^{18}O isotopes. The farnesol is a sesquiterpenic alcohol and is an intermediate in the biosynthesis of isoprenoids. Cantharidin was chemically isolated from M. *proscarabaeus* (Dixon et al., 1963). Employing standard practices of analysis, which involved infrared and NMR spectroscopy, thin-layer chromatography, elemental analysis, and determination of physical constants, Walter and Cole (1967) isolated cantharidin from *E*. *pestifera* in North America. It was, also, isolated from *Cyaneolytta sapphirina* Mäklin (Salama et al., 1974) and *Epicauta tomentosa* (Mäklin) (Hammouda and Salama, 1974). In addition, it was isolated and crystallized from the red-headed blister beetle *Epicauta hirticornis* in Assam, India (Verma et al., 2013). Concerning the biosynthesis sites, the highest concentration of cantharidin was observed in sexual organs, particularly in the ovary

(Nikbakhtzadeh and Tirgari, 2002; Nikbakhzadeh et al., 2007). In order to clarify the biosynthesis mechanism of cantharidin in *Mylabris calida* Palla, Jia et al. (2009) studied the protein expression profile during the early and advanced stages of the process. Jiang et al., (2012) investigated the relationship between cantharidin biosynthesis and the mevalonate pathway.

As reported in one of the oldest published books, that of Bartholow (1882), the principal constituent of cantharides is a neutral, crystallizable principle, cantharidin. Walter and Cole (1967) and Einbinder et al. (1969) indicated that cantharidin (2,3-di-methyl-7-oxabicyclo [2.2.l] heptane-2.3- dicarboxylic acid anhydride) is the principal active ingredient amongst the various compounds present in *Mylabris*. We can find an oil, fatty matter, and an odorous material in the cantharidin. The chemical structure and properties of cantharidin had been reported in the literature e.g (Dauben et al., 1980; Davidson and Williams, 1987; Tagwireyi and Ball, 2000; Schmidt, 2002). It is a bicyclic terpenoid or anhydride of cantharidic acid with chemical formula $C_{10}H_{12}O_4$. It has a plane of symmetry that goes through the middle of the bonds C2C3 and C5C6. It's a meso compound (2S, 3R) (Verma et al., 2013). The molecular weight is 196.2024 g/mol. At the usual temperature, it is an odorless and colorless solid, its melting point is 212 °C., white to light yellow crystal powder, readily soluble in various organic solvents, such as ether, chloroform and acetone, as well as in fixed oils, but only slightly soluble in water or almost insoluble in it. Cantharidin is incompatible with acids, strong oxidizing agents, alcohols, amines, and bases. Although cantharidin was purified and crystallized in 1810 by Robiquet from Spanish fly *Lytta vesicatoria* (Dixon et al., 1963; Prestwitch and Blomquist, 1987), it took 150 years of study to be fully synthesized (Prestwitch and Blomquist, 1987; Carrel et al., 1993). It was isolated and crystallized from the blister beetle *Epicauta hirticornis* (Verma et al., 2013).

1.4 Cantharidin determination

Different meloid species infesting the alfalfa fields in Colorado (USA) had been subjected to determine their cantharidin levels. Significant differences in cantharidin concentrations were found among species *E. pennsylvanica, Epicauta maculata* (Say) and *Epicauta immaculata* (Say)(Capinera et al., 1985). Also, cantharidin contents were determined in four *Epicauta* species abundant in northeast Kansas alfalfa fields and significantly more cantharidin was found in the three-striped blister beetle *Epicauta occidentalis* (Werner) and *E. pennsylvanica* than possessed by *E.* fabricii and *E. pestifera* (Blodgett et al., 1991). Among 35 meloid species collected from some Chinese provinces, there were 19 predominant species which had been undergoing quantitatively analysis to determine the cantharidin. The cantharidin levels varies among different species and also among individuals of the same species (Tan et al., 1995). From the methodological point of view, a simple and rapid gas chromatographic analysis was described by Li et al. (2006) for determining the cantharidin in *M. phalerata* from different places in China. Also, a simple, convenient and précised method for cantharidin determination in *Mylabris* was presented (Guo et al., 2007). The cantharidin content was measured in Michigan blister beetles as follows: each of *Epicauta pestifera* (margined blister beetle) and *E. pennsylvanica* (black blister beetle) contained low content (<0.5 mg/beetle), each of *E. maculae* (spotted blister beetle) and *E. murina* (dark blister beetle) contained medium content (0.5-2.0 mg/beetle) and each of *E. vittata* (striped blister beetle) and *E. fabricii* (ashgray blister beetle) contained high content (4 mg/beetle) (Difonzo, 2009).

Cantharidin titer in blister beetles depends on several factors including, age, sex and mating status (Carrel et al., 1993). Nine meloid species were collected from various host-plants in different Chinese districts in order to isolate and quantitatively analyze the cantharidin. Cantharidin content was higher in males than in females of the same species. Moreover, cantharidin content in the female collected after the copulation peak was higher than that before copulation peak (Yuling et al., 2001). The effect of mating on cantharidin content in a field collected sample of the blister beetles *Epicauta mannerhimi* was investigated (Yang et al., 2001). For the Iranian and non-Iranian meloid species, no significant difference in cantharidin titer was found. The male before copulation has a high titer, while it decreased significantly just after copulation because most of the toxin transfers to the females' sexual organ as a nuptial gift (Nikbakhtzadeh and Tirgari, 2002). Under laboratory conditions, Wang et al. (2008) analyzed the changes in the cantharidin level at different life stages of the blister beetle *Mylabris cichorii* Linnaeus. Their results showed that larvae accumulated cantharidin as they grow and develop and Adults exhibited a pronounced sexual dimorphism in cantharidin biosynthesis, but total content of cantharidin produced by sex-mixed rearing group was much higher than that by sex-segregated rearing group. As reported by Lowry and Bundy (2011), males generally have more cantharidin than females of six different species of blister beetles in New Mexico.

1.5 Cantharidin forms

Cantharidin forms had been investigated in 8 species of Meloidae by Li et al. (2007). They found that the contents of total cantharidin were higher than the contents of free cantharidin, as well as bound cantharidin may exist in the forms of magnesium cantharidate and calcium cantharidate. Using the gas chromatography, Li (2011) determined the bound cantharidin, free cantharidin and total cantharidin in 12 species of Meloidae in China. The results suggested that the existing form of bound cantharidin might be the magnesium cantharidate, calcium cantharidate, potassium cantharidate.

The gas chromatography was used, also, to compare the change of cantharidin content in *Mylabris* before and after biotransformation which had been determined in 0.7% and 1.29%, respectively (Xu et al., 2011). A headspace solid-phase microextraction (HS-SPME) coupled to gas chromatography-mass spectrometry (GC-MS) method was developed to determine cantharidin forms in the false blister beetles, family Oedemeridae (Mehdinia et al., 2011).

1.6 Cantharidin-related compounds

In a related matter, there are few compounds structurally similar to cantharidin, known as cantharidin-related compounds (CRCs), which have been found in blister beetles. Cantharidin has never been detected in plants, but the first CRC, palasonin (demethylcantharidin)($C_9H_9O_4$), which lacks one of the angular methyl groups of cantharidin, was characterized in 1960 (Bochis, 1960). It was initially isolated from the seeds of the Indian tree known as Flame of the forest, *Butea frondosa* (Leguminoseae: Fabaceae) (Raj and Kurup, 1967). The palasonin is chiral and exists with two enantiomeric forms where the 3-methyl group of cantharidin is missing (Bochis, 1960; Raj and Kurup, 1966; Rydberg and Meinwald, 1996; Dettner et al., 1997; Fietz et al., 2002; Dettner et al., 2003; Mebs et al., 2009). Although both cantharidin, palasonin share the same unique, angularly methylated ox-abicyclo skeleton, the toxins have never been reported to co-occur in either plants or insects. However, analyses of species from the families Meloidae, Cleridae, and Staphylinidae (Fietz et al., 2002) gave the first evidence for simultaneous presence of cantharidin and palasonin in the haemolymph and tissues of individual insects. Fietz (2011) was the first to detect palasonin in bodily extracts from a blister beetle (*Hycleus lunatus*) and a clerid beetle (*Trichodes apiaries*, Cleridae). Also, variable titers of palasonin were detected in two southern African species, *Hycleus oculatus* and *Hycleus tinctus* (Mebs et al., 2009).

Dettner et al. (2003) reported the second CRC, palasoninimide ($C_9H_{10}O_3N$). Cantharimides, whose anhydrideoxygen atoms are replaced by basic amino acids, and cantharimide dimers, which consist of two cantharimide units combined with a tri-, tetra-, or pentamethylene group, had been reported in the Chinese meloid *Mylabris phalerata* Pall. (Nakatani et al., 2004, 2007). Cantharidin and two CRCs, palasonin and cantharidinimide ($C_{10}H_{13}NO_3$), were extracted from the blister beetle *Mylabris impressa stillata* (Baudi) collected from Hamedan Province, Iran (Nikbakhtzadeh and Ebrahimi, 2007). In the blister beetle *Hycleus scabiosae* (Olivier), an inseminated female incorporates about 38.5 ng of cantharidin, 196.35 ng of palasonin and 269.15 ng of palasoninimide into each egg mass during oviposition (Nikbakhtzadeh et al., 2012).

2. Veterinary impacts of cantharidin

2.1. Prevalence of cantharidin toxicosis in animals

Most of the current studies on cantharidin are focused on the production site in blister beetles, cellular detoxification, *in vivo* biosynthesis and the intermediate compounds as well as the protein phosphatases' inhibitory properties (Liu et al., 1995; McCluskey et al., 2001; McCluskey et al., 2002). Numerous veterinary reports of cantharidin-caused poisonings were documented in the literature (Bahme, 1968; Schoeb and Panciera, 1978; Capinera et al., 1985; Graziano et al., 1987; Schmitz, 1989; Buntin, 1989). Some reported the cantharidin toxicosis in cattle, goats and sheep as well as some other animals such as rabbits, hedgehogs, mice and dogs (Polettini et al., 1992; Loftin, 2011). There have been few observations of meloid beetles being eaten by amphibians (Larson, 1943) and by a lizard, *Phrynosoma* (Selander et al., 1963). As observed by Cohen and Cohen (1990), 11 meloid beetles of A1egetra cancellata had been ingested by an individual Texas horned lizard *Phrynosoma cornutum*. The fish *Lepomis cyanellus* was allowed by Tafanelli and Bass (1968) to feed naturally on three species of the meloid beetles as well as members of the families Tettigoniidae and Cantharidae. The fish consistently took and then released the meloid beetles but retained the other insects. Cantharidin poisoning had been reported in chickens and emus (Guglick et al., 1996; Barr et al., 1998). Mortality of young chickens by the consumption of contaminated food with blister beetles was observed (Penrith and Naude, 1996). The emu case involved chicks feeding on blister beetles that were attracted to light from the chick barn (Mullen and Durden, 2009).

Sanchez-Barbudo et al. (2012) described the possibility of cantharidin intoxication of a wild bird, great bustard (*Otis tarda*).

As pointed out by numerous authors (Capinera et al., 1985; Graziano et al., 1987; Buntin, 1989; Schmitz, 1989; Polettini et al., 1992; Zhu et al., 1997; Helman and Edwards, 1997; Puschner, 2000; Loftin, 2011), many cases of the cantharidin poisoning of horses and other livestock were recorded in the field after feeding on blister beetles-contaminated alfalfa hay. Although cattle, goats, sheep and chickens are potentially susceptible to blister beetle poisoning, horses are the most susceptible. In USA, as for example, adults of blister beetles swarm and mate in summer when alfalfa is in bloom (Edwards et al., 1989). Alfalfa hay is vulnerable to the contamination when harvested during this swarming period, especially if the harvesting technique involves simultaneously cutting and crimping the hay, a common practice in many areas (Schmitz, 1989; Guglick et al., 1996). Because the beetles swarm in clusters, several insects can be trapped in a few hay bales or even in a portion of a single hay bale (Schmitz, 1989; Guglick et al., 1996). While 67 species of blister beetles had been identified in Oklahoma alone, the most common species associated with toxicosis in horses are the three-striped blister beetles, *Epicauta temexa* and *E. occidentalis*. The two species that pose the most risk for livestock poisoning in Arkansas are the three-striped blister beetle (*Epicauta vittata*) and the striped blister beetle (*Epicauta occidentalis*) (Ray et al., 1989; Edwards et al., 1989).

Blister beetle poisoning in cattle can result in significant economic losses because of a substantial drop in milk production, animal illness and death (Puschner, 2004). Niles et al. (2001) described blister beetle poisoning in the dairy cow herds. The most significant clinical signs were mass refusal to eat the freshly cut green chop alfalfa, although the cows appeared hungry, and the corresponding dramatic decrease in milk production.

2.2 Lethal potency of cantharidin in animals

Blister beetle toxicosis, owing to cantharidin, continues to be a cosmopolitan problem for livestock. Generally, severity of the animal reaction to cantharidin ingestion, ranging from temporary poisoning, to reduced digestive ability, to death, depends upon the amount of cantharidin ingested and the size and health of the animal (Townsend, 2000). Animal deaths have been most common in horses and poultry (Hoelscher, 1982). Cases of fatal poisonings of valuable horses by ingestion of blister beetles in baled alfalfa hay had been recorded (Schoeb and Panciera, 1979; MacKay and Wollenman, 1981; Kinney et al., 2006). Research works are available to indicate the cantharidin levels present in common meloid species, as well as the number of beetles necessary to provide a lethal dose to horses (Sansome, 2002; Kinney et al., 2006). Despite the relatively low toxin content in a single beetle, large number of beetles can be incorporated into alfalfa hay causing death to horses and other livestock (Blodgett et al., 1991). On the other hand, a few beetles with a high cantharidin level would kill a small horse, but quite a few with a low level would be required to kill a larger horse in Colorado. Only 40 individuals of the three-striped blister beetle would kill a 275-pound colt. As little as 4-6 grams of dried beetles can be fatal to a horse (Capinera et al., 1985). As reported by Davidson and William (1987), consumption of 1.6 g of pulverized beetles containing cantharidin led to death after 26 hours. Ten mg of pure cantharidin resulted in a fatality, whereas poisoning by 1.3 mg did not (Guglick et al., 1996). The lethal dose for cattle may be as low as 0.5 mg/Kg body weight (Gayle, 1981). The minimum lethal dose of cantharidin in horses may be less than 1 mg/kg of body weight (Loftin, 2011). In Southern Africa, two species of meloid beetles, *H. oculatus* and *H. tinctus*, were used to assay quantitatively cantharidin. The cantharidin concentration of more than 6 mg per beetle was measured poisoning to the high risk of severe and even fatal after ingesting these insects (Mebs et al., 2009). Blodgett et al. (1992) carried out a study on the cantharidin contamination in alfalfa hay, due to the blister beetle *Epicauta occidentalis* Werner, and concluded that the ingestion of crushed, dried beetles in the hay was a greater threat to livestock health than was contaminated hay free of blister beetles. Because of the stability of cantharidin and its remains in the dead beetles for a long time, animals may be poisoned by eating crushed beetles in cured hay. Beetle toxicity does not decrease during hay storage (Schmitz, 1989; Kinney et al., 2006).

2.3 Symptomatology of cantharidin toxicosis in animals

Although sudden death, with no signs, had been reported (Schmitz, 1989; Guglick et al., 1996), animal death may occur within 24 hours after cantharidin (contained in bodies of the blister beetles) ingestion (Puschner, (2000). Depending on the available literature, we have compiled herein most of the toxicosis symptoms. Cantharidin, absorbed through the gastrointestinal tract, produces systemic effects and is excreted in the urine resulting in inflammation of the kidneys and irritation of the urinary bladder (Krinsky, 2002). The irritation of the urethra will increase the blood flow to this region and might result in priapism, a persistent abnormal erection of the penis (Metcalf and Flint, 1962). Urination, hematuria, or straining to urinate, salivation, bruxism, diarrhea, reluctance to move, ataxia and recumbency had been recorded

(Helman and Edwards, 1997; Niles et al., 2001). The crystalline cantharidin in an alfalfa cake or in aqueous suspension was assessed on horses by Shawley and Rolf (1984) who observed the toxicity symptoms as increasing cardiac rate, respiratory rate and rectal temperature accompanied with decreasing concentrations of Ca, Mg and K in the total serum. Increasing temperature and heart rate had been also reported (Puschner, 2000).

Some of consistent clinical signs, such as anorexia and depression, severe gingival and oral mucosal erosions and washing of the muzzle in water, as well as drooling, pyrexia, diarrhea, dehydration, tachypnea, and tachycardia were documented (Shawley and Rolf, 1984). Colic and decreased appetite are most often related to abdominal pain caused by the vesicant effects of cantharidin on mucosal surfaces of horses (Schoeb and Panciera, 1978; Helman and Edwards, 1997). Some cantharidin-poisoned horses have myocardial necrosis. Necropsy findings may include mucosal hyperemia, hemorrhage, edema, vesication, and ulceration anywhere within the gastrointestinal or urinary tract (Schmitz, 1989). Cantharidin may also cause hypocalcemia and its associated clinical effects including muscle fasciculations, synchronous diaphragmatic flutter, abnormal gait, dysphagia, and abnormal behavior such as aggressiveness or disorientation (Guglick et al., 1996; Schmitz, 1989).

Diagnosis of cantharidin toxicosis in animals can be confirmed by testing the urine and gastrointestinal contents (Ray et al., 1980). Urine and ingesta from the upper portion of the gastrointestinal tract, containing from 1 to 20 ppm of cantharidin, were the most satisfactory samples for diagnosing toxicosis (Ray et al., 1979). Some veterinary diagnostic laboratories can chemically analyze hay, urine, serum or gastric content for cantharidin concentration (Campbell and Ensley, 2002). Insect parts can sometimes be identified in gastrointestinal contents or feces (Ray et al., 1989). Hypocalcemia and hypomagnesemia are consistent findings and can help for differentiating the cantharidin toxicosis from other causes of colic (Guglick et al., 1996; Helman and Edwards, 1997). As reported by Holbrook and Dacvim (2009) for the fatal poisoning, gross lesions may be minimal or unapparent and diagnosis must be confirmed by chemical detection of cantharidin in urine, blood, stomach or caecal contents.

Preventive measures and curative treatments

Cantharidin poisoning by blister beetles cannot be completely prevented, however, many management options are available, especially for horses. Each individual block or flake of alfalfa hay should be inspected for blister beetles. Cantharidin can continue to be toxic in bales after beetles have died (Puschner, 2000). Contaminated hay should be discarded rather than being fed after beetle removal because the remaining body fluids from the beetles contain cantharidin (Zhu et al., 1997). As modern agricultural practices, alfalfa should be harvested before it reaches full bloom when blister beetles are most attracted to the plants. Hay is less likely to be contaminated by crushed beetles when harvested with a self-propelled mower-windrower (Blodgett, 1995). As reported by Campbell and Ensley (2002), examining hay bales prior to purchase is difficult because the beetles tend to congregate, so most bales may be free of beetles, but a few may contain enough number of beetles to cause toxicity in horses. Careful examination when feeding alfalfa may allow detection of beetles if present.

No specific antidote is available for the cantharidin toxicosis in animals whereas its treatment is aimed at maintaining fluid and electrolyte homeostasis for minimizing the intestinal irritation and cantharidin absorption (Helman and Edwards, 1997). Fluid therapy and bicarbonate need to be used to alleviate shock and acidosis. Calcium, also, may be needed (Campbell and Ensley, 2002). Mineral oil is used commonly in horses that display colic signs. The use of mineral oil or activated charcoal may reduce toxin absorption (Schmitz, 1989) due to decrease transit time through the gastrointestinal tract and adsorb cantharidin, respectively (MacKay and Wollenman, 1981; Beasley et al., 1983; Flaminio and Oehme, 1997). Biosponge®, a Di-Tri-Octahedral smectite, has been used to adsorb clostridial enterotoxins and could be a viable adsorbent for cantharidin as well (Rateau et al., 1982; Martirosian et al., 1998). Recently, Qualls (2012) evaluated three gastrointestinal protectants in rats, as an animal model of equine cantharidin toxicosis. The results suggested the avoidance of treatment with mineral oil but with activated charcoal or Biosponge®.

3. Human cantharidiasis

To shed some light on the impact of cantharidin and cantharidin-producing beetles upon the human health, only some of the identified 3000 species of true blister beetles (family Meloidae)(Ghoneim, 2013 d) and of the identified 1500 species of false blister beetles (family Oedemeridae)(Kriska, 2002; Vazquez-Albalate, 2002; Abtahi et al., 2012) in the world are injurious. Historically, the best known true blister beetle is the Spanish fly *Lytta vesicatoria* Linnaeus which fills its breathing tube with air and closes its breathing spiracles (pores) to elevate body pressure in order to force out some droplets of haemolymph containing the toxic cantharidin through its leg joints (Sierra et al., 1976; Holz et al., 1994; Schmidt, 2002; Nikbakhtzadeh et al., 2007, 2012). Taken internally or absorbed through the skin, cantharidin

(or cantharides) is highly toxic to mammals. For man, the most common beetle injury is not from a bite or sting but from the formation of blisters (dermatosis) when roughly contacted with the soft skin and from the cantharidiasis (cantharidin poisoning) when ingested orally (Aiello, 1998; Mizota, 2001; Nikbakhtzadeh and Tirgari, 2008; Davidson et al., 2009).

From a medical standpoint, literature contains many recorded cases of human cantharidiasis. Cantharidin poisoning from the meloid beetles can occur as a result of overdosage of cantharidin used as a counterirritant (Avery, 1908) or accidentally when using it as a bait in fishing (Lecutier, 1954). Cantharidin poisoning usually results after aphrodisiac ingestion. The extreme toxicity of cantharidin makes any use as an aphrodisiac highly dangerous because it can easily cause death. As a result, it is illegal to sell (or use) cantharidin for this purpose in many countries (Karras et al., 1996). Beetle ingestion by children has also caused poisoning (Wertelecki et al., 1967; Mallari et al., 1996).

Cantharidin seems to be a dangerous substance with the same toxicity as the most violent poisons like strychnine and cyanide (Aiello, 1998). The clinical signs of cantharidin poisoning are nonspecific. Gas chromatography/mass spectrometry can be used to confirm cantharidin poisoning (Ray et al., 1980; Hundt et al., 1990). The fatal dose of cantharidin is estimated to range from 10 to 65 mg (Polettini et al., 1992), with the median lethal dose being approximately1mg/kg (Matsuzawa et al., 1987); however, individuals have survived after consuming oral doses as high as 175 mg (Oaks et al., 1960).

3.1 Human cantharidiasis in the world

Several cases of human intoxication with cantharidin of blister beetles had been described for human adults and children in the world (Andrewes, 1921; Simpson, 1935; Nicholls and Teare, 1954; Wertelecki et al., 1967; Ewart et al., 1978; Tagwireyi et al., 2000). An earlier report of cantharidin poisoning was given by Jefferiss (1876) for his neighborhood that died few days after swallowing the poison. Statistics of criminal cantharidin poisoning in France, in 1847, was compiled as many as 20 murders or attempted murders occurring within a few years in which cantharidin powder had been mixed as a spice in the soup of the intended victims (Beatrice et al., 1961). Some other earlier cases had been reported (Maclagan, 1877; Martley, 1904; Pearce, 1913; Lipsitz et al., 1917; Andrewes, 1921; Dieffenbacher, 1929; Nickolls and Teare, 1954; Lecutier, 1954; Capper, 1955; Dunlop, 1955).

In Europe, Polettini et al. (1992) described a case of 38-year old Italian man who voluntarily ingested cantharides powder made from dried blister beetle, *Lytta* (=*Cantharis*) *vesicatoria* containing 26-45 mg of the toxic principle, cantharidin, in a cup of tea for aphrodisiac purpose. Almost immediately, he suffered a burning sensation of the tongue and pharynx, intense dysphagia and sialorrhoea, and then died about 30 hours. Another case of fatal poisoning for Italian man due to voluntary ingestion of cantharides powder for aphrodisiac purposes was reported (Marcovigi et al., 1995). Beatrice et al. (1961) documented a case of cantharidin poisoning on a young Dutch seaman aged 22 years who did not take any drug. The clinical investigation revealed the presence of cantharidin in his fluids which might have been mixed up in food or drink by another party with the usual intent to produce sex stimulation.

In Africa, cantharidin poisoning may be responsible for some of the unexplained neurological presentations in Black South Africans. Zouvanis et al. (1994) clinically investigated 47 patients suffering neuromuscular respiratory failure between January 1983 and December 1990. Depending on their results, the cantharidin poisoning may be a cause of "Guillain-Barre-like" syndrome. Another case of cantharidin poisoning was documented when 35-year old South African male suffered an acute shortness of breath. A nurse noticed a bottle containing an unknown liquid amongst his possessions. She thought to contain a "muti" (traditional African drugs) and thus transported it to laboratory. During a few days, further symptoms had been noticed including diarrhea, confusion and vascular collapse ending in the death. The analytical investigation of the unknown liquid revealed the presence of cantharidin (Fenyvesi et al., 2011). Tagwireyi et al. (2000) reported a case of ingestion of the blister beetle (*Mylabris dicincta*) by a 4-year old girl in Zimbabwe. She presented with many of the classical signs and symptoms of cantharidin poisoning including haematuria and abdominal pains. She was managed and recovered after 9 days. In addition, cantharidin poisoning may be responsible for some of the unexplained neurological presentations in Black South Africans (Harrisberg et al., 1984).

In Asia, eight Saudi men had been presented to King Khalid Hospital because of the complaining of haematuria and dysuria after eating hunted wild birds on 15 of April 1999. The ornithologists identified the birds as a species in the family Glareolidae and the insect taxonomists identified the insects in the bird gut as blister beetles (Al-Rumikan and Al-Hamdan, 1999). Also, the signs and symptoms of meloid beetle ingestion by Saudi Arabian male and female children were reported and the clinical investigation revealed the cantharidin intoxication following ingestion (Al-Binali et al., 2010). On March 30, 1994, cantharidin poisoning was reported in the Royal Hospital in Muscat (Oman) since repeated episodes of blood-stained vomitus and passage of reddish-colored urine were observed for two siblings after ingestion of a beetle *L. vesicatoria* they caught in a garden (Mallari et al., 1996). Twu et al. (2012) carried out a study in Taiwan to explore the effects of cantharidin on luteal cell steroidogensis and to compare its effect with that of norcantharidin. The luteal cells were isolated from corpora lutea of native Taiwan goats, maintained in vitro, and treated for 4 and 24 h with

cantharidin and norcantharidin (0.1, 1.0, and 10 µg ml(-1)). Their results suggested that ingestion of cantharidin may decrease luteal steroidogenesis, and the decline in luteal P(4) levels may disrupt reproductive functions in humans as well as animals.

Soldiers may encounter the blister beetles (Meloidae or Oedemeridae) when working outdoors. Indeed, there are numerous examples of cantharidin affecting military operations. Oedemerid beetles had caused blistering among troops in New Zealand (Christmas et al., 1987). A large number of French Legionnaires were hospitalized in Algeria for cantharidin poisoning after eating frogs that had ingested meloid beetles (Eisner et al., 1990). A case of reckless 23-year-old soldier eating a blister beetle (*Berberomeloe majalis*) was reported. Six hours later he had suffered from abdominal pain, dysuria, gross haematuria with clots, hypotension, fever and renal insufficiency (Cotovio et al., 2013).

3.2 Toxicity and clinical symptomatology

Although some individuals have survived after consuming oral doses as high as 175 mg cantharidin (Oaks et al., 1960), the fatal dose of was estimated to range from 10 to 65 mg (Polettini et al., 1992). In a fatal case of human cantharidin-poisoning, the post-mortem serum from the died patient was found to contain cantharidin at a concentration of 72.3 ng/ml whilst the cantharides powder contained 0.87% cantharidin (Hundt et al., 1990). Although the median lethal dose (LD50) was determined as approximately 1mg/kg (Matsuzawa et al., 1987), Binder (1979) and Wanless (2001) reported that is about 0.5 mg/kg body weight, with a dose of as little as 10 mg being potentially fatal in human. The ingestion of blister beetle by spur-winged geese (Plectropterus gambensis) was that their flesh is toxic. Eating one can-apparently-result in death (Wanless, 2001).

Oral ingestion of cantharidin can initially cause damage to the epithelial lining of the gastrointestinal and urinary tract, and may also cause permanent renal damage (Binder, 1979; Honkanen, 1993) as well as liver intoxication (Zou et al., 2002). Acute renal damage after cantharides poisoning was, however, documented as long ago as 1913 since Pearce (1913) described the physiological disturbances of kidney function by cantharidin as due exclusively to a vascular injury, and in regarding cantharidin nephritis as a pure type of vascular nephritis. Fatalities usually result from renal failure, and severe morbidity can result from injury to the gastrointestinal tract (Karras et al., 1996).

In some cases, sudden death had been reported with no signs of struggle (Schmitz, 1989; Helman and Edwards, 1997). Although the cantharidin poisoning by oral ingestion can be suspected in any patient presenting with unexplained haematuria or with gastrointestinal haemorrhage (Zouvanis et al., 1994), there are several clinical symptoms confirming the cantharidin poisoning. With cantharidin ingestion, a burning sensation of the lips, mouth, and pharynx occurs within minutes (Oaks et al., 1960; Polettini et al., 1992). Blisters form shortly thereafter, leading to dysphagia, hematemesis, and vomiting. Total loss of normal mucosa of the gastrointestinal tract may occur (Oaks et al., 1960). Colic, depression, and decreased appetite are most often related to abdominal cramping caused by the vesicant effects of cantharidin on mucosal surfaces (Shawley and Rolf, 1984; Guglick et al., 1996; Schmitz, 1989; Helman and Edwards, 1997). Damage is dose dependent and is directly related to the amount of fatty food within the gastrointestinal tract at the time of ingestion, as fats and lipids promote absorption (Mallari et al., 1996).

Symptoms of cantharidin poisoning include, also, haematemesis (vomiting of blood), electrolyte disturbance, irritation of the urinary tract result in frequent urination, haematurea (finding blood in the urine), or straining to urinate (Binder, 1979; Guglick et al., 1996; Helman and Edwards, 1997). Lumbar pain, dysuria, proteinuria, hematuria, and renal failure can result (Browne, 1960; Cheng et al., 1990). Coagulopathy (Karras et al., 1996), and a Guillain-Barre-like flaccid paralysis had been reported (Harrisberg et al., 1984; Zouvanis et al., 1994). Also, cranial nerve palsies and fixed dilated pupils were reported. Priapism (continuous erection of the penis), seizures, and cardiac abnormalities are less commonly seen (Karras et al., 1996).

Cantharidin may also cause hypocalcemia and its associated clinical effects including muscle fasciculations, synchronous diaphragmatic flutter, abnormal gait, dysphagia, and abnormal behavior such as aggressiveness or disorientation (Schmitz, 1989; Guglick et al., 1996). Hypocalcemia and hypomagnesemia are consistent findings and can help differentiate cantharidin toxicosis from other causes of colic (Guglick et al., 1996; Helman and Edwards, 1997). Other abnormal laboratory findings can include hypoproteinemia, azotemia, increased creatine kinase activity and hyposthenuria (Shawley and Rolf, 1984; Guglick et al., 1996).

3.3 Physiological activity of cantharidin

It may be important to mention that protein phosphatase type 2A (PP2A) is an enzyme operating in the metabolism of glycogen and involved in the control of cell proliferation, activity of membrane-associated channels and receptors, modulation of protein kinases and phosphataes (Eldridge and Casida, 1995). Moreover, protein phosphatases (PPP) are

an integral part of reversible protein phosphorylation processes that regulate a variety of cell functions including gene transcription, protein-protein interactions, cell cycle progression and apoptosis (Honkanen and Golden, 2002).

Cantharidin binds with high affinity to a protein (Graziano et al., 1988), which was thereafter identified as PP2A (Li and Casida, 1992; Eldridge and Casida, 1995). Biological activity of cantharidin is described as a natural toxin inhibiting the protein phosphatases 1 and 2A, similar to okadaic acid (Ewart et al., 1978; Honkanen, 1993). Subsequent studies revealed that cantharidin functions as an inhibitor of several PPP, family serine/threonine protein phosphatases (PPases), acting as a weak inhibitor of calcineurin (PP2B) and a potent inhibitor of three families (PP1, PP2A, and PP5) of structurally related PPases (Honkanen, 1993; Hastie and Cohen, 1998). Cantharedin action as a protein phosphatase inhibitor was then confirmed (Knapp et al., 1999; Wang et al., 2000; McCluskey and Sakoff, 2001; Honkanen and Golden, 2002; Huh et al., 2004; Thaqi et al., 2010; Bajsa et al., 2011).

For more details, some structural studies revealed that the cantharidin-sensitive PPases share a common catalytic mechanism (Swingle et al., 2004), and structure/activity relationship studies indicated that cantharidin act to inhibit the catalytic activity of the same family of PPP (Buck et al., 2003). The cantharidin binding site was identified in liver (Graziano et al., 1987) and other tissues of the mouse including heart, kidney, lung, pancreas, skin, spleen, brain, blood and stomach (Graziano et al., 1988). At the cellular level, cantharidin disrupts the metaphase alignment of chromosomes and produces a prolonged mitotic arrest, with the onset of apoptosis occurring before the onset of anaphase. The role of cantharidin-sensitive phosphatase to prevent the onset of apoptosis in cells arrested during mitosis was discussed by Bonness et al. (2006).

3.4 Preventive measures and curative treatments

The treatment of cantharidin intoxication is largely supportive because there is no known antidote (Mallari et al., 1996). For oral ingestions, several support measures may be taken. The stomach must be at once emptied, and as thoroughly as possible washed out. Large quantities of albuminous and mucilaginous drinks should be given, warm baths to relieve the strangury, and stimulants if necessary. Activated charcoal may also be administered (Karras et al., 1996).

If possible, the patient should swallow generous quantities of water but must avoid oils, glycerin and fatty foods (such as milk) because they increase cantharidin absorption. Vomiting should not be induced, as oropharyngeal and esophageal damage is increased with reexposure (Mallari et al., 1996). Cardiovascular, respiratory and renal failure are all managed using standard principles (Worthley, 2002). Hospitalization may be necessary for supportive care and pain management (Karras et al., 1996).

CONCLUSION

Cantharidin toxicosis in animals had been widely documented but the literature reports on birds are still limited. Cantharidin toxicosis to horses and livestock was sufficiently investigated including causes, pathology, symptomatology, prevention and cure. With regard to human dermatosis, cantharidin had been intensively studied. Nevertheless, the mode of action is still in need of further studies. In addition, curative treatment of human cantharidiasis wass not adequately reported in the available literature. Although cantharidin can be used in diluted solutions for some medications and treatments, such as warts and tattoos, it has several medical risks. Therefore, it has been included in a list of "problem drugs" used by dermatologists and emergency personnel. Also, it is illegal to sell it (or use) in many countries.

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