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**Review article**

# Human dermatosis caused by vesicating beetle products (Insecta), cantharidin and paederin: An overview

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## Abstract

Three major families in the order Coleoptera have been found to produce vesicant toxins, Meloidae (true blister beetles) and Oedemeridae (false blister beetles) produce cantharidin and Staphylinidae (rove beetles) produce paederin. Some of the most important distribution, biological and ecological aspects of these beetle families had been studied because of their products cause human dermatitis. The detection, biosynthesis and chemistry of both cantharidin and paederin were discussed. The prevalence of Paederus dermatitis (skin blistering inflammation) in the world was reviewed. Also, the diagnostic characterization, clinical symptoms of dermatitis and conjunctivitis, the mode of action and pharmacological properties of each vesicant product, preventive measures and curative treatments of the human dermatitis had been included in the present review. 

**Keywords:** biosynthesis, conjunctivitis, endosymbiont, Meloidae, Oedemeridae, Staphylinidae, toxicity, symptom.

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## Introduction

The order Coleoptera constitutes almost 25% of all known life-forms [1]. The available literature contains information on the development, biology, morphology, epidemiology and control of Coleoptera of medical importance [2]. Ill-effects of Coleoptera range from the immediate trauma of a bite to the effects of the vesicating beetles and also the acute corneal erosion that is attributed to the small beetle *Orthoperus* sp. (family Corylophidae). Other effects are, also, known as a result of beetle metabolites or structures, such as "carpet beetle dermatitis" from the irritating hairs of *Anthrenus* larvae (family Dermestidae), and inhalational asthma from beetles, notably the grain weevil *Sitophilus*, the causative agent of certain cases of grain-worker's asthma. The medical significance of the vesicating darkling beetles (family Tenebrionidae) has been reported [3-6]. The human dermatitis was, also, reported for the tiger beetles (family Cicindelidae) but the mechanism by which the beetles provoke skin symptoms is still a matter of debate [7]. Also, tiger beetles had been reported to cause ocular damage and conjunctiva [8]. In addition to these beetle families, contact with other beetles of family Dermestidae can produce a variety of skin disorders such as dermatitis, vesicular, pustular and vasculitic lesions. Also, there may be pruritus, desquamation and papular urticaria [9, 10].

In Coleoptera, only Meloidae, Oedemeridae and Staphylinidae are the beetles releasing vesicant known chemicals, the first two release cantharidin and the latter releases paederin [11]. Cantharidin is among the most widely known insect natural products [12, 13]. It usually attracted a great attention of many investigators and research institutions because of its toxicosis for 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 [14-25]. Paederin is a vesicating agent found in the haemolymph of the *Paederus* genus. It differs from cantharidin, in its chemical and biologic properties [26]. The paederin manufacture is largely confined to adult female beetles. Larvae and males only store paederin acquired maternally (i.e., through eggs) or by ingestion [27].

Human dermatitis is widely reported in the world after contact with the coleopterans in three major families, Meloidae, Oedemeridae and Staphylinidae [28-30]. Bullous lesions are produced when the active ingredient cantharidin is released at the time the beetle is crushed or rubbed upon the exposed skin within hours [31, 32]. Cantharidin can cause severe skin blisters, especially when the insects discharge it from their junctions as a defense measure or get crushed on a human body [33, 34]. Cantharidin in both sexes of *Oedemera podagrariae ventralis* (Oedemeridae) was found in an average of 3.89 µg/beetle in males and 21.68 µg/beetle in females, which are amounts sufficient to irritate human skin [35]. Christmas et al. [36] described seventy-four New Zealand Army personnel with a distinctive bullous dermatosis caused by an endemic beetle *Thelyphassa lineata* (Fabricius) (Oedemeridae) as the first reported cases. Paederus dermatitis (PD) is a blistering inflammation caused when the *Paederus* beetles are accidentally crushed on the human skin [37].

The present review primarily deals with the human skin dermatosis caused by cantharidin or paederin and secondarily is interested in the major three families producing these vesicating chemicals, Meloidae, Oedemeridae and Staphylinidae.

## 1. Major Beetle families responsible for human dermatosis

### 1.1. Cantharidin-producing beetles

Family Meloidae (true blister beetles) is virtually cosmopolitan but absent only from New Zealand, Antarctica and most Polynesian islands [38-43]. They primarily occur in temperate steppic and arid regions, and in sub-tropical and tropical savannas or other open habitats [44]. Different biological aspects of this family had been reviewed by Ghoneim [45] as well as various agronomic and biodiversity impacts of these beetles had been reviewed by Ghoneim [46]. These beetles are commonly known as "oil beetles" because the adults 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" which acts naturally as an aphrodisiac for adult males and females (for review, see Ghoneim, 47). It is surprising that the larvae manufacture and accumulate cantharidin as they feed and grow in size. 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 [48].

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 [49]. 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 authorities have coined the name pollen-feeding beetles [49]. The available literature contains several reported works on the distribution and systematics of the family Oedemeridae in the Old World regions and countries, such as Russia [50], southeastern China [51], Japan and Taiwan [52], Korea [53], Iran [35], southern Africa [54,55], tropical Africa [56], Socotra Archipelago (in the northwest Indian Ocean)[57], Iberian peninsula [58], eastern Mediterranean region [59], Greece [60], Latvia [61], Bulgaria and Turkey [62, 63], Sweden [64], and some other regions [65-68]. 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 [69], Kriska [70], Majka and Langor [71], Webster et al. [72] for Canada; Blackwelder [73], Lawrence and Newton [74] and Patrice et al. [75] for Central America and South America; Paula [76] for New Zealand; and Arnett [77] for some other regions and countries.

Cantharidin detection and quantitative determination in different species of Oedemeridae had been studied [35, 78-81]. Since most adults of Oedemeridae are soft-bodied flower feeders it is thought that they employ the cantharidin to deter potential predators [70]. Although there are few references in the medical literature, blister beetle dermatosis caused by oedemerids may be more common and widespread than currently recognized [26]. From a public health standpoint, some of the blister beetles swarm during certain seasons and the large numbers of them pose a considerable threat [82] because they exudate droplets of haemolymph which produce blistering on contact with human skin [15].

**1.2. Paederin-producing beetles**

The family Staphylinidae (rove beetles) currently comprises 3,847 genera and 56,768 species throughout the world [83]. The distribution and systematics of Staphylinidae had been studied in different parts of the Old World such as China [84, 85], Turkey [86, 87], South Africa [88], Madagascar [89, 90] and Australia [91]. On the other hand, some works had been carried out on the distribution and/or systematics of Staphylinidae in several parts of the New World [92-99]. Staphylinid beetles are completely harmless though their habits make them unappealing. They are found in or near decaying organic matter, especially dead animals. They have the interesting (though unpleasant) habit of feeding on other insects such as fly maggots that infest carrion (less often dung or fungus) [100]. Dekeirsschieter et al. [101] reported the monitoring of the presence of adult rove beetles on decaying pig carcasses during early spring in urban, forest and agricultural biotopes of Western Europe.

From the medical point of view, only three different genera can cause PD: *Paederus*, *Paederidus,* and *Megalopaederus* [102]. Although the genus *Paederus* includes several hundred species, it is believed that only 20-30 of them can cause dermatitis [104]. The genus *Paederus* is widely distributed in the world, especially in all temperate and tropical continents, north and south of the equator [105]. There are no species of *Paederus* in Antarctica [106]. The genus *Paederus* includes more than 622 species [103, 107-109] and is represented in the Palaearctic region with approximately 85 species or subspecies [110]. Among the species living under moist conditions, some have attained their life cycle according to seasonal variations [111]. Temperate-zone species may have a single annual breeding season in the warmer months, but in tropical species timing of the breeding season appears to depend upon rainfall seasonality. Widely distributed species with a broad latitudinal range seem to be multivoltine, with more generations at lower latitudes [106]. Species living in temperate regions may have a single breeding season only in the hot months, but in tropical areas the breeding season depends upon rainfall. The faunal diversity of this genus, especially in the Iranian fauna **,** was reviewed [24]. The adult beetle does not bite or sting, but accidental brushing against it or crushing it over the human skin provokes the release of its coelomic fluid, which contains a strong blistering chemical, paederin [112].

*Paederus* beetles are usually bicolourous, black or blue and red, sometimes entire body is black or blue or even reddish. Because of the medical and predatory importance of *Paederus*, the life history had been studied. In some studies of *Paederus*, life history had been conducted to know its predatory potentials by using different pests as a prey [106] and some researchers studied its life history by providing artificial diets [113]. Nasir and Akram [114] studied its life history by providing natural conditions (aphids as food) in the laboratory. In the field, eggs are laid on moist substrate singly and are in danger of desiccation. The larval instars are predatory as do adults in moist habitats. A female laid more number of eggs in moist soil rich in organic matter but very few in dry sandy and clay soil [115]. As reported by Laba and Kilin [116], the larval and egg stages of *Paederus fuscipes* Curtis were 9.2 days and 3.8 days, respectively. The adult longevity was 113.8 days for females and 109.2 days for males. The total number of eggs laid was 106 eggs. Incubation period of egg was 4 days. In the laboratory, eggs hatch at about 14 days. Larvae are whitish with black markings [117]. Pupation occurs in earthen cells [34, 118, 119].

The presence of large numbers of the rove beetle *Paederus alfierii* Kock in Egypt, due to the less use of insecticides for cotton pests, is the cause of PD [120] and this beetle flies to the residential buildings being attracted by bright lights. However, it cannot fly for a long distance unless being disturbed by a provocative like smoke arising from the burning dry remains of rice in the intermediate area of cultivable land [121].

The rove beetle *P. fuscipes* is commonly known as the 'Beetle Tomcat' because its shape looks like an American fighter aircraft, TOMCAT. It is common and widely distributed insect throughout the world, except America, since it is recorded in Europe, North and central Africa, Asia, New Guinea, Australia, India, Pakistan, etc. In Italy, *P. fuscipes* lives in the cultivated maize fields, hence the common use of the term "the maize field wildfire" to indicate the dermatitis provoked by this beetle [122, 123]. Some bioecological aspects of *P. fuscipes* were studied in the north-west parts of Mazandaran province (Iran) by Abbasipour [124]. It appears in May and lasted until October and they spent 6-8 months in hibernation according to different localities. The daily and seasonal activities were recorded. The seasonal outbreak of PD, in Permatang Pauh, Malaysia had been described [125]. Huge paddy field areas and high amount of rainfall are the main factors increasing *P. fuscipes* density and PD cases. In Malaysia, also, Bong et al. [126] investigated the life history characteristics of *P. fuscipes* under laboratory conditions using three field strains. The total developmental time of immature stages differed significantly among the three strains. Nasir et al. [127] investigated and related *P. fuscipes* assemblages to cultivated soils and forest parameters of the Punjab, Pakistan during 2008-2009. It was mainly recorded from maize (*Zea mays*) and clover (*Trifolium alexandrinum*) crops due to presence of soft bodied insects. It preferred damp soil rich in organic matter for egg laying under natural conditions. As reported by Caroline [100], the net reproduction rates ranged from 40.09 ± 7.39 to 42.34 ± 8.25 offspring. The rove beetles *Paederus ilsae* (Bernhauer) and *Paederus iliensis* (Coiffait) were identified in the central and western parts of Fars province, Iran. The adults have 5 months activity in average, begin lately in April and then continue until early September; soon afterwards they endure the inclement climate. This over wintering period takes 6-8 month long according to the region [128].

With regard to the ecological and behavioural patterns of *Paederus* beetles, the adults and larvae often live in damp environments [129]. Unlike most staphylinid adults, which avoid daylight, *Paederus* adults are active in the open in daylight. However, flight seems largely restricted to nights of high temperature. Adults of some species are wingless, and in other species adults show individual variation in wing length [106]. The population of *P. fuscipes* was observed under the heaps of leaves to conserve temperature and to keep the habitat wet [130]. In Punjab (Pakistan), *P. fuscipes* was found of its maximum population from grasses near water, from vegetable land and from those crops which had soft bodied insect pests like aphids, mites, leaf hoppers on them [124, 127, 130]. The results of a field study indicated that there was a positive correlation between decaying organic matter (especially dung), soil moisture contents and *P. fuscipes*'s population. This difference was due to biotic factors such as different crops and abiotic factors such as use of pesticides, temperature and soil moisture contents [131, 132]. Seasons also affect the population, e.g. by rain fall [34]. The seasonal effect of moonlight on the vertical distribution of *P.* A*lfierii* was studied in Qena (Egypt) during two years (1982-83). Moonlight had no significant influence on flight activity in any one season at 1.5 m and at 18.5 m its influence was negligible, even when both years were combined [133].

The *Paederus* adults are active during the day and are attracted by incandescent and fluorescent lights at night, which can bring them into contact with humans [106, 134, 135], especially in tropics and some temperate countries [114]. Black ray was most attractive to the adult beetles and they showed highest daily activities between 21-22 hours at night in Iran [124]. The fluorescent lamp usages at night and accommodations that permit *P. fuscipes* entrance into buildings had contributed to PD incidence in Permatang Pauh, Malaysia [125]. Light had attractive effect on *P. fuscipes*, so maximum activity was observed in the Punjab (Pakistan) during night. Its activity was greatly influenced by light and soil moisture contents [127].

### 1.3. Beneficial *Paederus* beetles in agriculture and medicine:

It may be important to mention that *Paederus* beetles are beneficial insects because they are carnivorous and eats smaller pests. Large populations of *Paederus* spp. had been recorded from agricultural habitats which make them beneficial due to their feeding on insect pests of major crops, particularly insect pests like the rice moth *Corcyra cephalonica* (Stainton) (Lepidoptera: Galleriidae), the cotton bollworm *Helicoverpa* (=*Heliothis*) *armigera* (Lepidoptera: Noctuidae), the cotton aphid *Aphis gossypii* Glover (Homoptera: Aphididae), the spotted bollworm *Earias vittella* (Fabricius)(Lepidoptera: Noctuidae), the cotton leafworm *Spodoptera litura* (Fabricius) (Lepidoptera: Noctuidae), the rice leaffolder *Marasmia patnalis* Bradley (Lepidoptera: Pyralidae), the soybean aphid *Aphis glycines* Matsumura (Homoptera: Aphididae), fruitfly and many other dipterous and other arthropods [119, 135,136].

As natural predators, *Paederus fusca* is well known in the rice fields of Southeast Asia, *Paederus crebinpunctatis* and *Paederus sabaeus* Erichson occur in East Africa, as well as *P. cruenticollis* is important in Australia. In Indonesia, naturally occurring populations of *P. fuscipes* play an important role in suppressing the soybean aphid. As many as twenty-two different species of prey were predated upon by the predator *P. fuscipes* when offered in the laboratory [137]. In Indonesia, also, *P. fuscipes* is an important predator in soybean fields, including toward *Helimverpa armigera* [138]. The latter authors indicated that population of this natural predator in soybean field were very complex and potential to be used for control the pest populations. In New Delhi (India), the bionomics, predatory potential, field population levels and seasonal incidence of the predator *P. fuscipes* were studied. This predator had a feeding potential of 0.6 rice leaf folder larvae per individual per day and thus it is an effective predator [139]. Liu and Zheng [140] conducted a study on the predation of *P. fuscipes* on the turnip aphid *Lipaphis erysimi* (Kaltenbach)(Homoptera: Aphididae) and interference with each other. When *P. fuscipes* density grows up, its predation to *L. erysimi* is going to decline. They affect each other. Padmavathi et al. [141] investigated the prevalence, prey preference and predatory potential of *P. fuscipes* in rice. This predator preferred brown planthopper and white backed planthopper nymphs to other prey species tested. In Egypt, Tawfik et al. [142] reported the rove beetle *P. alfierii* as common insects in the fields of maize, cotton and clover. It has a great agricultural benefit as a predator of aphids. The occurrence of *P. alfierii* adult beetles in maize, cotton and clover fields in Giza seemed to follow a certain seasonal succession. Such succession appears to be closely related to the seasonal abundance of their different preys on these crops [143]. Shebl et al. [144] found *P. alfierii* as one of the most common natural enemies associated with pests in alfalfa fields in some parts of Egypt. Field data revealed that *P. alfierii* was found as one of the common insect predators in the fields of Egyptian cotton [145, 146] and of soybean fields [147]. Also, *P. alfierii* was observed among the natural predators of soft scale insects in Egypt [148, 149]. *P. sabaeus* was among the natural predators recommended for controlling the rice yellow mottle virus vectors in some sites of northern Cameron [150]. Thus *Paederus* beetles play an important role as a biological control of insect pests [100]. In addition to its role as a biological control agent, *P. fuscipes* decomposes the organic matter in the soil and hence increases the fertility of soil through recycling of nutrients [127].

Influenced predatory potential of *Paederus* spp. by some of the commonly used insecticides has attracted the attention of some researchers in different parts in the world. Yoshisato [151] evaluated the contact toxicity of several insecticides against *P. fuscipes* under laboratory conditions. It was observed that lindane was most toxic and then DDT. Beta-cyfluthrin was found to be the least toxic to *P. alfierii* and other tested natural enemies of the silverleaf white fly *Bemisia tabaci* (Gennadius) (Homoptera: Aleyrodidae) on cotton in Assiut (Egypt) [152]. A laboratory experiment was conducted by Devi et al. [153] to evaluate the toxicity and residual toxicity of some common insecticides against *P. fuscipes* adults. Their results revealed that neemarin and biorin did not show any toxicity whereas cypermethrin, endosulfan, metasystox and fenvalerate proved highly toxic to this predator. Under laboratory conditions, Meng and Zheng [154] studied the mortalities and effects of bisultap on the predatory function of *P. fuscipes*. The experimental results indicated that the pesticide bisultap has less effect on mortality and predatory function of *P. fuscipes*, but the effects on predatory function of survival individuals are stronger than that on lethality. Using the soaking technique under laboratory conditions, Wang [155] determined the inflict casualties of five kinds of common pesticides on *P. fuscipes*. The results of bioassay showed that: toxicity of 10% chlorpyrifos plus deltamethrin was the strongest, 40% omethoate was the second strongest, 22% imidacloprid plus buprofezin and 50%phoxim plus fenvalerate were comparatively weak, and that of 18% bisultap aqueous solution was the weakest.

From the medical point of view, paederin (the *Paederus* secretion as will be discussed later on) has suppressed cancerous tumors in mice, rats, and plants, has stimulated regeneration of damaged tissues, has healed chronic, necrotic lesions in geriatric patients, and has induced cell fusion in human skin fibroblasts [106]. Paederin is important in cancer and cellular biology [156]. It is worth pointing out that some other agents had been identified and purified from certain *Paederus* beetles. Pavan [157] seems to be the first who dealt with its biological activity, by working on possible influence of paederin derived from *P. fuscipes* on tumor fragments. He reported that 'paederin' reduced or completely prevented tumor growth and that it acted as an antimitotic, provoking chromosomal alterations and blocking the formation of the spindle at metaphase. Hisada and Emura [158] carried out a cytological study on the antitumor action of paederin, use being made of crude methanol extract from *P. fuscipes*. The extract exerted a considerable influence upon both interphase and mitotic cells, inhibiting mitosis.

Much research has been focused on antimicrobial peptides derived from insect immune defense reactions due to their potential in the development of new antibiotics. Using the gel filtration and reverse-phase high-performance liquid chromatography, Memarpoor-Yazdi et al. [159] identified and purified a new antimicrobial peptide from *Paederus* spp., named sarcotoxin PD which had broad-spectrum inhibitory effects on the examined microbes (bacteria and fungi). The authors suggested the role of sarcotoxin Pd in the treatment of systemic microbial illnesses.

## 2. Beetles' vesicating products

### 2.1. Cantharidin

Generally, autogenous producers of cantharidin ($C_{10}H_{12}O_4$) (haemolymph exudation through leg joints or/and antennal pores) occur exclusively within the coleopteran families of Meloidae [13, 48, 161, 162] and Oedemeridae [26, 78, 79, 80, 163, 164] in which it occurs in the haemolymph and other tissues [38, 39, 40, 165]. Cantharidin 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 [166]. It is highly toxic to a wide variety of animals, including birds, amphibians and mammals [13].

It was suggested that cantharidin might be used by the beetle female when selecting a mate at close range [12]. 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 [167]. Cantharidin production varies widely depending not only on the species but also on the sex, time of year and food source [40] as well as the mating status [48]. 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. [168].

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) [169] and/or by some species of Miridae (Heteroptera) [170]. 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 [47], cantharidin is considered responsible for the repellent properties of meloid haemolymph against a wide variety of predators.

Although the cantharidin biosynthesis in the blister beetles had been studied by some researchers [48,171,172], 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* [173].

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 [174]. Under laboratory conditions, Wang et al. [175] 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.

### 2.2. Paederin

As aforementioned, paederin is a vesicant toxic agent found in the haemolymph of the *Paederus* genus. It differs from cantharidin **,** in its chemical and biologic properties [26]. The paederin manufacture is largely confined to adult female beetles. Larvae and males only store paederin acquired maternally (i.e., through eggs) or by ingestion [27]. On the other hand, some authors reported only small quantities of the toxin (0.1 to 1.5 µg) in the adult males, while females present up to ten times more paederin (0.2 to 20 µg). Females, themselves, can also be divided into two groups according to the paederin proportion [123]. Positive (+) females predominate in every generation, whereas the negative ones (-) are the minority. So, there is a polymorphism in hemolymph toxin of *Paederus* beetles. Paederin polymorphism is another factor that must be considered in the provocation of linear dermatitis, since positive females constitute most of the *Paederus* population [100]. In the *Paederus* beetles , paederin serves as a chemical defense against predators such as spiders [118] which has not been correctly demonstrated [100].

It has been demonstrated that the paederin is produced not by the beetles themselves but relies on the activities of some species of endosymbiont bacteria within the beetle. According to 16S ribosomal DNA data, only these paederinsynthesizing females harbor a bacterium with the closest relationship to *Pseudomonas aeruginosa* (Schröter) (Pseudomonadales: Pseudomonadaceae) [176]. Not all species of the genus *Paederus* contain endosymbiotic bacteria and uninfected beetles do not produce paederin [177]. Paederin circulates in the haemolymph of a beetle, so it can be carried over to the offspring (egg, larva, pupa, and beetle). For some details, adult females that are infected with endosymbiotic bacteria produce eggs containing the bacteria in the outer shell walls. Subsequent generations of beetles acquire these endosymbiont bacteria by ingesting some of the 'infected' egg shells or by cannibalizing larvae containing the bacteria [27, 34]. If eggs of such beetles are fed to nonproducing females, paederin is again synthesized in their offspring [178].

Piel et al. [179] had sequenced an extended region of the symbiont genome to gain further insight into the biology of this as-yet-unculturable bacterium and the evolution of paederin symbiosis. Their data indicated that the endosymbiotic bacterium *P. aeruginosa* acquired several foreign genetic elements by horizontal gene transfer. Besides one functional tellurite resistance operon, the region contains a genomic island spanning 71.6 kb that harbors the putative paederin biosynthetic genes. Costa-Sá et al. [180] focused on a search of *Pseudomonas* species and functions of amino acid sequences in the paederin family. They had a better understanding of amino acids paederin cluster and its related functions with the likely *Pseudomonas* species providing that new insights emerge of these genes and proteins to delineate molecular targets for future development of pharmacologically active products.

Chemically, paederin ($C_{25}H_{45}O_9N$) is a toxic amide with two tetrahydropyran rings. It depends on the beetle species and may be one or a combination of several similar molecules including paederone and pseudopaederin [106, 181]. Paederin and several analogues had been prepared through an efficient route that proceeds in ten steps (longest linear sequence) from isobutyraldehyde [182]. Paederin has been synthesized and, in pure form, is a crystalline amide soluble in alcohol and water [100].

Concerning the toxicity, paederin is a potent vesicant toxic, more potent than cobra venom. The toxic effects of paederin were unknown to Western medicine until this century, but they were known to Chinese medicine 1,200 years earlier [106, 114]. It is more toxic externally and internally to rabbits, rats, mice, and guinea pigs than to hedgehogs, chickens, frogs, and toads. It is not known to be toxic to insects, is not attractive to insects, and has little effect against bacteria [183]. It is worthy pointing out that paederin is of natural products with potent antitumor and antiviral activities [184].

## 3. Prevalence of Paederus dermatitis in the world

Although blister beetles are recorded causing human dermatitis, due to their cantharidin [185], meloid or oedemerid dermatitis is not as widespread as PD and remains a minor rural health problem [11]. The dermal effects of paederin from staphylinid beetles have received several names in different countries, but the widely applicable name is linear dermatitis or dermatitis linearis and some of the preferred names are PD and blister beetle dermatitis [108,186]. The irritant contact dermatitis can be caused by the settlement of or accidentally crushed *Paederus* beetles against the skin [187], releasing the paederin [11]. Wet and sticky skin may facilitate local penetration of insect toxins and therefore enhance deleterious effects in use [188,189]. However, *Paederus* species may cause linear lesions [190, 191] and the so-called "kissing lesions", due to the contact between two peculiar skin surfaces, as for example the creases of axillae and elbows [122, 187]. Epidemics caused by *P. sabaeus* is called "bruleuses" in Guinea [191], "skirt and blouse" in Southern Nigeria [190, 192], in Uganda [193], "rove beetle" in South West Africa or the "escaper" in several African countries [142,194], as well as “panchos” in Mexico [195].

PD has been spread in different parts of the world and outbreaks were reported in various countries including Australia [4,196, 197], Japan [198, 199], China [155, 200, 201], Malaysia [3, 125, 126, 202, 203], Korea [204, 205, 207], India [11, 207-211], Sri Lanka [5, 212, 213], Pakistan [214], Iran [34, 103, 128, 215, 216], Iraq [217], sub-Saharan Africa [218], Central Africa [219], Nigeria [190, 220, 221], Tanzania [222], Guinea [191, 223, 224], Uganda [193], Gambia [225], Kenya [217, 226], Sierra Leone [106, 227], Congo [228, 229], Malawi and Namibia [194], South Sudan [230], Egypt [188, 231], Italy [122, 123], France [232, 233, 234], Turkey [202, 235, 236, 237], United States of America [238], Brazil [28], Venezuela [239], Venezuela [240, 241], Mexico [195], Argentina [242], Peru [243], Ecuador [244] and some other countries of Latin America [245].

Skin disorders and dermatitis had been documented among persons in military units or troops in different parts in the world [246, 247, 248, 249]. Christmas et al. [36] described seventy-four New Zealand Army personnel with a distinctive bullous dermatosis caused by an endemic beetle *Thelyphassa lineata* (Fabricius) (Oedemeridae) as the first reported cases. PD was reported in a military unit training in the Arizona desert (USA) during heavy rain and flooding [238]. The first report to an outbreak of PD among U.S. personnel deployed to Pakistan was described. Up to 10% of the base population was afflicted with a pustular eruption and an accompanying halo of erythema [214]. *P. sabaeus* was responsible for a widespread occurrence of PD in United Nations (UN) troops posted in Congo [229].

## 4. Clinical Symptoms of human dermatitis and conjunctivitis

### 4.1. Dermatitis

Cantharidin signs and symptoms usually begin within 12 to 24 hours, which is sooner than paederin's effects (Alexander, 1984) while some authors pointed out that a slight redness of the affected areas within the first 12-24 hours is usual in PD [106, 193, 250]. Another difference is that victims usually remember coming into contact with Meloid or Oedemerid beetles because of their large size. Many victims are not aware that *Paederus* were ever crushed on their skin because of their small size and the delayed onset of blistering [82]. In addition, Singh et al. [251] noticed that signs of blister beetle dermatitis practically appeared on most of the patients in early morning after sleep [108] and Padhi et al. [252] reported the same observation.

With regard to the diagnostic features, it is difficult to differentiate PD from other inflammatory skin conditions, without prior experience of managing the infection. The uncommon association of acute dermatitis with minimal or no complaints, which would be noteworthy in the case of chemical or thermal burns, facilitates diagnosis which is corroborated by the season and by the case history [253]. History, predilection for exposed parts, linear nature of primary lesion and presence of kissing lesions are important clue for diagnosis [209]. Capture of the insect, epidemiologic features and a high clinical suspicion can aid in making the correct diagnosis of PD [245].

The common symptoms of PD are skin lesions as well as respiratory, eye or skin allergies that are caused by contact with *Paederus* beetle haemolymph and/or toxic secretions, hairs or frass of larvae [106, 254, 255]. Different responses are seen in the skin depending upon the paederin concentration, duration of exposure, and individual characteristics [250]. In mild cases, there is a slight erythema lasting for a couple days. The erythema is followed by a squamous stage when the blisters dry out over a week, and then a stage when they desquamate, leaving hyper- or hypopigmented patches. The lesions are characteristically linear due to smearing the crushed insect across the skin [118]. As recorded by Assaf et al. [231], blisters caused by the rove beetle *P. alfierii* exhibited a linear configuration in 40% of the patients and kissing lesions were observed in 13%. Multiple lesions occurred in 78% of the patients. The onset of blister formation was reported on the 2-4$^{th}$ day followed by pain [256]. The blister formation may be a response to serine proteases and neutrophil elastase released in response to paederin [257, 258]. Following blister formation there is the appearance of linear lesions (that look like whip injuries) and are also known as mirror image or kissing lesions [239]. Severe cases may demonstrate additional symptoms, such as fever, neuralgia, arthralgia, and vomiting [118, 250].

Concerning the affected parts of the human body, PD symptoms appeared over the exposed areas, usually face, neck and upper extremities [5, 11]. In a study, the most common location of rash was the neck and face (31%) and so hand (30%) but in other studies, the face was the most commonly involved site [231] and the trunk was the least common site [216]. As observed by Ahmad et al. [125] in Malaysia, face and neck were found to be the most frequent sites of PD.

### 4.2. Conjunctivitis

As previously mentioned, skin blistering by *Paederus* beetles most often occurs on exposed skin of body parts such as the neck, face, arms, and legs where a beetle is felt crawling on the skin and subsequently crushed. On the other hand, paederin is sometimes transferred to other sensitive areas of the body such as eyes or genitals by paederin-contaminated hands [259] as reviewed herein.

Conjunctivitis results from transferring the toxin of crushed beetles by finger to the eyes as a secondary infection [5, 103, 190, 223, 260]. These ocular and periocular lesions in the conjunctivae and eyelids are commonly known as "Nairobi eye" in east Africa [82, 261] caused mainly by the rove beetles *P. sabaeus* [262] and *P. fuscipes* ("spider lick")[263].

Some attention had been paid to the human conjunctivitis as caused by *P. crebipunctatus* [264]. In India , the commonest insect causing Ophthalmo-dermatozoosis is *P. fuscipes*. In the eye-lids, there may be oedema and tenderness. Occasionally there may be conjunctival hyperemia, chemosis and corneal abrasion [265]. Cases of *Paederus basalis* Bernhauer dermatitis were reported among people of rural areas of Saharanpur and Haridwar districts (India). In the case of infection on eye, odema of eyelid develop and acute conjunctivitis occurs. Eyelids get swollen and eye is closed [210]. Verma and Gupta [266] reported some ocular manifestations due to the rove beetle *P. sabaeus*. Morsy et al. [267] proved experimentally that an extract from *P. alfierii* causes conjunctiva in 75% of used mice. Hashish [188] recognized periorbital dermatosis in people inhabiting the surrounding area of Tanta (Egypt) as caused by *P. alfierii*. He concluded that contact of cornea with paederin from this beetle explained the superficial punctate keratitis and might explain sub-conjunctival hemorrhage or the hemorrhage might be attributed to excessive rubbing of the eye, i.e. mechanical. In a number of patients, clinical findings on the eyelid skin were observed by Canan et al. [268] as erythematous patches and plaques with multiple pustules, erosions and bulla remnants on an erythematous base, squamous and crusted patches and plaques, and erythematous patches. However, conjunctivitis from *Paederus* is rare in the world [269].

## 5. Mode of action of cantharidin and paederin

Cantharidin is absorbed by the lipid layers of epidermal cell membranes. Application of cantharidin onto the epidermis results in the activation or release of neutral serine proteases that cause degeneration of the desmosmal plaque, leading to the detachment of tonofilaments from desmosomes. This process leads to acantholysis and intra-epidermal blistering, and nonspecific lysis of skin [270]. Lesions heal without scarring, as acantholysis is intra-epidermal [271].

Paederin is a toxic alkaloid, vesicant capable of blocking the mitosis at levels as low as 1 ng/ml, by inhibiting protein and DNA synthesis without affecting RNA synthesis [106, 272], so it prevents the cell division leading to cell death [27]. Histopathological examination of the blister area caused by *P. alfierii* or *P. basalis* revealed features of acute irritant dermatitis in the upper epidermis. Mitotic figures and apoptotic changes such as chromatin condensation and DNA fragmentation were identified in the basal and suprabasal layers [210, 231]. Additionally, foci of acantholysis attributed to the release of epidermal protease have been reported [250]. On the other hand, Caroline [100] hypothesized the transference of endosymbiotic *Pseudomonas* from the beetle to the skin and continues to produce paederin which then leads to the symptom of dermatitis.

## 6. Preventive measures and curative treatments of dermatitis

*Paederus* beetles can be prevented by increasing public awareness [273]. They do not enter houses if the windows and doors or ventilation openings are covered with mosquito netting. The beetle usually prefers the bright lights at night, so turning off the lights at night while sleeping or decreasing use of artificial lighting and avoiding fluorescent lights may be useful [230, 245]. If a *Paederus* beetle lands on the skin, it should be blown off and the area in contact should be immediately washed with soap and water [274]. Also, simple preventive measures include an insect repellant cream on exposed parts of the body at night [209]. Ghaffari et al. [275] investigated the repellency effect of the neem oil (*Azadirachta indica* Juss), as a personal protection method against *Paederus* beetles. The results showed that protection produced by Neem oil at 2.5, 5 and 10 % dose was 46.2, 69.3 and 84.62 %, respectively. If the beetles are found on the skin, brushing them off, rather than crushing them, avoids producing PD [230]. The Public Health and Municipal Authorities can control the swarming of rove beetles in residential areas by applying insecticide *via* thermal fogging or target spraying using Pesguard FG 161 (d-tetramethrin 4.4% w/w/ cyphenothrin 13.2% w/w) glue traps, electric insect traps, etc [100].

Cantharidin-caused skin blisters occur on the neck and arms and other uncovered areas of the body as previously mentioned. General handling of adult beetles seldom results in blistering unless the haemolymph contacts the relatively thin skin [32]. There is no known antidote for the cantharidin-caused dermatosis [276]. The blistered site should be cleaned with cool wet soaks [259]. Beta-adrenergic agonists and antagonists inhibited the cantharidin dermatitis [277]. Treatment with acetone, ether, fatty soap, or alcohol helps to dissolve and dilute the cantharidin [278]. Iserson [230] suggested rapid washing the affected area, applying cold, wet compresses, and possibly treating with antihistamines.

In East Africa, local remedies (e.g. toothpaste and mud) are used to treat PD, though all are ineffective. The use of cold compressed magnesium sulphate is replacing older remedies [260]. On the basis of its pharmacological properties, Wang [272] applied Moist Exposed Burn Ointment (MEBO) to treat the PD, and it had proved better than traditional methods for its remarkable analgesic, rapid wound-healing and potent anti-infective effects. Nikookar et al. [279] carried out a study to compare the therapeutic effects of atorvastatin for treatment of PD on an experimental group (15 patients) with the control group (15 patients) received placebo. In West Africa, Qadir et al. [227] studied 50 cases of PD at Sierra Leone aiming to determine clinical patterns of PD and its response to topical steroids, with and without antibiotics. They concluded that the better response to a combination of topical steroids, such as betametasone hydrocortisone1% ointment or other anti-inflammatory ointments, and oral antibiotics may indicate concurrent bacterial infection. In Eastern China, the relationship between the toxin of *P. fuscipes* and PD was studied by Wang et al. [155] who observed severe PD and inflammation of eyes in the experimental rabbits caused by the beetle soaked in 70% alcohol for six months. The toxic effect of the beetle on the skin could be inhibited by storing the beetle at 4℃ for 6 hours before spreading. In Northern Iran, Davoudi et al. [280] investigated the efficacy of fluocinolone cream, triclocarban (TCC) soap and betamethasone lotion in comparison with placebo in the treatment of PD. They concluded that topical corticosteroids displayed a relative and significant improvement in PD. In Northern Iran, also, Nikookar et al. [279] compared the effectiveness of triamcinolone ointment and atorvastatin tablet with placebo in treatment of PD. The results showed both of triamcinolone ointment and oral atorvastatin had similar effect on PD. Because the PD is a self-limited disease use of topical therapy for treatment of the disease is recommend.

After causing PD in the guinea pig, as an experimental animal, the application of potassium permanganate with calamine to heal PD was more effective than fluocinolone treatment. This topical corticosteroid is thus considered less able to avert the cytotoxic action of paederin on the skin than the antipruritic and cleansing agents [281]. Narendhirakannan et al. [282] assessed a new combination of seven medicinal plants against blisters and infection caused by the rove beetle *P. fuscipes*. Further wound healing property of each plant had been determined which shows Neem with high wound healing power followed by turmeric, *Triphala*, African spider plant and wheatgrass.

The use of steroidal topical preparations, pain killers and anti-histamines as beneficial agents had been recommended for the prevention of secondary infections. If there is a secondary infection, removal of irritant, initial washing with soap and water, and application of cold wet compresses followed by steroid and antibiotics should be recommended [5, 103, 187, 190, 209, 223]. Recovery is a slow process and the climatic conditions including high humidity may delay the process of recovery [283]. Recovery occurs within 8-10 days as the lesions dry and dark scales appear [106, 193]. After four weeks the black scales start to peal of, exposing new pink skin. After 6-12 months the scars vanished [283].

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