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Review Article

TOXIC AND IMMUNE ALLERGIC RESPONSES OF ANT VENOM TOXINS: A REVIEW

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ABSTRACT

Present review article explains ant venom components and its allergic and biological effects in man and animals. Red ants or small fire ants secrete and inject venom very swiftly to defend their nest against predators, microbial pathogens, and competitors and to hunt the prey. Ant venom is a mixture of various organic compounds, including peptides, enzymes, and polypeptide toxins. It is highly toxic, allergic, invasive and venomous. It imposes sever paralytic, cytolytic, haemolytic, allergenic, pro-inflammatory, insecticidal, antimicrobial, and pain-producing pharmacologic activities after infliction. Victims show red ring-shaped allergic sign with regional swelling marked with intense pain. Ant venom also contains several hydrolases, oxidoreductases, proteases, Kunitz-like polypeptides, and inhibitor cysteine knot (ICK)-like (knottin) neurotoxins and insect defensins. Ant venom toxins/proteins generate allergic immune responses and employ eosinophils and produce Th2 cytokines, response. These compounds from ant venom could be used as a potential source of new anticonvulsants molecules. Ant venoms contain many small, linear peptides, an untapped source of bioactive peptide toxins. The remarkable insecticidal activity of ant venom could be used as a promising source of additional bio-insecticides and therapeutic agents.

Keywords: Ant, Venom glands, Peptide toxins, Allergens, Immune responses and biological effects

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INTRODUCTION

Ants represent a taxonomically diverse group of hymenopterans (formicidae) with over 13,000 extant species, the majority of which inject or spray secretions from a venom gland. Ants is mostly due to the unique eusociality that has permitted them to develop complex collaborative strategies, partly involving their venom secretions, to defend their nest against predators, microbial pathogens, ant competitors, and to hunt immobilize or kill prey for food, Ant venom contains a range of activities including antimicrobial, haemolytic, cytolytic, paralytic, insecticidal and pain-producing pharmacologies. Worker ants generate about 1.17 µg/day. Ant venom toxins can be used to generate bioinsecticides and therapeutic agents [1]. Members of sixteen ant families possess stinger and inflict toxic venom for defense against predators, competitors and microbial pathogens, as well as for social communication (fig. 1). Hymenoptera venoms, mainly ants secrete natural toxins which could be used to synthesize novel therapeutic agents. Ant secretes toxic venom that shows diverse bioactive molecules. Ant *Odontomachus bauri* crude venom presents several protein bands, with higher staining for six proteins with gelatinolytic activity venom showed high proteolytic activity on azocasein at optimal pH 8.0 and 37 °C. The South American giant ant, *Dinoponera quadriceps* produces proteinaceous venom. Its toxins are polycationic linear toxins which show multiple biological activities such as antinociceptive, neuroprotective and antimicrobial effects. Ant venom is also used for the treatment of asthma, rheumatism, earache and back pain. Venom from *D. quadriceps* shows anticoagulant antiplatelet and anti-inflammatory activities [2].

Ant venom is a rich resource depository of natural compounds with tremendous pharmacological properties. It is also rich in alkaloids and hydrocarbons. It also contains protease inhibitors as aprotinin, leupeptin the venom showed antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli* as well as anti-parasitic activity against *Toxoplasma gondii* [3]. Ant venom contains a range of activities including antimicrobial, haemolytic, cytolytic, paralytic, insecticidal and pain-producing pharmacologies. Worker ants generate about 1.17 µg/day. Ant venom toxins can be used to generate bioinsecticides and therapeutic agents Mass spectrometry techniques revealed that most peptide toxins are small polycationic linear toxins, which show antibacterial and insecticidal activity. The venom of the ruby ant *Myrmica rubra* is a rich source of peptides [4]. The present review explains ant venom toxins from various species, its composition, allergic and toxic effects with important biological activity and therapeutic use.

Source of information

For writing this comprehensive research review on *ant* toxins/ allergens, various databases were searched. For the collection of relevant information, specific terms such as medical subject headings (MeSH) and key text words, such as “ant venom allergens”, “biological and pharmaceutical effects”, therapeutic uses” published till 2021 were used in MEDLINE. *Most specially* for retrieving all articles pertaining to the use of VIT for insect venom allergy, electronic bibliographic databases were searched and abstracts of published studies with relevant information on the venom toxins/allergens were collected. Furthermore, additional references were included through searching the references cited by the studies done on the present topic. Relevant terms were used individually and in combination to ensure an extensive literature search. For updating the information about *a subject* and incorporation of recent knowledge, relevant research articles, books, conferences proceedings’ and public health organization survey reports were selected and collated based on the broader objective of the review. This was achieved by searching databases, including SCOPUS, Web of Science, and *EMBASE*, Pubmed, Swissprot, Google searches” From this common methodology, discoveries and findings were identified and summarized in this final review.

Ant venom composition

Ant species *Odontomachus bauri* cotains six proteins that possess mol wt. e. g. 17, 20, 26, 29, 43 and 48 kDa) its non-toxic fraction is used in chemical communication involving trail and sex pheromones, deterrents, and aggregators. Ant venom also contains several enzymes i.e. hydrolases, oxidoreductases, proteases, Kunitz-like polypeptides, and the less abundant inhibitor cysteine knot (ICK)-like (knottin) neurotoxins and insect defensins. Few of them showed high proteolytic [5]. The venom is 95% water-insoluble alkaloid, with the remaining 5% being an aqueous protein solution. Ant venoms contain a range of monomeric, homodimeric and heterodimeric peptides with one or two inter-chain disulfide bonds possessing pore-forming, allergenic and paralytic actions. The crude venom contains volatile and non-volatile compounds such as alkaloids and hydrocarbons [6]. The fire ant (*Solenopsis invicta)* contains Solenopsin, the alkaloidal

component that is an inhibitor of phosphatidylinositol-3-kinase signaling and angiogenesis [7]. More often, alkaloids in the ant venom causes a sterile pustule at the sting site and show cytotoxic and hemolytic properties [8] (fig. 2).

Ant species belong to family formicinae possess formic acid (methanoic acid) as a predominant compound. By self-grooming their acidopore, *Lasius neglectus* (Formicinae) workers uptake venom into their mouth and spray acid on brood in their colony to inhibit the growth of fungal pathogens [9]. These also contain formic acid, at a concentration of up to 70% (*v*/*v*). It also functions as an alarm pheromone. Both formic acid and acetic acid, work an efficient defensive compounds against competitors and predators, including vertebrates [10]. The major precursors for its biosynthesis are the amino acids serine and glycine [11] (fig. 2).

Over 95% of the venom components are water-insoluble piperidine alkaloids. Piperidines include *trans*-2-methyl-6-n-undecylpiperidines, *trans*-2-methyl-6-n-tridecylpiperidine, *trans*-2-methyl-6-(*cis*-4-tridecenyl) piperidines, *trans*-2-methyl-6-n-pentadecylpiperidine, *trans*-2-methyl-6-(*cis*-6-pentadecenyl) piperidine and 2,6-dialkylpiperidines. The ant venom is possesses *trans*-stereoisomers as specific ingredient [12]. *trans*-2-Methyl-6-n-undecylpiperidine (solenopsin) has been shown to have cytotoxic, hemolytic, necrotic, insecticidal, antibacterial, antifungal, and anti-HIV properties [13]. From *Solenopsis invicta* four protein allergens have been characterized, so far i.e. Sol i 1-4. Of these, Sol i 3, is part of the antigen 5 family, and Sol i 1 is a phospholipase A1B; Sol i 1 shows a close relation with wasp venom phospholipases the protein portion contains the allergens (fig. 2). These proteins also cause anaphylactic reactions in humans sensitive to the venom [14]. The protein portion contains the allergens. The reactions range from immediate localized wheal and flare responses to large, local or systemic reactions.

Anti-inflammatory activity

The crude venom of *D. quadriceps* shows an anti-inflammatory effect in mice and *in vitro* [15]. Ant venoms express surface molecules that participate in antigen presentation involving pro-and anti-inflammatory cytokines. Samsum Ant Venom treatment restores the normal biochemical and oxidative stability by improving the TNF-α/NF-κB mediated inflammation in CCL4-treated rats [16]. SAV-treated animals significantly reduce concentrations of both IFN-γ and IL-17 in comparison with the control group. However, intraperitoneal and subcutaneous SAV-treated rats were able to upregulate the expressions of MHC-II, CD80 and CD86 on PMNs in comparison with the control, respectively [17]. The subcutaneous SAV-treated rats presented decreased levels of glutathione with increased cholesterol and triglyceride levels. SAV also significantly lower down Fas gene expression comparing to the LPS group and restore the level of IFN-γ mRNA expression [18]. Ant venom also removes of CCl4-induced acute liver toxicity in an animal (rat) model (fig. 3).

Anticancer activity

Ant venom contains pharmacologically active compounds that are capable of protein synthesis inhibition, induction of angiogenesis and show apoptosis [19]. Samsum ant venom (SAV) *Pachycondyla sennaarensis* shows anti-neoplastic activity in different cell lines HepG2, MCF-7, and LoVo. It shows the differential dose-dependent antineoplastic effect with an increased level of significant cytokines, including Interleukin (IL)-1β, IL-6, and IL-8 and transcription factor, nuclear factor-kappa B (NF-κB). It can be used to treat certain types of cancer [20]. SAV injection also restore oxidative stability, anti-inflammatory, and show hypolipidemic bioactivity in rats after induced disruption of these parameters by LPS injection [21]. This improvement by SAV was mediated by upregulation of AKT1 signaling in rats at the dose of 100 µg/kg body weight (fig. 3).

Table 1: Showing peptide toxins secreted from various species of ant and its biological effects

S. No.	Ant species	Peptides	Biological activities	Against	References
1.	*Neoponera goeldii*	Ponericins	Haemolytic, antibacterial, insecticidal activity	Gram-positive and Gram-negative bacteria	[1]
2.	*M. rubida*	decapeptide U-MYRTX-MANr1	Insecticidal activity	*Acyrthosiphon pisum*	[4]
3.	*Odontomachus monticola.*	Pilosulin-like peptides	Antimicrobial, hemolytic, and histamine-releasing activities.	Gram-positive and Gram-negative bacteria	[28]
4.	*Dinoponera quadriceps*	sDq-2562 and sDq-3162	Microbicide bacteriostatic and bactericidal effect	antibiotic-resistant bacteria	[31]
5.	*Tetramorium bicarinatum*	bicarinalin	Antimicrobial, antifungal and antiparasitic activities	*Helicobacter pylori,* Staphylococcus and Enterobacteriaceae	[32]
6.	*Odontomachus bauri*	Serine proteases	Anti-parasitic activity	*Toxoplasma*	[35]
7.	*Ectatomma quadridens*	Ponericin	Antimicrobial	Gram-positive and Gram-negative bacteria	[37]
8.	*Myrmecia pilosula*	Pilosulin 3, pilosulin 1 and Pilosulin 4	Allergenic activities	*Staphylococcus aureus*	[44]
9.	*Dinoponera australis*	Dinoponeratoxins	antimicrobial and insecticidal activities	Gram-positive and Gram-negative bacteria	[49]

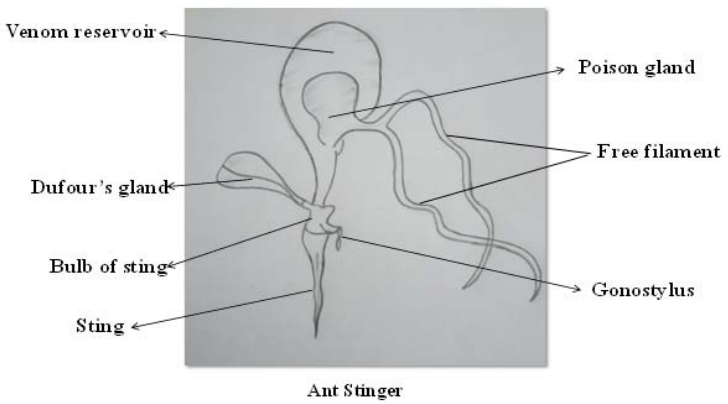

Fig. 1: Showing diagrammatic sketch of ant stinger

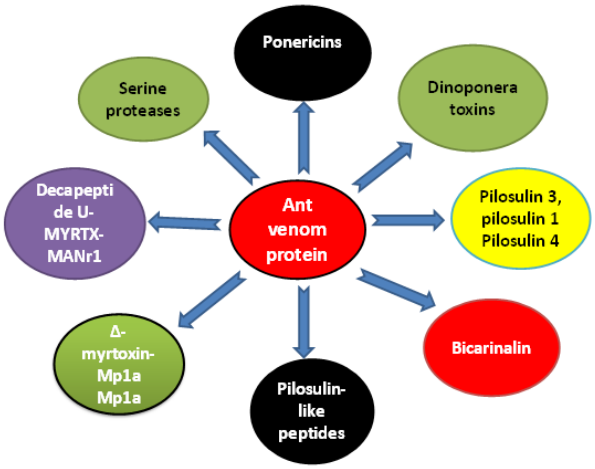

Fig. 2: Showing various toxin peptides isolated from ant venom toxins

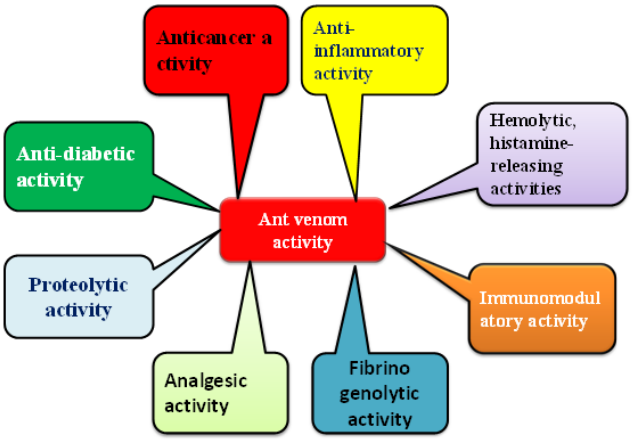

Fig. 3: Showing biological activity of ant venom toxins

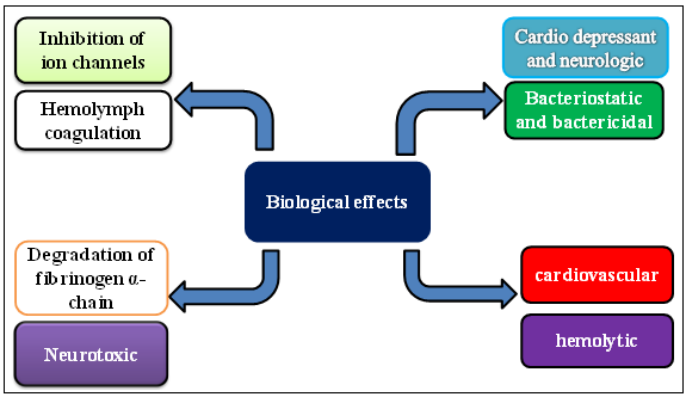

Fig. 4: Showing different effects of ant venom toxins

Proteolytic activity

The crude venom showed high proteolytic activity on azocasein at optimal pH 8.0 and 37 °C. In the presence of protease inhibitors as aprotinin, leupeptin and EDTA, the azocaseinolytic activity was reduced by 45%, 29% and 9%; respectively, It clears that the enzymes present in the crude venom is serine proteases (fig. 3) [22].

Allergic and immune hypersensitivity

Australian ant *Myrmecia pilosula* sting causes allergy a gives rise to immune hypersensitivity reactions that become severe and results in death of patients. M. pilosula venom contain Pilosulin 3, pilosulin 1 and Pilosulin 4.1. Among which as a major is major allergen while pilosulin 1 and Pilosulin 4.1 are minor allergens. Venom toxins impose minor skin reactions to severe and sometimes fatal anaphylaxis with high allergenic activities [23]. Fire ant stings induce eosinophil recruitment and production of Th2 cytokines [24]. WBE of fire ants was found useful for skin test diagnosis of sensitive individuals. It shows cross-reactive or shared antigens between fire ant venom, It show the passive transfer of skin reactivity to non-sensitive individuals through sera from sensitive individuals [25] *Ectomomyrmex* spp. show sting hypersensitivity with many incidents of allergic reactions synthesis of the high level of specific

IgE. It mediates type I hypersensitivity in patients [26]. Similar systemic hypersensitive reactions can pose life-threatening complications are also seen in red Imported Fire Ant (RIFA) *Solenopsis invicta* Buren (Insecta: Formicidae). Is one of the most dangerous invasive pests. It shows immediate effects due to the presence of major (>95%) toxic alkaloids [27]. The local reactions of the fire ant sting can cause anaphylaxis, which is a response to the aqueous protein solution. Fire ant stings also are capable of causing serum sickness, nephrotic syndrome, seizures, worsening of pre-existing cardiopulmonary disease, and anaphylaxis (fig. 3).

Hemolytic and histamine-releasing activities

A pilosulin-like toxin peptide 1¯6, isolated from the predatory ant *Odontomachus monticola* displays hemolytic, and histamine-releasing activities (fig. 3) [28].

Analgesic activity

D. quadriceps is a predatory giant ant, its venom toxins damage cell membranes and tissue, to cause neurotoxicity, induce allergic reactions, causing long-lasting local pain, involuntary shaking, lymphadenopathy, and cardiac arrhythmias, among other symptoms (fig. 3) [29].

Fibrinogenolytic activity

Ant *Odontomachus bauri* crude venom degraded the fibrinogen α-chain faster than the β-chain, while the fibrinogen γ-chain remained unchanged. It is due to presence of serine proteases Silva (fig. 3) [30].

Bacteriostatic and bactericidal effects

The predatory giant ant *Dinoponera quadriceps* secretes a complex mixture of bioactive peptides in its venom. It contains five classes' e. g., dermaseptin-, defensin-, ICK-, pilosulin-and ponericin-like antimicrobial peptides [31]. Its synthetic templates sDq-2562 and sDq-3162 are ponericin-like dinoponera toxins. The most effective peptide, the 28-residue sDq-3162 displayed a significant bacteriostatic and bactericidal effect with minimal inhibitory concentrations. Similarly, venom peptide bicarinalin, from the ant *Tetramorium bicarinatum*, shows strong antimicrobial activity with a broad spectrum of activity against *Helicobacter pylori* [32]. Bicarinalin can significantly decrease the density of *H. pylori* on gastric cells. It shows both curative and preventive use. Bicarinalin shows low cytotoxicity against human lymphocytes at bactericidal concentrations and its long half-life in human serum [33] (fig. 4). Bicarinalin broad antibacterial activity was much similar in magnitude o Melittin and other hymenopteran antimicrobial peptides such as pilosulin or defensing [34] In addition, the venom showed antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli* as well as anti-parasitic activity on *Toxoplasma gondii* infection *in vitro* [35] (fig. 4).

Similar antibacterial activity is reported in synthetic fire ant venom alkaloids trans-2methyl-6-(cis-6-pentadecenyl)piperidine against *Staphylococcus aureus* and *Escherichia coli in vitro* (Jouvenaz *et al.*, 1972) [36] Venoms from three poneromorph ant species (*Paraponera clavata*, *Ectatomma quadridens* and *Ectatomma tuberculatum*) showed growth inhibition of Gram-positive and Gram-negative bacteria at a low concentration. These venom toxin peptide are linear and show low similarity to ponericin peptides [37]. *Dinoponera quadriceps* ant venom (DqV) was found effective against *S. aureus* [38] (fig. 4).

Antifungal activity

Venoms from *Dinoponera quadriceps* ant possess five known classes of antimicrobial peptides e. g., dermaseptin-, defensin-, ICK-, pilosulin-and ponericin-like types). Pilosulin-and ponericin-like peptides were active against bacteria, fungi, and parasites. Synthetic pilosulin-(Dq-2562, Dq-1503, and Dq-1319) and ponericin-like (Dq-3162) peptides showed fungicide and fungistatic activities against different species of *Candida* [39] (fig. 3).

Cardiodepressant and neurologic effects

The fire ant (*Solenopsis invicta)* venom possesses alkaloid components which produce cardiovascular and central nervous system toxic effects in mammals. But synthetic *S. invicta* alkaloids i.e. isosolenopsin A and solenopsin A show cardiorespiratory depressant effects in rodent models. Moreover, solenopsin A injection (30 mg/kg intravenously) caused seizures, respiratory arrest, and death. Two alkaloid components of fire ant venom possess the cardiorespiratory depressant activity and elicit seizures in the rat [40] (fig. 4).

Insecticidal activity

The crude venom of the predatory ant, *Manica rubida*, control pea aphid (*Acyrthosiphon pisum*), a common agricultural pest developed through parthenogensis. *M. rubida* venom possesses decapeptide U-MYRTX-MANr1 (NH_2-IDPKVLESLV-$CONH_2$) Both crude venom and U-MYRTX-MANr1 reversibly paralyzed injected aphids and induced a loss of body fluids, reduced the survival and heavily affects its reproduction [4]. This remarkable insecticidal activity of *M. rubida* venom can be used as a resource of bio-insecticides. Fire ant venom shows strong insecticidal activity against *Plutella xylostella* (Lepidoptera: Plutellidae) Larvae [41]. Myrmicine ants mainly "plant-ant" *Tetraponera aethiops* synthesize defensive venom toxins which protect host plants is an association (fig. 4) [42].

Ant venom immunotherapy

Jack Jumper ant venom is quite toxic, for neutralization of its effect, antibody immunotherapy (JJA VIT) is used. However, for the production of antibodies, purified ant venom toxins are mixed with Advax adjuvant, and injected in experimental animals for immunogenicity [43]. Similarly, whole-body extract (WBE) of fire ant *Solenopsis invicta* is used immunotherapy mainly to cut down hypersensitivity in sting patients [44]. Only one sting episode in this group (2.1%) produced an anaphylactic reaction. WBE therapy was found highly effective and lower down the risk of allergic and systemic reactions [45]. Fire ant venom immunotherapy is not recommended for children with large local reactions. These reactions were in range from local pustules and large, late-phase responses to life-threatening anaphylaxis [46].

Mode of action

Dinoponera quadriceps venom (DqV) toxins significantly alter membrane permeability in *Staphylococcus aureus* and show bactericidal action [47]. AMPs from ant venom interact with microbial membranes [48]. M-PONTX-Dq3a could be used in prevention of biofilm formation through the development of anti-adhesive surface coatings on medical devices. These are most effective against drug-resistant strains which cause skin or soft tissue infections. This remarkable activity is only after the diffusion of venom toxins through cell wall and membrane [49]. Similarly, the insecticidal activity of *M. rubida* venom is also due to absorption of toxins through insect integument [50]. These results indicate that C11 causes initial permeability changes in the plasma membrane followed by lytic release of histamine and other cell components. Moreover, dialkylpiperidine component of the venoms provides from fire ants act as a defensin and may nonspecific in action and quickly inflict in the membrane [51].

Phospholipid ethers have been demonstrated to have activity against Akt, as well as potential alternative targets [52]. Solenopsin shares the long alkyl side chains seen in phospholipids ethers and resembles miltefosine and perifosine by having a positively charged amine group and alkyl chain. Which quickly pass in side muscle cells of the human being [52]. Solenopsin make permeability changes in the plasma membrane followed by lytic release of histamine and other cell components, while dialkylpiperidine shows nonspecific action and provides the fire ants with a sizable defense of general applicability. Due to membrane pore formation and channel binding inhibition, most of the activities of ant venom are paralytic, cytolytic, haemolytic, allergenic, pro-inflammatory, insecticidal, antimicrobial, and pain-producing in nature, while non-toxic functions include roles in chemical communication involving trail and sex pheromones, deterrents, and aggregators [53]. Within ants, alkaloids are found in venom and function as potent weapons against heterospecific species, which show membrane lytic activity [54]. Besides, this solenopsin also inhibits a group of cellular kinases and Akt selectively in an ATP-competitive manner, without affecting

its upstream activator PDK1 or PI3K [54]. However, in cells, solenopsin prevented the activation of PI3K, the phosphorylation of Akt-1 at both Thr308 and Ser473, and the phosphorylation and subsequent subcellular localization of forehead box 01a (FOXO1a) [55]. Solenopsin exerts its effects on Akt activity in cells by inhibiting a step in the signaling. Various ant species possess unique natural bioactive toxin peptides, which show diverse biological activities [56], much similar to defense molecules found mainly in venomous animals [57].

CONCLUSION

Fire ants or red ants are invasive and venomous arthropod pests. These synthesize and secrete a biological cocktail of organic compounds, including peptide and polypeptide toxins. Ant venom possesses several hydrolases, oxidoreductases, proteases, Kunitz-like polypeptides, and cysteine knot (ICK)-like (knottin) neurotoxins and insect defensins in a very low concentration These very swiftly use their venom secretions to defend their nest against predators, microbial pathogens, competitors, and to hunt prey. Ant venom venom possesses pharmacologically important bio-molecules which have shown cytolytic, haemolytic, allergenic, pro-inflammatory, insecticidal, antimicrobial, and pain-producing pharmacologic activities. Ant envenomation is more frequent, sometimes group of red forests attack the human footpad that causes redness of area, sever irritation, pain and heavy swelling. Ant venom allergens are mostly lethal-like proteins and esterases and a minor peptide framework composed of inter-specific structurally conserved cysteine-rich toxins. Ant venom imposes toxicity and allergic responses as post-stinging eosinophil and production of The cytokines get increased. Few species of predatory giant ants inoculate venom that causes severe local pain for long time, evokes involuntary shaking, lymphadenopathy, and cardiac arrhythmias. Ant venoms contain many small, linear peptides and a good source of bioactive peptides/toxins. These show various biological targets, including inhibition of ion channels and hemolymph coagulation activities. Ant venom shows excellent antineoplastic activity, and that can be directly used to treat certain types of cancer. These could be used as a potential source of pharmaceutics, insecticides and therapeutic agents. Ant venom toxins have agricultural importance; they could be used for the control of insect pests of various crops. V These could become the solution of the environment and human health because these could replace synthetic chemicals and can easily kill insecticide-resistant pest populations. This could be used as a source of alternative, environmentally-friendly bio-insecticides.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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