American Journal of Pharmacology & Therapeutics

Review Article

The Potential Uses of Insect Biochemicals in Medical Therapeutics -

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Submitted: 21 September 2021; **Approved:** 04 October 2021; **Published:** 07 October 2021

Cite this article: Turaman C. The Potential Uses of Insect Biochemicals in Medical Therapeutics. Am J Pharmacol Ther. 2021 Oct 07;6(1): 009-018. doi: 10.37871/ajpt.id26

ABSTRACT

By virtue of research activities, our knowledge on various molecules extracted from the insects that are beneficial to human, is constantly increasing along with the increasing knowledge on the nature of their physiology, morphology and behavior. This article investigates the therapeutic benefits of the insects for humans. The analysed articles chosen out of numerous articles written in this field, shows there are many beneficial secretory or excretory components of the insects having many various effects. Therapeutic molecules that may be beneficial in the treatment of human diseases, probably with much less side effects may be obtained by following this path.

Keywords: Insects; Extracts; Saliva; Venom; Therapeutics

INTRODUCTION

Insect is an arthropod animal with a three sectioned trunk, two pairs of wings and three double pairs of articulated legs with its skeleton outside the body. Insecta is by far the best, adorable species with an incredible biodiversity and ability to adapt to different habitats and environmental conditions. Eventhough there are people who consider the insecta on the lower steps of evolution, many characteristics of their lives show us how developed they are in terms of evolution. One outcome of this evolutionary development is their biodiversity which is much larger than the more evolutionally developed vertebrates. Their high fecundity, their ability to easily adapt to different environments such as high altitudes, poles and deserts, freshwater and seawater; their extraordinary strategies of migration and expansion; their defense mechanisms and living habits of some of their groups are stunning. Apart from their splendid biodiversity and their ability to adapt and colonize new niches and nutritional resources; Insects deserve a special place amongst all living creatures with their strong immune response ability. The physiology, morphology and habits of the Insecta have been used in numerous beneficial ways in the favor of humans and it is certain that this benefit will grow as we get to know Inscts better [1]. This article investigates the potential therapeutic benefits of the insects for humans where insects and humans interact. There is a vast literature which investigates the therapeutic value of insects, which proves our growing interest to insects. The examples given below and many other research activities which exceed the limits of an article show that insects have plenty of other secretory or excretory components awaiting to be discovered alongside their anti-viral, anti-fungal and anti-inflammatory effective substances and again effective substances which exist in the insect symbiosis, parasitoid and teratocyte and anti-microbial saliva and venoms. Dr. Tom Eisner from Cronell University states that "it is possible to find numerous new molecules in insects that will occupy the drug industry for years" and defines the research activities carried in this field as "chemical gold rush" [2].

SCOPE

There exist thousands of ramified publications on the subject some of which present classical, some more specified approaches. The aim of this article is to raise pioneering arguments on this wide field, by means of revising of such publications. This pre-analysis aims to higlight the importance of strategic pharmaco-plans through a comprehensive meta-screening of all the research activities on the relative topic with a more systematical approach.

METHODOLOGY

The articles which were considered to be significant by the author were randomly chosen and summarized in order to answer the question of "which new ideas can be derived from this knowledge that would serve for the benefit of humans?"

FINDINGS

Miscellaneous observations

Octopamine and nutrition regulation: The habit of nutrition is a complex behaviour which is organized by means of the nervous system and several chemicals. Octopamine regulates the negative electirical input signals that come from the ressessive receptors found in the neural network that covers the crop and oesophagus in the negative direction or inhibits them [3]. These should be post-synaptic facts. The positive signals they send to the central nervous system enable the control of nutrition. These facts which control the crop motility are not completely understood. There are numerous pomps and sphyncters which move the nutrition through the digestive system [4].

Magical nuptial feast amongst the angel insects: Zoraptera is a tiny insect group which is closely related to hoppers; they are rare and their adult members might not carry wings. The male *Zorotypus barberi*, a member of this genus, has a cephalic gland in the middle of its head. During courtship the male excretes a liquid from this gland and offers it to the female. The acceptence of this drop by the female relaxes the actions and enables mating [5].

Egg glue of the butterfly: Genus Opodiphthera type Saturniidae: Lepidoptera moths stick their eggs on plants with a strong glue. The egg is stuck on the leaves with the help of a rapidly drying glue that deforms the leaves. The glue is seen easily like a kind of membrane which surrounds the mount of the egg. The nature of this glue is unknown and is worth researching. The pupa of the moth also releases the same glue in order to protect the setae of its cremaster. The glue is so strong that it is not possible to detach the silk pillow from the setae [6].

G protein coupled receptors: G Protein Coupled Receptors (GPCR) is a large protein family and is found in almost every eukaryotic organisms. These proteins include numerous receptors which exhibit structural differences and function as mediators that have various functions like sense and feeling regulation, hormone and pheromone production, immune and nervous system functions. These receptors play roles in many human diseases and have become the focus of research activities [7].

Antifreeze proteins of various insects: Thermal hysteresis (the difference between the freezing and melting points) is characteristic of the existence of Antifreeze Proteins (AFP's). AFP's are found in, Chrysomelidae, Silphidae and Coleoptera of the Carabidae family, Neuroptera, Diptera: Tipulidae and Hemiptera *Elasmostethus interstinctus* Pentatomidae, *Limnoporus dissortis* Gerridae type insects. AFP's protect the organism from freezing. Terestrial artropods which produce AFP's are protected from freezing. Some

DOI: https://dx.doi.org/10.37871/ajpt.id26

of theses AFP producing insects can tolerate freezing under very low temperatures (-40 / -70°C) [8].

Diapause hormone in the flies: Diapause is the spontaneous cease of development and reproduction in some animals caused by the decrease of metabolic activities and dehidration. It is observed in insects, mites, some crustaceans and snails. The phenomenon of the suspension of development is a sign of the approaching negative environmental conditions. Diapause is a behaviour adapted by the insects in order to protect themselves from hard conditions like the winter. Therefore, over-nutrition and increase in the fatty tissue prior to diapause is a 'must'. Insects may enter diapause in any stage of their lives; however diapause during the pupa stage is more common. For the survival of the insect and its species, nutrition-reproduction coordination and the timing of entering and exiting the diapause is crucial. The behaviour of diapause is defined genetically however it might disappear under changing environmental conditions [9]. The levels of chemicals, like sterols decrease in the insects in diapause. In this stage, the sterols enter the ovaries and fill them; this stage does not ocur in the females in diapause. One of the hormones regulating the diapause in moths is a 24-aa neuropeptyde; which is called as the Diapause Hormone (DH). The cease of DH pupal diapause in the agricultural pest *Helicoverpa/Heliothis* complex members is accelerated. There are more active DH agonists then the DH's which cease the diapause. One of these agonists prevents the larvea from entering the pupal diapause when given to a larvea which is programmed for diapause depending on the environmental conditions [10].

Fly Kuzbanian protein: ADAM's (A Disintegrin and Metalloprotease (Kuzbanian protein)) are a transmembrane protein family and play a central role in transforming the membrane into a soluble form by proteolitic means. Enzymes which have a proteolitic transformation function are believed to take part in the emergence of congenital diseases like the Alzheimer's disease. ADAM's also play a crucial role in the formation of the heart and blood vessels of the vertabrates, thus the mutaions in the ADAM genes may be the cause of congenital heart anomalies. The zygotic loss of active Kuzbanian protein form in the fruit fly Drosophila, along with the loss of pericardium cells, causes an excessive cardiomyocits augmentation. Another function of the Kuzbanian may be cardiac-cell morphogenesis [11].

Anaphylaxis treatment with cicada: Anaphylaxis is a chain of reactions which occurs through the release of histamine stemming from the degranulation of mast cells and bazophils when an antigen defined as "alien" by the organism holds on to receptors by the IgE's which are immediately released. This may occur in various clinical forms; even though it is rare, it may risk the life of the patient in a state of shock. It is caused by an "alien" drug (penicillin and its derivations, analgesics, iodine-based radiological diagnosis molecules, etc.), pollens or insects bites; rarely less serious cases may occur from food (seasame, eggs, sea products, strawbeery, tomatoe, etc.) [12]. *Cryptotympana atrata* Hemiptera is a Cicada species found in Eastern Asia. *Cryptotympana atrata* extract enables a rapid recovery from the anaphylactic shock syndrome. The extract of this insect has proven to prevent histamine release from mice periton mast cells. This extract was used on humans via IV in differing doses and intervals: This extract has proven to prevent histamine release for a long period during continuous, repressive treatments; as well as dramatic conditions like anaphylaxis [13].

Thermolysin of the butterfly: *Galleria mellonella*: Lepidoptera is known as the greater wax moth. They are considered as pest because their larvae attack honey combs. However, it has a beneficial side because they are used as models for infecitous diseases. Even though the insects have no adaptive immune response, they have a very similar one to vertebrates' innate immune response. *G. mellonella's* immune response is used as model for the diagnosis of Gram-positive and Gram-negative bacteria virulence assessments. Moreover, *G. mellonella* is used in assessing the effect of antimicrobial agents. Thermolysine type metallaproteanes like aureolysine, pseudolysine and basillolysine, represent virulence factors of various bacteria and enables innate immune response. Cryptococcosis is a deep mycosis hard to treat which became frequent parallel to the prevelance of HIV infection and is common amongst people whose immune system is deppressed. *G.mellonella* is a suitable model organism for *Cryptococcus neoformans* infection. Injecting thermolysine to *Galleria mellonella* larva increases the acquired immunity of the larvae against *Cryptococcus neoformans* infection by means of the small protein fragments which ocur due to hemolymphe protein proteolysis [14].

Insect-microbe symbiosis

Cockroach: Blattodea have been in a symbiosis with the special bacteroides they carry in their bodies for millions of years. These bacteroides live in a cell called mycetosit and is transmitted to next generations by the mother cockroach. In return of this comfortable life they leed in the adipose tissue, bacteroides create all the necessary vitamins and amino acids for the insect; this is the secret lying beneath the ability of the cockroaches to transform everything into nutrients. Nitrogen intake and digestion is one of the basic functions of the insects which fed on plants. For example, their ability to produce nitrogen from effluents, offers a crucial resource to insects, in terms of this rare substance, if they acquire the mechanisms which can transform nitrogen [15,16].

Animals stock the excess of uric acid; this would cause problems like kidney diseases and gout in the humans because of their long life span. Uric acid and urea are nitrogen effluents which the animals can't consume as nutrition. However the cockroach which can cooperate with a bacteri is able to use this source in order to produce protein and this means a very distinctive life form; this success depends on the insect-microbe cooperation. *P. americana*, although being a herbivore like many other cockroaches, can become an opportunist carnivore and feed on human wastes. The primary requirement of the cockroach is nitrogen. Other instects eliminate nitrogen as uric acid whereas cockroaches store this substance in their body. Because the cockroach can store nitrogen as uric acid, it can produce nitrogen when needed. According to estimations, for over 140 million years, cockroaches have been in cooperation with a bacteriel endosymbiont, *Blattabacterium* that lives in the fatty tissue of their body. This bacteri have two functions: Production of nutrients and keeping the insect from dying by regulating the uric acid level of its body. This bacteria, is able to produce all the essential amino acids along with other types of amino acids and various vitamins. It produces nutrients by means of uric acid breakdown products, urea and ammoniac. *Blattabacterium* transforms the waste nitrogen and enables the cockroach to reproduce consuming poor nutritions and benefit from wastes that contain nitrogen; this characteristic may be a speciality which designates the dispersion of cochroach types. Blattabacterium is a Gram-negative bacteria which is transmitted vertically. The bacteria do not have uricolytic enzymes but contains urease and glutamat dehydrogenase enzymes, with which it is able to transform uric acid breakdown producys into glutamate [17-19].

DOI: https://dx.doi.org/10.37871/ajpt.id26

Beetle: The chemical mediator of *Xyleborus dispar*, Scolytidae: Coleoptera and fungi mutualism is a poly unsaturated peroxide produced by a bacteri. The elective toxicity of this molecule against the insects fungal (ambrosia) antagonist is bacteria-based and indicates a mutually evolved insect-microbe cooperation [20,21].

Wasp: Adult Braconidae: Vespidae is a caterpillar parasitoid and injects its venom and its symbiotic polydnavirus to the *Manduca sexta*: Lepidoptera caterpillar together with its eggs. This venom is not effective on its own; its effect increases in the existence of the polydnavirus. When the eggs hatch in the body cavity of the caterpillar, particular cells produce from their chorion. These cells, called Teratocytes grow into giant cells; the hormones they release decelerate the growth of the host together with the released hormone and the venom. The larva which completes its development in this medium come out of the caterpillar and pupate; later on adult vespids grow out of these pupas. The benefit of the virus from this bargain, which is unable to replicate on its own, is the existence of these genes in the genom of the vespid. The female vespid has particular cells in her ovaries, called calix, and carries virion particles. The viral sequence exists in the male vespid but the virus is not produced in the males. The viral sequence is transmitted to the female during mating, thus the female acquires the ability to replicate virions. Later on, when injected to the host during ovipositioning together with the venom, the Polydnavirus replicates and prevents the growth of the host. The infected host does not go through a methamorphosis but grows into a giant continuing its development and prolongues its life. The injected Polydnairus also oppresses the immune system of the host caterpillar [22-27].

Butterfly: The effect of *Bacillus thuringiensis* used as a biological insecticide depends on the existence of enteric bacteria in the hemolymph of the insect (*Escherichia coli* and *Enterebocter spp.*). This spore-producing bacteri which can be found anywhere kills the insect larvea by means of insecticide crystal proteins. *Escherichia coli* which is designed for producing *B.thuringiensis* toxin, kills the forest pest *Lymantria dispar* moth caterpillars. *E. coli* and *Enterobacter* sp. can reach up to huge population amounts in the insect hemolymphe, contrary to the *B. thuringiensis* which is immediately killed in the insect hemolymphe [28].

Parasitoid wasp-host relations

Parasitoid is an organism which lives on or in a host organism and eventually causes its death. Most of the parasitoid insects are included in the Hymenoptera order; approximately 10% of the insect species are parasitoids. Most of them inject their eggs on the host organisms through with their ovipostors. The juveniles that hatch out the egg nurture on the internal organs of the host. The consumed organs are not vital ones at first, thus does not cause the death of the host immediately. Later on, the parasitoid larvae either attacks the vital organs of the host or pupates inside the body of its host; in the first scenario, the host dies immediately and in the second scenario, the host dies while the adult parasitoids hatch out of their pupas. Parasitoids are beneficial in terms of pest control. Potential host insects, on the other hand, have developped various protection mechanisms against this entomophage species. These are effective mechanisms against the predators and parasitoids such as escape, mimicry, repellency and cuticula barrier. These insects also have a second defense line against parasitoids and parasytes, called the "immune mechanism". For example, in Africa, *Anopheles gambiae*, the primary vector of human malaria, is able to kill the malaria parasite by enclosing it inside a melanine-rich capsule in its midgut. Several loci responsible of this encapsulation reaction have been found. This discovery may play a crucial role in malaria control [29-31].

Anaesthesia to the cockroach: Ampulicidae: Vespidae is a solitary and entomohage parasitoid family member of the wasp group mentioned above. One species of this family, *Ampulex compressa* is found in South Asia, Africa and the Pacific islands and shows up during hot months of the year. The mating habit of the female is interesting; she lays its eggs inside the body of a cockroach (*Periplaneta americana* **or** *Periplaneta australasiae*) which she stings and spaces out two times. The first sting transfuses the venom through the protorasic neural ganglion of the cockroach and hempers it from using its forelegs. When the cockroach becomes immobile, with the second sting, the venom is transfused through the sub-esofageal neural ganglion and the cockroach is no longer able to escape. The active substances of the venom are Gamma Amino-Butyricacid (GABA), taurin and beta-alanine; GABA shows its effect by blocking the neurotransmitter octopamine receptors and thus ceasing the cholinergic transmission. Taurin and beta-alanin, creates an agonist effect prolonging the short-term effect of GABA. Later, the vespid makes use of the effect of the venom and chews the tentacle of the cockroach thus succeeds to immobilize the cockroach without killing it. When she is convinced the effect of the anesthesia is optimal, she drags the cockroach to her nest. There, she lays her eggs inside the abdomen of the cockroach. In order to prevent someone else jerk her precious trophy away, she closes the entrence of her nest with pebbles. When the larvae hatches out of the egg they begin their **e**ndoparasitoid lives; they slowly consume the organs of the cockroach keeping it alive long enough and eventually pupate inside the cockroach and finally the adult vespids emerge out of the stomach of the cockroach and begin their new life. The venom shows its basic effect by spoiling the octopaminergic modulation. Octopamine is a neurotransmitter that plays a central role in controlling sudden movements [32-35].

Prevention from the mosquito defense: Parasitoid insects have also developped various methods in order to overcome the potential host defense mechanisms. Encapsulation of the above mentioned alien organisms is a common defense mechanism amongst insects. Co-evolution of the hosts immune response and these protective methods developped against this response, have created a delicate balance between the two. A series of different loci were found amongst anopheles mosquitos which have the ability to create a melanotic encapsulation againts malaria parasites. However, some of the human malaria parasite strains are able to escape from this immune response.

Similar interactions with parasitoids have been proven to exist in *Drosophila melanogaster*: Diptera too, however, parasitoids with high virulance are able to oppress the immune system of this fly. Both of these flies must be encoding the gene products of the encapsulating loci parasitoid recognition and alarm systems in eraly stages. Membrane receptor molecules may be playing a crucial role in the encapsulation process [36-39].

Virus partnership: The polydnaviruses of the endoparasitoid vespid repress the encapsulation reaction of their hosts by means of an unknown molecular mechanism. The beginning of the micro-particle production with the encounter of cell membrane glycoproteins and the virus is a part of the immune response against alien organisms and this is the first step of the cell-mediated encapsulation process. The proteins encoded by the virus may be important means of respressing the host cellular immune response; this method can explain the

DOI: https://dx.doi.org/10.37871/ajpt.id26

repression of the host immune response attacked by a parasitoid [40].

Teratocytes alliance: Various parasitoid insect species, the serosa membrane tears off and produces teratocyte cells when hatching out. Teratocytes are beleived to have several functions as immunosupression, secretion and nutrition in the host-parasitoid relations. The teratocytes growth model reflects whether there is a suitable host or not for the parasitoid. Amongst Braconidae: Hymenoptera species, the teratocyte derives from the serosa membrane of the developing parasitoid embryo. This membrane decomposes into teratocytes while hatching and begins to move through the hemolymph of the host. Teratocytes which develop from trophamnion in most of the parasitoid hymenoptera develops resistance against the defense mechanisms of the host insect. When they are first resolves from the mebrane of the embryo, these cells are little however they grow three thousand times in the circulation of the host. This growth is enabled by nutrition from the host circulation; in return, it represses haematopoiesis in the host hemolymph and protects the juvenil parasitoid from haemocytic activity [41].

Insect antimicrobial peptides

Antimicrobial Peptides (AMP) are multi-functional components of the innate immune system arsenal used both by the procaryotic and eucaryotic organisms. During recent years, most of these peptides have been isolated from insects. What paved the way for these researches was the observation of the resistance of the insects against bacterial infections. Insects resist the pathogens by means of cellular and especially humoral (innate) immunities. With the identification of the bacteria, an intricate genetic steps system is triggered and finally AMP's are released into the circulation of the hemolymphes. The structures of these peptides are simple and are composed of 20-40 amino acids. As opposed to the differences in terms of their sizes, amino acid sequences and structures, the insect AMP's can be classified under three groups. Peptides rich in proline and glycine are active against gram-negative bacteria; however the defensins kill the Gram-negative bacteria in an elective way, whereas the secropins are active against both of the bacteria groups. The effect of the insect AMP's are immense; most show its effect by damaging the bacteria membrane or decompose into the membrane structure. AMP's like drosocin, apidaecin and pyrhocoricin which show its effect by deactivating the bacterial proteins are exceptions; these stop the growth of the in vivo tumor by means of their cytotoxic specialities. One pyrrhocoricin analog protected a mouse from experimental *Escherichia coli* infection. Generally, insect AMP's are not cytotoxic and their range of effect is wide however how they effect is not completely understood. The effects may be emerging from peptide-lipid interaction or receptor-mediated recognition. The insect immune system which relies only on innate immunity, work with alternative antimicrobial strategies. One of these strategies is rapid and dense AMP production. However, ability to produce ample and various AMP's is not solely characteristic to insects. Approximately 700 AMP have been recorded in the literatüre exist also in microorganisms, other animals including mammals and plants [42-44].

Hover flies: Realisation that the antimicrobial peptides existing in Syrphidae and probably other Diptera vastly vary, is promising both in terms of the treatment of dangerous human infections which emerge due to bacteria endotoxins and understanding how closely the moleculer evolution of the Diptera genetic immunity and the ecological harmony are related. For example, *Eristalis tenax*, Syrphidae: Diptera have developed an ability to survive in wet places like cesspits and animal dunghills where microbial pressure is very high. The benefit of living in such places should be protection from predators, opponent species and parasitoids; in return of this evolutionary sacrifice, they managed to invest in immunity against microbial stress, showing that multiple AMP's exist in insects [45].

Black soldier fly: *Hermetia illucens*: Stratiomyidae larval secretion and exstract contains substances rich in antimobrobial characteristics which were previously unknown; the characteristics can be crucially effective weapons that can be used against nosocomial infections, especially the Methicilline-Resistant *Staphylococcus aureus* (MRSA) [46]. *H. illucens* larvae, a considerable part of this wide AMP spectrum must be deriving from nutrition with high bacterial loaded diet; meaning, larvae AMP expression depends on the diet. The number of AMP's and the level of AMP expression maximizes when the larvae feed on proteins and sunflower oil. The expansion of the AMP expression repertoire of the larvae should be fascilitating its adaption to extraordinary diets thanks to the intestinal microbiata. By force of this ability, it is possible to assume that *H. illucens* is reliable sources for waste control that can be used in organic waste recycling. Using fly maggots in the treatment of wounds that don't heal and multiple-resistant infections is vastly accepted. It is possible to produce antibacterial substances against Gram-positive *Staphylococcus aureus*, MRSA and Gram-negative *Pseudomonas aeruginosa* from *Hermetia illucens* larvae. That is to say, the larvae extract exhibits a wide antibacterial spectrum, especially against MRSA, *H. illucens* larvae secretions may be promising instead of antibiotics [47,48].

Insect saliva

Hematophagy is a convergent behavior in evolution; it developped independently in worms, artropods and mammals. Each one of them has developped different mechanisms in order to inactivate host defense, thus these mechanisms are specific to genus and the family and show an immense abundance. Tha saliva of the blood sucking insects contains hundreds of polypeptides. One of these nutrition-dependent adaptations is the equipment of these insect saliva molecules which derive their hosts from haemostasis, inflammation and immune response weapons. Insect saliva contains hundreds of polypetides which are mostly specific to their own genus or family [49,50].

Mosquito: The blood sucking artropod saliva contains a clotting inhibitor, an antiplatelet agent and a vasodilatator subsctance as a rule. Mosquito saliva, (as in tick and phlebotominae) apart from its ability to retard host vessel collaps, to prevent haemostatic and immune responses, also decreases the early expression of interferon α/β, thus enables reproduction of viruses like the West Nile Virus within its host. The components of the saliva which prevent clotting can be friendlier and effective agents compared to clotting preventing and vasodilator agents that are currently being used in medicine. Mosquito saliva can also be beneficial in controlling the bacteria that reproduces in sugary environments because it contains enzymes that help consommation of the glycose in the blood of vertebrates. Mosquito saliva composition is quite simple, contains less than 20 essential proteins. Despite the well-rounded knowledge on these molecules, what more than half them serves is still unknown. For example, producing coagulation-preventing and capillary expanding agents can be very helpful in the control of cardiovascular diseases because they are consumer-friendlier compared to the drugs in use [51-54].

Assasin bug: Reduviid predators *Rhynocoris marginatus* (Fab.)

DOI: https://dx.doi.org/10.37871/ajpt.id26

and *Catamirus brevipennis* (Servile) use their venoms to paralyze their pray. Both the venoms are proteins with low molecular weight. These two Reduviid venoms have been proven to have antibacterial activities against seven gram-negative and four gram-positive bacteria. The venoms of these two insects exhibit a strong antibacterial activity by preventing the bacteria to nurture and also preventing the agregation of haemocytes. The *R. marginatus* venom has shown antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Salmonella typhimurium*, *Streptococcus pyogenes*; and the *C. brevipennis* venom has shown antibacterial activity against *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Salmonella typhimurium, Bacillus subtilis*, *Staphylococcus aureus* and *Bacillus sphaericus* [55,56].

Venomous insect secretions

Arctiidae butterfly aposematism: Most of the animal species, consume chemicals which taste bad or poisonous from the plants they live on, apart from the nutritious substances they consume. Some of them produce defensive substances from these chemicals. The most important of such chemicals are cardiac glycosides, pyrrolizidine alcaloids, pyrazines and histamins. Aposematism is the term used for indicating that a living creature is dangerously poisonous or has a very bad taste; these have very bright colours. A good example for this is the Cinnabar: Arctiidae Lepidoptera moth larvae. There are horizontal orange/black stripes on the body of this larva. *Jacobaea vulgaris* plants on which these caterpillars feed is rich in alcaloids. The caterpillar that feeds on the leaves of this plant accumulates this poison and preserves the alcaloid until it becomes adult. The aposematic colouring of the caterpillar indicates it is poisonous and warns the predators. Arctiidae: Lepidoptera larvae and the adult have a complex allelochemical sequestration strategy. Arctiid uses two mutually independent defensive signs in courtship; these are secondary chemicals and the ultrasound. Pyrrolizidine alcaloids are the defensive tool of the larvae, however they have become the courtship pheromone of the adult male in most of the lineages. The ultrasound is developped as a means of protection from the bats and is also being used in courtship games [57-61].

Lonomia butterfly: *Hemileucinae*: Saturnidae caterpillar lives as a community on a host tree, they have stinging bristles and those of *Lonomia* contain a poison which can be fatal for humans. *Lonomia* genus caterpillar venom is one of the most fatal animal venoms and its **LD_{50}** value has not been meausred so far. A typical intoxication with the caterpillar of this moth takes place if the victim leans against the host tree. Because the tree hosts numerous caterpillars, the clinical picture can be dramatic; it results in disseminated intravascular coagulation and consumption coagulopathy, hemorrhagic syndrome; massive internal hemorrhage, renal failure and hemolysis are the components of this clinical picture. This syndrome is called Lonomiasis and has been reported in 1967 for the first time. *Lonomia oblique* caterpillar venom exists in the sacs at the bottom of the spikes on its body. These spikes which are empty inside like a pipe, when stung to a vertebrate, transfuse the venom to the victim. The effect of this venom emerges as prevention of blood clotting. In order to be effected the victim should be stung 20-100 times; because the caterpillars live as a community it shouldn't be hard to be stung so many times. The fatality rate has been reported as 1.7-2.5%. An anti-venom is being produced in Brazil [62-65].

Pederin: Molecules which can potentially be used as drugs, tested on numerous marine and terrestrial invertebrates, are probably the metabolites of bacterial symbionts of these organisms. For example, anti-tumor polycetides pederin family isolated from coleoptera and sponges, indicates an evolutionary relation between the two species. Pederin is a strong DNA inhibitor which exists in the hemolymphe circulation of some Paederus, Paederinae: Staphylinidae species in all stages of their lives. This molecule is produced by the endosymbionts of some adult females and is transferred to their eggs; thus is transfused to the larvae and the pupa. The male insect can only procure this molecule by consuming the eggs. Pederin is an effective defense mechanism against predator spiders, however despite the fact that it is known as one of the most powerful animal toxins, its insecticide effect has not been proven so far. It causes dermatisis in humans and causes heavy tissue damage if it contacts the eye. If these strong effects can be repressed, it might be possible to use it in healing chronic wounds and ceasing tumoral growth. The examples of this species elevated under laboratory conditions are aposymbionts; they can not biosynthesize venom molecules because they don't have endosymbionts [66-71].

Cantharidin: Another Coleoptera genus, Epicauta, exists in trefoils; this is highly toxic for the horses that feed on trefoils and may cause the death of the horse. One other coleopter species *Lytta vesicatoria,* have been used in traditional medicine exercises and poisoning cases have been reported. The active agent of this insect venom is cantharidin and when it contacts the skin it causes dermatitis. We know that 449 species including the Oedemeridae: Coleoptera family, produce cantharidin. The lethal dose of cantharidin for the humans is as small as 0.03g. Symptoms of intoxication are oversalivation, headache, vomiting and bloody diarrhea; central nervous system symptoms can also be observed but death is rare. It has been used in traditional medicine in the treatment of rheumatism, pneumonia, inflammation and gout. It is also being used as a love potion and most of the intoxication cases emerge as a result of abusive usage as such. Cantharidin is being used in modern medicine in the treatment of molluscum contagiosum [27,72,73].

Lucibufagins: Lampyridae are known as unsavory and sometimes poisonous by the vertebrates and are not consumed. A steroid pyrone group known as lucibufagins is responsible for this protection and its effect is similar to the cardiotonic bufadienolides existent in poisonous salientians. Bufadienolides are a steroid hormone group, they are found in blood and are eliminated through urine. Their effect emerges by means of adenosine triphosphatase sodium-potassium pump inhibation. This effect causes in increase of the sodium elimination, vasoconstriction and hypertension; they work as cardiac inotropes. Bufadienolids are responsible for hypertension related to volume expansion; they hinder cell proliferation and inhibit cell maturation. Resibufogenin, an atagonist of one of the most analysed bufadienolids marinobufagenin, can be beneficial in the treatment of diseases where high levels of marinobufagenin plays a role in their pathophysiology. For example, preeclampsia is a condition with heavy fetomaternal complications and with no definitive treatment. Marinobufagenin should be playing a role in preeclampsia etiology and can be easily used among pregnant women to screen preeclampsia signs in the urine [74-76].

Mastoparan: Vespidae Hymenoptera is a large, varied, cosmopolit and spinule wasp family with nearly 5000 different species; almost all the social wasps are included in this group. Mastoparan is a peptide

DOI: https://dx.doi.org/10.37871/ajpt.id26

extracted from vespid venom and is probably the active agent of the vespid venom. It shows its effect by directly increasing the GTPaz activity and the G proteins. The effect of the venom depends on the type of the cell, however exocytose is the main phenomenon. Mastoparan causes histamine release from mast cells; it causes serotonin release from thrombocytes and catecholamine release from chromaffin cells, prolactine release from anterior hypophysis [77].

CONCLUSION AND SUGGESTIONS

ADAM protein which is existent in vertebrates and plays a central role in the formation of heart, also plays an important role in the proteolytic transformation of the membrane binding proteins in insects. Proteolytic transformation enzymes are believed to play a crucial role in congenital diseases. Kuzabanin protein can be used in the treatment of Alzheimer and cardiac birth defects.

Octopamine is believed to regulate nutrition in insects. Octopamine is used as a sympathomimetic in emergency medicine. It might be used for regulating the digestive system activities in lower dosages.

AFP's (Anti Freeze Proteins) are shown to exist in 75 different insect species's (Chrysomelidae, Silphidae, Carabidae, Neuroptera, Tipulidae, Tingidae, Pentatomidae, Gerridae) hemolymph in the Artctic Region and their effective mechanisms are still subject to argumentations. In exposure injuries, purified AFP can be a life saver. Scientists who risk to be exposed to cold (not military brigades!) can be premedicated with AFP.

When the sterol levels of Musca: Diptera in diapause decreases, the ovariol development cease. It might be an opportunity to decide about contraception and time to conceive? Several agonists have been developed inspired from DH structure and from these, DH antagonists were produced which aims to control the pest species that enter diapause during winter. By this means, entering the diapause in these pests are prevented. Preventing the pest species from surviving the winter can be an effective pest control strategy. In manic depressive psychosis, respectively DH agonists (manic period) and antagonists (depressive period); also in sleeping disorders, attention deficit disorders and hyperactivity disorders, DH agonists and antagonists can be a solution.

If the behaviour observed on female zorapters are dependent on the psychoactive effect of the male cephalic gland components, it may be beneficial to anaylse how this effect functions and to evaluate it on humans, and to use it for anaesthesia and the control of psychiatric disorders.

Study of the interaction of food-borne bacterial infections which cause dangerous intestinal diseases in humans with *Bacillus thuringiensis*, can be helpful in the control of *E. coli* toxic shock syndrome.

The effect mechanism of *Cryptotympana atrata*: Hemiptera extract, suggests that this extract may be used in the treatment of auto-immune diseases. Presuming that approximately 1/3 of the humans face an auto-immune disease in their lives, the importance of a simple and inexpensive treatment becomes evident. Treatment with *Cryptotympana atrata* extract, awaits clinical research studies.

Usage of Mastoparan can be used in the treatment of diseases caused by the lack of histamin release, in increasing the effect of mental functions and control of sleep.

The venom of vespid contains GABA, taurine and beta-alanine which accomplish its effect. These substances, when injected at the right place, block the motor nervous action potential temporarily. This blocage emerges through repression of cholinergic transfusion by increasing the chlorure conductivity in the synapses. It is worth the try to use it in local anesthesia, sympathectomy practices (buerger disease, electric injuries, viperidae bites) and pain control in some cancers.

In AIDS patients, along with antimicotics implementations, the success of the treatment depends on strengthening the immune system and preservation of T4/T8 balance is crucial. Thermolysin can be an option in some cases.

Insect egg glues can be useful in curing operation wounds and other clean wounds.

Cockraoches benefit from the vitamins produced by bacteria, in return to supplying the bacteria a living space. In Coleoptera, the polyunsaturated peroxide produced by bacteria has a selective toxicity against fungal antagonists in insects. A way to producing natural vitamins and antimicrobial agents.

Antibiotic-producing microbe-insect mutualism can pave the way for producing antimicrobial components that can be used for treatment of infectious diseases.

The ability to kill Plasmodium by producing a melanin-rich capsule in the midgut of the *Anopheles gambiae* can present an important opportunity in malaria control.

Insect parasytes and parasitoides, prevent the immune response of their host insect by means of an unknown effect they create in membrane receptor molecules, thus prevent encapsulation response of the host. Preventing the encapsulation response of the host insect emerges by the repression of the cellular immune system with the effect of the polydnavirus-transformed proteins. The mechanism of Ichnemonid that prevents the cellular immune response by use of polydnavirus can be used in preventing tissue rejection in organ transplantations.

Braconid, by injecting together the venom and symbiotic virus to its host, produces hormones that prevent the growth of the host; teratocytes grow and work in cooperation with the virus in this process. What causes the reproduction of the virus is the Braconid genom. It can be a friendly immune response repressor in organ transplantations.

Teratocyte cells have several mediator functions like immunosupression on parazitoid species. In Braconid species, they wrap the developping parasitoid embrio and during ecdyses, it transfuses in the host haemocel by resolving into individual cells. The basic role of the giant teratocytes which grow from the trophamnion in parasitoid hymenoptera is to resist the host defense mechanisms. These cells which are small while they resolve inside the embrio membrane, then transfuses in the host haemocel and grow by means of the nutrients existent in the micro-environment. The host hematopoiesis is repressed depending on the existence of teratocytes and the effectiveness of the hemosite response is decreased. Apart from the diseases related to humoral immunity, the ones that are characterized with the over-increasement of hematopoiesis, myeloproliferative diseases like polisitemia, hematological malignancies like lymphomas, hemoglobinopathies, hemophilia, coagulopathies, AIDS (which indirectly effect the hematopoietic

DOI: https://dx.doi.org/10.37871/ajpt.id26

system even though it is related to cellular immunity), autoimmune diseases can be controlled with teratocytes.

It may be possible to create user-friendly alternatives to antimicrobials by selecting and evaluating the molecules extracted from insect AMP's and expanding their scale of use. AMP existence in humans should also be investigated. Understanding their effects on preventing and treating infections can be a pioneering discovery.

What conclusions can be drawn from the fact that the mosquito saliva prevents interferon response? It can be an opportunity in preventing immune response in organ transplantation. It is certain that it plays a crucial role in preventing and treating diseases related to thromboembolism; taking into consideration the extensity of deaths related to cardiovascular diseases, the importance of this area is not even questionable. It can also be an important agent in controlling the blood sugar. It can be beneficial in controlling the sugar-consuming ferment activity in wine and beer production.

Reduviidae saliva can be an effective biological agent in treatment of local and systemic infections and pest control. Its value as an anaesthetic should also be analysed.

Cinnabar: Arctiidae moth larvae takes pyrrolizidine alcaloides from the plants they consume and use them in defense; this substance turns into pheromones used by the adult male at the end of the metamorphose. It is used extensively for inflammatory diseases in Chinese medicine. Its antimicrobial effect should be investigated.

Numerous studies have been made in order to understand the medical value of *Lonomia oblique* caterpillars' venom. Especially, the anticoagulant and anti-apoptotic characteristic of the "lopap" (*L. obliqua* prothrombin activator protease) component of this venom is worth the attention. The most dangerous species of the family is *Lonomia obliqua* (Walker), therefore the pharmacological research are focused on this species. It may be useful in preventing coronary thrombosis by means of its anticoagulant effect.

Pederin is a strong toxin. It may have a strong effect on cancers and chronic wounds. It increases the effect of the used antibiotics. It may also be useful in antitoxin and anatoxin production. How come the toxin circulating in the Paederinae: Staphylinidae hemolymph, without harming the insect? A possible anti-pederine substance may be as important as the pederine itself. This molecule can be life saving in antibiotic resistant Gram-negative sepsis. Understanding the antimitotic role of pederine can be useful in developing a user-friendly drug in cancer treatments.

The highly toxic and caustic effect of cantharidin can emerge through consummation of and contact with the Coleopter. It effects bristle growth and was used in traditional medicine. Its toxic effect can be useful in producing antitoxin and anatoxin. Its antimitotic activity should be investigated. Its probabale aphrodisiac effect can be a huge commercial effect. Its sympathomimetic activity can be beneficial in some intoxications.

The structure of lucibufagins are similar to those of cardiacglycosides and has a cardiotonic effect. It may be playing a role in preeclampsia etiopatology. Its cardiac inotrop effect can be useful in schock treatment. It can be used a scanning test for preeclampsia. If its antitoxin can be produced, it can be a user-friendly drug in hypertension and hyperemesis gravidarum treatment.

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DOI: https://dx.doi.org/10.37871/ajpt.id26