Insectome: A treasure trove of pharmaceutical compounds

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Quite often we hear people talking about microbiome disturbance leading to unhealthy aging and going back to our ancestral habits including paleo diet has the potential to cure many diseases. This folk wisdom is supported by some recent scientific publications. However, we have majorly neglected the fact that paleo diet eating and cave-dwelling ancestors of ours had several insects on their bodies and inside caves, they constantly fought with insects. Thus we argue, if modern habits are responsible for the current epidemic of metabolic/cardiovascular/neurological and other degenerative diseases, may be insects also had some role to play in healthier aging of our ancestors as compared to us. In this blog post, we would like to review benefits of insect bitings/stings published in literature. Thus we will examine, if an apparent parasitic interaction between Human and insects is a mutualistic relationship in disguise. When an insect bites/stings us, it releases a barrage of biologically active compounds, including those with potential to act as anticoagulant/vasodilator. Can these chemicals be exploited to cure Cardio-Vascular-Diseases/dissolve internal blood clots? More importantly, there are other chemicals which have virucidal, anti-cancer and antimicrobial properties, which in either native or modified form can be repurposed for pharmaceutical applications.

"Nothing makes sense in biology except in the light of evolution"

This famous statement was given by an American evolutionary biologist in the 1970s (Theodosius Dobzhansky 1973), but even after 50 years of his idea, this makes complete sense to examine insect mammal relations in an evolutionary perspective. Monkeys, dogs, and rats still carry a variety of insects on their body, it is to be tested experimentally if getting rid of all of them leads to diseases. But we can certainly look at it from the perspective of insects, "how they may derive benefits from a healthier host?"

When a sick individual goes to a pathology laboratory for a blood test, differential blood count shows reduction in erythrocytes/red blood cells and concomitant increase in leukocytes/white blood cells. At molecular level, these individuals would have much higher ratio of number of

antibody molecules to rest of the protein molecules when compared to healthier individuals, if such individuals remains ill for prolonged time the ratio is expected to get even higher. Any such individual when utilized by a blood sucking insect as host, it finds harder to digest antibodies when compared with other blood proteins, as apparent from the fact that antibodies linger much longer than the major blood protein albumin and appear in insect counterpart of blood also known as hemolymph, after disappearing from the gut[1,2](Leighton *et al.* 2008, Hatfield 1988). This means that an insect biting to a sick host for blood meal/nutrients would require more number of feedings when compared with biting a healthy host. Also, when blood meal contains significantly more titer of antibodies more energy would be required in digesting and expelling waste out of the gut. One may have a counter argument that these lingering antibodies are actually a heck developed by insects to use these antibodies against invading pathogenic microbes of insects. However, it is not very practical for two reasons

(1a) if the insect is residing on one particular host, the host could be having decent neutralizing antibody titter against its own salivary proteins.

(1b) if the insect is jumping hosts, not just the possibility of salivary proteins, but cross reacting of antibodies from one host to another would be a big problem. It would become even more pertinent, when these two host belongs to two different species.

(2) Without an active adoptive immune system differentiating between antigen/antibody bound form and free antibodies would be nearly insurmountable challenge.

Even if we assume, that this is indeed a deliberate/active selection, pharmaceutical industry may greatly benefit from learning

(a) Identification of cross reactive/ self-recognising antibodies accurately and methods to neutralize them, especially when insects are not equipped with adoptive immune system, such a technique could be used universally, in blood transfusion products.

(b) Segregation of antibodies from a very complex mixture of blood proteins. This could be exploited for purification of industrial scale mAbs, without chromatography/ time consuming gradients!

Furthermore, loss of host is certainly not beneficial for insects, although a rapidly spreading viral disease with high fatality ratio might act as a temporary bonanza for insects but at the level of population/species, extinction would be looming from loss of hosts/habitat. One may argue that these could be plausible for infectious diseases and not the degenerative diseases of age, however, same antibody logic is applicable in case of autoimmune disorders. Also many of non-winged insects spend their entire life on the body of a single host and jumping

host is a rare occurrence, if such a host has problems related with health, its ultimately not in favour of parasitic insect.

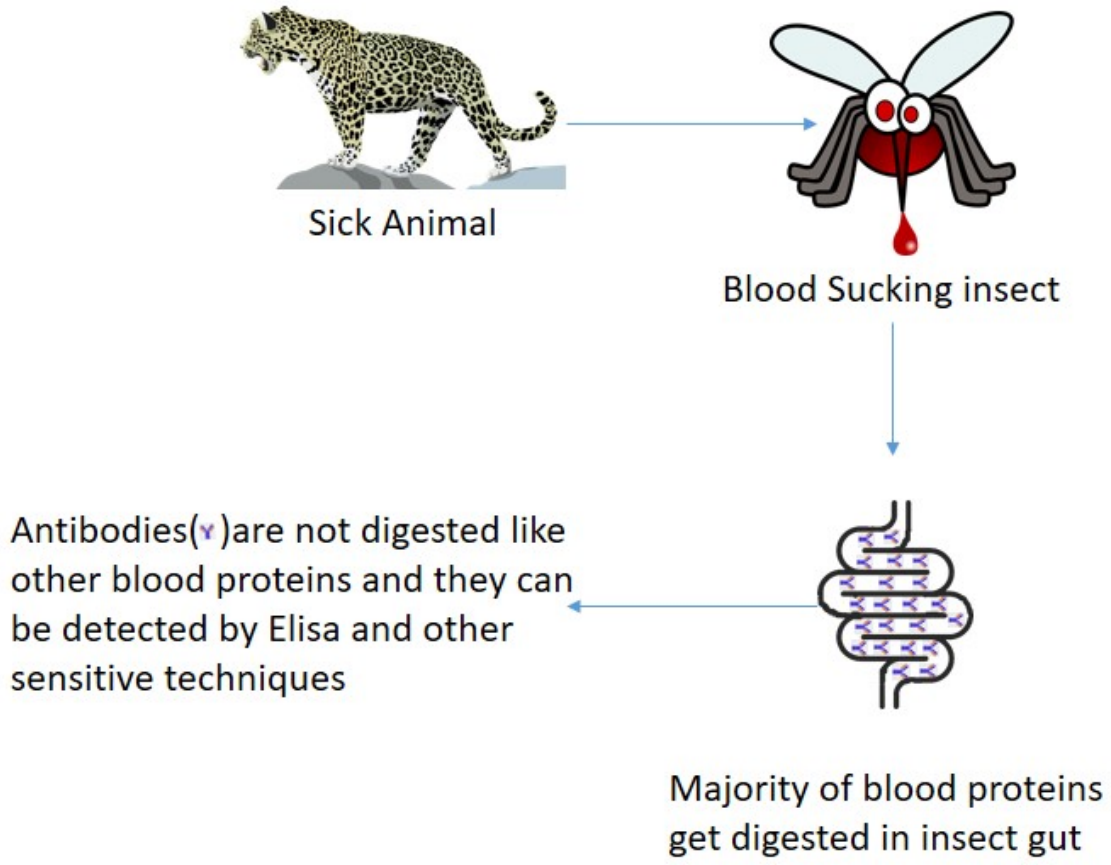

Figure 1: A sick host is not in the best interest of insects!

These logics are applicable to any blood-sucking (hematophagous)insects, but in the wild, there are a vast number of insects that do not bite but use their sting either as a defensive or offensive weapon. At the molecular level, these insects release potent toxins to leave the subjects paralysed/stunned. Cocktail of these toxins/venom block the cellular function of essential machinery, therapeutic doses of these are already being utilized, to treat conditions when the same essential cellular machinery becomes rouge/overactive. From an evolutionary point of view, killing an animal several orders of magnitude larger than the insect might not serve any function for it, instead, social animals learn and pass on information about pain to group/next generation, most commonly we can observe this when we see dogs running away from the smell of honey. Thus, it's possible to utilize non-lethal doses of toxins delivered as a drug substance.

Entomotherapy: A direct evidence of utility insects for medicinal purpose

Insects are used for food and medicine in many aboriginal tribal communities world-over. However, most of them derive these benefits from killing the insect and eating/harvesting parts of insect for this purpose[3,4].(Mozhui *et al* , 2021, Costa-Neto, 2005) Utility of live insect, which is main focus of this review is understudied. However, we have 4 prominent research backed examples to indicate utility of coexistence of live insects and humans.

(a) Helminth Therapy: In less developed part of the world and pre-industrialization world everywhere, existence of variety of worms protected us from auto immune disorders. Clinically it was found that in inflammatory bowel disease and multiple sclerosis removal of naturally acquired worms worsens the disease condition. Whereas introduction of helminth helped patients cope with disease[5].(Correale *et. al.* 2011). Very recently an animal model study found promising results of Helminth in alleviating obesity[6].(Tong *et al.* 2023)

(b) Apitherapy also known as Bee Venom Therapy: Variety diseases treatments are being attempted from the sting of honey bee. The applications include immune boosting to, treating pain of arthritis, viral diseases to even cancer (Alibraheemi *et al.* 2022)

Figure 2: Bee sting is a potential cure for a variety of diseases!

(c) Muggot Therapy: Global wound burden is rising and untreatable wounds can be cured with the help of muggots. *Lucilia sericata* larva is applied in most clinical settings for this purpose however other fly larvae are also being developed for this purpose. The fly larvae eat up dead skin leaving healthy cells behind and secret antimicrobials to

prevent infection. Even diabetic wound or high degree burn wound can be cured with help of fly larvae[8]!(Frank, 2022)

(d) Hirudotherapy or Leech Therapy: Ancient Egyptians depicted leech therapy in hieroglyphics, Indian Ayurvedic text mentioned it, and traditional Chinese medicine mentioned various benefits of it. Leeches suck blood and releases chemicals in blood stream that has therapeutic potential to cure inflammation/skin and infectious diseases. Scientific literature survey proves that if used with caution leech therapy is very promising[9].(Şenel *et al.* 2020)

Figure 3: Bloodletting by Leeches can relieve you of disease.

Apart from these we have research publication to make point that saliva from mosquito/lice and other blood sucking insect can leave beneficial effects on vertebrate host.

Conclusions:

Insect co-habitation could have therapeutic benefits, however, there is need to be careful as blood-sucking animals spread variety of diseases themselves. We suggest that pharmaceutical companies should identify and explore potential of such compounds from insects. These compounds can be harvested or synthesized and characterized for safer applications. Ancient Ayurveda mentions that disease and its cure exist at the same place, the study of insects living with our ancestors might just prove it!

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