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MEDICAL ENTOMOLOGY - A GREAT DISCIPLINE PROMISING INNOVATIONS, INVENTIONS AND ENTREPRENEURSHIP

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ABSTRACT

Medical Entomology is a highly fascinating and enterprising discipline with infinite possibilities of generating novel knowledge, on one hand, and innovative entrepreneurship, on the other. Insects, being spectacular, abundant and diverse group, are also most prodigious arthropods. They are important in the functions and processes of most ecosystems. Insects, arachnids, and other terrestrial arthropods comprise at least 75% of all the species of animals in the world. A great deal of scientific information on life come mostly from insects. Their dominance is a fundamental scientific insight yet not widely acknowledged. On one hand, some of these insects, especially hematophagous, are serious pests and vectors of serious diseases to both humans and animals. Such diseases warrant discovery of new insecticides, drugs, vaccines and tools for their management. The 2021 Nobel Prize to Dr Wu Tutu has been awarded for her discovery of a novel antimalarial, *Artemisinin*. On the other hand, a large number of insects and other arthropods are highly beneficial to humans as they are (i) sources for new protein molecules to be used in medicine, industry or insecticide production; (ii) saliva of certain insects, such as mosquitoes, is now being explored for producing anaesthesia; (iii) the flour-mite gene has a solution to epilepsy and (iv) certain carrion insects deserve a special attention for correctly pinpointing the post-mortem time interval (PMTI) of a dead-body. Medical entomology has thus earned a commensurate sobriquet, "employment & trade discipline of future."

Keywords: Medical, entomology, insects, arachnids, knowledge, industry

At the outset itself, it is to be borne in mind that because of high popularity and global acceptability of the term Medical Entomology where, besides insects of public health significance, even other arthropods carrying medical importance are conventionally included for the sake of convenience only, I am herewith continuing to use the term medical entomology in the same liberal sense to explain the larger world of medically useful arthropods (Service, 2014; Tyagi, 2003; 2020).

Arthropods, particularly insects, have been biomedically understood to be more hazardous than beneficial. On one hand, several of the arthropods are without doubt mediating as nefarious vectors in transmission of a large number of deadly and debilitating diseases such as malaria, lymphatic filariasis, dengue etc. across the world and sapping countries off their invaluable resources like health, economy and intelligentsia; on the other hand, many of them offer a highly fascinating and beneficial aspect of their life where from an immense potential for deriving either new molecules or processes in modern medicine can be traced. It is a pity, however, that our knowledge pertaining to this arcane discipline of invertebrate bioprospecting is woefully abysmal despite the fact that invertebrates forming more than 90% of all the world's extant fauna of which over 50% are the arthropods. Use of insects in medicine has a good reason to depend upon in the future. Simply because of their enormous range of adaptability, insects have been awfully dominant in conquering most of the available niches on the planet; terrestrial, aquatic, aerial, marine, on or inside other animals, on or inside plants; and as a result these also show a great biodiversity and a tremendous range of unusual and often bizarre chemical solutions to their lifestyle challenges!

Use of natural products in the discovery of medicines has been the single most successful strategy. This is mainly because natural materials have less undesirable properties ("side effects") than synthetic chemicals. Plants owing to their highly advantageous sedentary habits and a huge diversity of microbes and bacteria have long been targets for discovery of therapeutic drugs, but insects have been left virtually untouched. In recent years, however, interest has been turning to the insects as a source of detection of new chemicals and materials of immense application in remedying human sufferings. Drugs derived from plants are common but insects are an untapped resource. Interestingly, while there are only 250,000 plant species on Earth, there are possibly more than 4,000,000 (i.e., 16 times more than the plants) extant insect species. These insect species (i.e., of which at least 2 million species are actually catalogued) have developed sophisticated immune system over 500 million years, allowing them to produce a range of molecules to fight bacteria and other pathogens.

Medical entomologists today have many important jobs, such as the study of classification, life cycle, distribution, physiology, behaviour, ecology, and population dynamics of vectors of serious human and animal diseases. They also study urban pests, forest pests, agricultural pests of medical and veterinary importance and their control. Through feeding, insects and other arthropod vectors transmit diseases to humans. Medical entomologists and other medical professionals have helped to develop vaccines, (e.g., RTS, S-AS01) that can prevent humans from contracting some of the diseases such as, malaria – the oldest vector-borne disease in the annals of human evolution which continues to inflict 2.5 billion people and kill over 400,000 of them worldwide annually (Fig. 1). They have also developed ways to prevent the arthropods from biting humans such as the development of repellents, e.g., N' N' Diethyl Phenyl Acetamide (DEPA), an Indian product (Kandasamy, 2021).

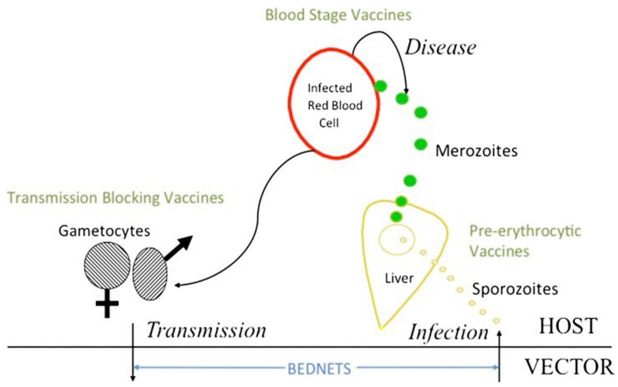


Fig. 1. Three-dimensional approach to develop malaria vaccine, where medical entomology plays an important role

GREATEST DISCOVERY OF THE MILLENIUM

In the mid-19th century, hundreds of vector-borne diseases have been described in humans, pets, livestock and wild animals. The pathogens involved include viruses, bacteria, protozoa and filarial worms, and the vectors belong to several groups of arthropods. But there are many arboviruses whose vectors are yet to be pinpointed or whose vertebrate hosts (if they have only been isolated in arthropods) have not yet been identified. Medical and veterinary entomologists still have plenty of discoveries to make (Duvallet et al., 2017).

Although the foundation of medical entomology was made by Dr Patrick Manson through his pioneering discovery of connection between human lymphatic filariasis and mosquito (*Culex pipens*), while working as a medical officer in China, in 1878, it was however Ross (1897) who truly deciphered the age-old mystery of transmission of malaria by demonstrating the inexorable connection of malaria parasite with the anopheline mosquito, *Anopheles stephensi*. His peregrination into malariology is a great lesson in science where nothing short of maddening focus and dedication alone fetch the desired results of experiments. Dr Ross prepared a manuscript on his discovery, titled, "On some peculiar pigmented cells found in two mosquitoes fed on malaria blood" which was published in The British Medical Journal on 18th December, 1897. Later he confirmed the finding in another type of 'dappled Winged Mosquito'

(*Anopheles culicifacies*) (Fig. 2). Dr Ronald Ross was awarded Nobel Prize for his discovery in 1902.

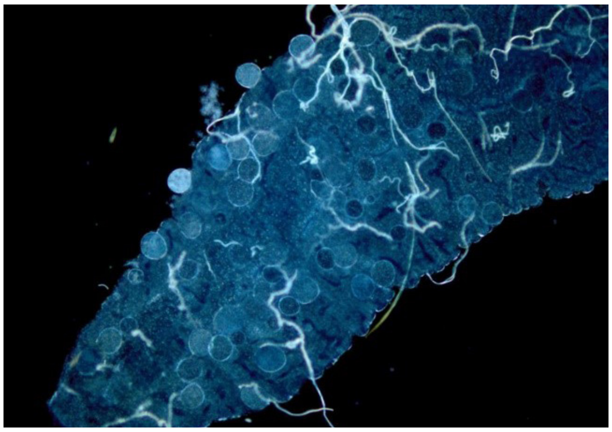


Fig. 2. Mosquito stomach showing Oocysts which were originally noticed by Ross (1897)

SHIFT FROM THEORETICAL TO APPLIED MEDICAL ENTOMOLOGY

Today's entomologists are required to take a new approach to the insect science, especially those which carry biomedical significance such as "vectors", by placing them in a historical, medical, socio-economic and environmental context and drawing on a wide range of complementary disciplines, from taxonomy to public health, and their control through consilience. This transformation from a theoretical to applied biology of insects is filled with fables of innovations, inventions and discoveries. Entomologists themselves are often unaware of the importance of this historical dimension - the subtility of observation. Our predecessors trod a long and difficult path before eventually reaching the conclusion which today seems so obvious, for instance, Ross' (1897) epochal discovery of the inextricable relationship between mosquito and the malaria parasite led to our understanding about a certain way to control the deadly malaria vis mosquito control. Young entomologists will do well to reflect on the foresight, dedication and bravery displayed by those who went before them to provide us with the body of knowledge we take for granted today. We should draw inspiration from our forebears when we are called to investigate a new research question. Who knows, some budding medico-entomologists may even see their own names go down in history because of their discoveries and research!

BIOMEDICAL SIGNIFICANCE OF NON-VECTOR INSECTS/ ARTHROPODS

Insects are potentially a vast area of medicinal research. They are vectors of serious diseases like malaria, filariasis, dengue and many others caused by protozoans, helminths, viruses etc. They produce molecules that kill cancer cells, proteins that prevent blood from clotting, enzymes that degrade pesticides, proteins that glow in dark, substances maneuvered to develop an antidote for treating life-threatening fungal infections, and anti-microbial peptides and toxins. It is argued, however, that those insects which undergo through a full metamorphosis tend to produce more potent peptides, that is small proteins that can be used as drugs.

Milking the potential of insects to combat diseases, instead of abhorring their nefarious acts of transmitting deadly diseases, marks the dawn of a new era in modern medicine. The science of medicine is ushering into an altogether new and exciting world of resources, the insects, and now it is up to scientists to identify the novel compounds found in these fantastic creatures and how these benefit health. Two examples will more than justify the need to look at the kingdom of the "jointed legs", particularly the insects, for a great science in the offing.

(i) bloodless fruit flies have been identified to possess a gene that makes human blood clot and which helps venomous cone snails, another invertebrate members, produce an experimental drug against epilepsy, and

(ii) the flour mite, *Acarus siro*, has been identified to contain an anti-microbial peptide having activity against *Bacillus subtilis* and *Pseudomonas fluorescens.*

Insects as protein factories

Insects are being reared to raise raw pharmaceutical proteins, to directly benefit humanity. Recombinant baculoviruses have been used before to develop a panorama of pharmaceutical proteins, these were done so using the insect cell culture method which is, in fact, a time consuming and expensive methodology. On the other hand, rearing proteins in insects is substantially less expensive than cell culture. Efforts are afoot to harvest the beneficial protein from the infected larvae of lepidoptera (moths and butterflies). Though the use of genetically engineered baculoviruses attacking the inside of the larvae and initiating a wholesale, metabolic change to kill the insect. The protein is harvested just before the insect dies. This protein can later be refined into pharmaceuticals. There is adequate information that recombinant baculoviruses have been used for vaccine production. Some diseases that can be fought include human papillomavirus, human T-cell leukemia virus, hepatitis C virus, Norwalk virus, rotavirus, porcine parvovirus and African swine fever virus. Farming pharmaceuticals from these little protein factories is a highly enterprising and big leap in biomedical sciences.

Medicines from transgenic plants or animals have become quite accepted principle but this is quite amazing to produce drugs from insects. Genetically engineered "Medfly" a fruit pest in the Mediterranean region, is on the anvil of being used to produce human growth hormone. Plans are also floored to produce genetically engineered flies for the life-saving drug, alfa-glucosidase. The drug is used against a debilitating muscle condition in human called Pompe's disease.

Insect as source of antimicrobials

The optimism that the current antimicrobial chemotherapy will last well into the future is declining as new and re-emerging outbreaks of antimicrobial drug resistant infections continue to spread. Infectious disease will remain a significant problem that will need to be continually and effectively controlled. Managing this issue will require increasing surveillance, establishing proper use of antibiotics in the community and encouraging antibiotic research not only in small companies but in larger pharmaceutical corporations (Brogdon and McAllister, 1998). Ignoring the speed of the evolution of resistant pathogens will only lead to expensive and disastrous losses when all traditional means for infectious agent control finally fail.

Due to the urgent need for a new class of antibiotics, a minority of research groups and pharmaceutical companies are still seeking out unique strategies and are proving that there are still a few discoveries to be made (Wang et al., 2000). Recently, the clinical development of "nature's antibiotics", cationic peptides, has been growing. About 20 years ago, they were identified in the lymph of insects and on the skin of frogs. To date, more than 600 cationic peptides have been observed in virtually all known plant and animal species and have been proven to be an important component of immunological systems. In mammal tissues, several different peptides per single tissue have been found, each at relatively low concentrations. These peptides have been shown to kill microorganisms directly and may do so through several proposed mechanisms. To cross the outer membrane of bacteria, cationic peptides are thought to use self-promoted uptake. Unfolded cationic peptides associate with the negatively charged bacteria surface. They either neutralize a large patch of the membrane or bind strongly to it, effectively disrupting the membrane and translocating across (Rash and Hodgson, 2002; Hancock, 2001). Once across the outer membrane, the cationic peptides insert into the cytoplasmic membrane leading to bacterial death through four possible outcomes: cell lysis, pore formation in the cytoplasmic membrane, cytoplasmic membrane dissolution, or by attacking internal targets. There is evidence that not only are the cationic peptides antibacterial, they also have important roles in innate immune system function.

SPIDER TOXINS AS INSECTICIDE LEADS

Insecticides have so far been derived from plants and microbials, but it appears that animal-based insecticides will also be available before long; after neris and termites it is the spider which is the central attraction of all scientists who are busy isolating and characterizing the novel insecticidal neurotoxins. In addition to their utility as insecticide leads, these toxins have enabled the identification and validation of novel insecticide targets, and ultimately these are expected to be valuable pharmacological tools.

Insecticide design: what can we learn from venomous spiders?

Most spider venoms are likely to be rich sources of insecticidal compounds since their primary role is to kill or paralyze arthropod prey (Fig. 3). Thus, it seems surprising that spider venoms, which are likely to contain more than a million different pharmacologically active peptides, have not been explored as thoroughly as those of other venomous creatures such as scorpions and cone snails. While numerous peptide neurotoxins have been isolated from spider venoms (Escoubas et al., 2000), most were purified based on activity against vertebrate targets. These toxins generally show little or no preference for invertebrates and hence they are not particularly useful as insecticide leads.

Fig. 3. Milking a blue mountain funnel-web spider.

Isolation and characterization of insect-specific spider toxins might be useful as insecticide leads and for defining novel insecticide targets.

Australian funnel-web spiders: the lead for a potential insecticide toxin:

Spiders are taxonomically divided into two major suborders, Araneomorphae and Mygalomorphae. The Araneomorphs, or modern spiders, evolved after the appearance of flying insects, and they now represent ~90% of the world's spiders. Many of these spiders have devised elaborate means of using their silk to capture flying prey, the most spectacular being the orb-web weavers. Araneomorphs generally live for only 1-2 years, and, because of their small size, venom acquisition often requires electrical stimulation or complete removal of the venom glands.

The ancestral lineage of the Mygalomorphs, or primitive spiders, dates back 360 million years, before the evolution of flying insects (Brunet, 2008). These spiders have several qualities that recommend them as a venom source for insect-toxin screens. First, Mygalomorphs only use silk in a rudimentary manner, relying instead on their physical size and often massive venom apparatus to immobilize prey. Second, Mygalomorphs usually have long-life spans, with the females of many species living longer than 20 years. Third, when provoked, many of these spiders adopt an aggressive/defensive "ready-to-strike" stance with forelegs and palps raised and fangs exposed. This enables venom to be aspirated directly from the fang tips without the need for electrical stimulation which can contaminate the venom with enzymes from saliva and digestive fluids. The combination of long lifespan and facile milking enables sufficient venom to be obtained from a relatively small cohort of captive spiders for detailed biochemical and biophysical characterization of individual venom components.

A detailed screen of venom from the Blue Mountains funnel-web spider, *Hadronyche versuta* has made many revelations. This analysis led to the discovery of several families of novel insect-specific neurotoxins as well as additional members of the w-atracotoxin-1 family. It should be stressed that these toxins are highly insect-specific; they have no activity in any vertebrate system that has been tested thus far.

INSECT LUMINESCENCE AND FLUORESCENCE AS SOURCE OF NEW MOLECULES IN MEDICINE

Several arthropods, particularly insects, are a rich source of biochromes including carotenoids, chromans, flavonoids, porphyrines, melanins, phenoxaxines, purines, pteridines, isoalloxazines and quinines as well as biochromic proteins. These biochromes have multifarious roles in insects' life. In addition to visual and primary metabolic functions, these biochromes provide a chemical protective environment against predators, infections and climatic calamities etc.

These also serve as precursors to bioluminescence and fluorescence.

There are no luminous flowering plants, amphibians, reptiles, birds or mammals, so invertebrates have this trait pretty much to themselves, albeit some deep water mine fishes do have this special characteristic. Bioluminescence is manifested by many insect groups such as Collembola, Homoptera, Diptera and Coleoptera. Insects are capable to luminesce on their own as well as by associating with certain fungi and bacteria. Self–luminescence in these group-insects is due to the action of a 100,000 Dalton enzyme, luciferase, on the biochrome luciferin in the presence of ATP.

Fluorescence, like luminescence, is common amongst invertebrata, particularly molluscs, and quite many arthropods specialize in this field (e.g., copepods, centipedes, millipedes and insects). The phenomenon of fluorescence is by intracellular calcium movements or, as recently demonstrated, by the aequorin gene in jellyfish *Aequoria victoria*. Aequorin or GFP (green fluorescent protein) is a calcium-dependent fluorescent protein which has been expressed in fungi, bacteria as well as plants. As obvious from its name the GFP emits green light upon excitation with ultraviolet to blue light.

Bioluminescence

Bioluminescence is the emission of visible light by living organisms for communicative purposes. It is found in bacteria, fungi, algae, coelenterates, annelids, arthropods and fishes.

Bioluminescence is generated in special kind of cells called photocytes. Inside the photocytes, the light is generated by the efficient conversion of potential energy of chemical bounds into light during oxidative reactions. These reactions involve the oxidation of organic compounds generically known as luciferins by oxygen generating energy rich peroxy intermediates. The spontaneous breakdown of these unstable peroxy intermediates produces electronically excited products (oxiluciferins) that decay to the ground state emitting photons of visible light. Luciferases are the key-enzymes that make such processes possible, by catalyzing these reactions with extreme efficiency. Despite the use of the generic terms luciferin and luciferases, these compounds are different from one organism to the other.

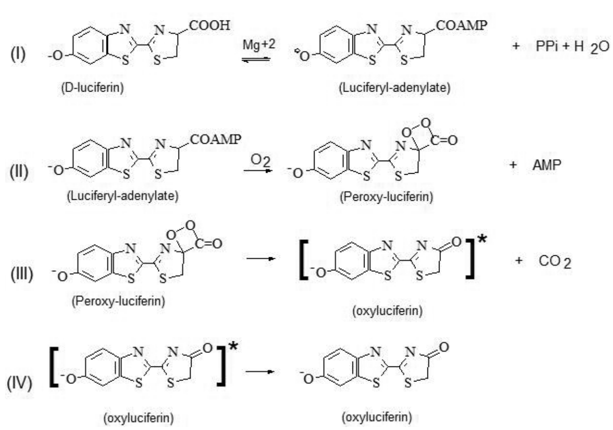
Insect bioluminescence

Among all arthropods groups, or for that matter all the invertebrates, the insects have the largest number of luminescent species (Fig. 4, 5). Luminescent species are found in Collembola (springtails), Diptera (fungus-gnats; Mycetophilidae) and Coleoptera [Fireflies (Lampyridae), click beetles (Elateridae) and railroad worms (Phengodidae)]. Bioluminescence in insects assume different biological functions: (sexual attraction) fireflies use their flashes for courtship; (defence) click beetles use their thoracic lanterns to startle enemies; (illumination) railroad worms may use their head lanterns to hunt their preys; (prey attraction) fungus-gnat larvae and some click beetle larvae that live in termite mounds use their luminescence to attract preys.

Fig. 4. A bioluminescent arthropod larva

In insects, there are at least three known bioluminescent systems which are biochemically distinct:

(1) the bioluminescence system of the Australasian glowworm Arachnocampa;
(2) the bioluminescent system of the North-American mycetophilid Orfelia fultoni, and
(3) the well-known system of fireflies and other beetles.



Certain important bioluminescent molecules in formulae

In the case of beetles, bioluminescence involves ATP, a benzothiazol luciferin and homologous luciferases. In the first step, beetle luciferases catalyze the activation of luciferin at expenses of ATP. In the second step, the activated luciferin (adenyl-luciferin) is oxidized producing the peroxy intermediate whose breakdown will lead to oxyluciferin, carbon dioxide and light. Besides catalyzing the light emitting reaction, the luciferases are also responsible for the different colors of bioluminescence observed in beetles.

Why bioluminescent insects are so important?

Besides their beauty and scientific interest, bioluminescent species are very important to society because their luciferases and luciferins are currently used as very sensitive tools in biotechnology and biomedicine. Beetle luciferase genes are used as bioluminescent markers to measure gene expression in living cells and tissues, to diagnose bacterial and viral diseases such as tuberculosis and HIV, for fast screening of anti-microbial drugs against these pathogens, and as biosensors for the presence of pollutants and environmental disruptors among many other applications.

Structure/Function relationship of insect luciferases

Scientists are currently embarking on many aspects of insect bioluminescence. The main focus is the structure/function relationship and origin of insect luciferases, particularly with reference to the relationship between luciferases structures and bioluminescence colors using railroad worm and click beetle luciferases as models. In the past years scientists have successfully cloned several of these beetle luciferases which produce different bioluminescence colors, among them, the green and red emitting luciferases of the beautiful *Phrixothrix* railroad worms. Using site-directed mutagenesis and protein engineering techniques efforts are underway for identifying regions and residues important for bioluminescence coland activity. Among them, the region between residues 215-344 and the residues Arg215 and Thr226 in pH-insensitive luciferases are important for bioluminescence colors.

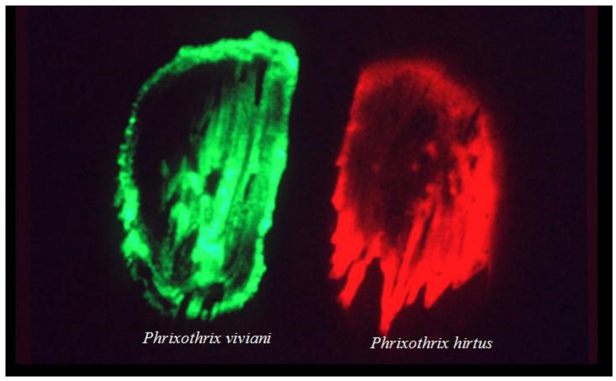


Fig. 5. Two bioluminescent *Phrixothrix* species

According to their spectral properties, beetle luciferases are grouped in pH-sensitive (fireflies) and pH-insensitive (click beetles and railroad worms) groups. The green and red luciferases of *Phrixotrix* railroad worms are models for the study of the relationship between luciferase structures and bioluminescence colors. Through protein engineering techniques using these luciferase models, we have also constructed color mutants that produce yellow and orange bioluminescence. In the Fig. 4 one can see bioluminescent *E. coli* transformed with the cDNAs for the green and red-emitting *Phrixothrix* railroad worm luciferases.

More recently, researches are directed towards investigating the bioluminescent systems of the fungus-gnats *Orfelia fultoni* and *Arachnocampa* spp (Diptera: Mycetophilidae) which produce blue light. The fungus-gnats include bioluminescent species with anatomically and biochemically distinct luminescent systems. One of the most fascinating phenomena scientists are deciphering involves investigating the origin and molecular evolution of insect luciferases and their bioluminescence so that these studies will help to develop new luciferases with specific properties for biotechnological and biomedical purposes. The whole phenomenon of insect/arthropod bioluminescence also throws sufficient light on conserving an array of luciferases in various tropical forest ecosystems, thereby directly advocating protection and preservation of an already declining verdure of our planet.

> Beetle luciferases arose from ancestral AMP-ligases. After the bioluminescent activity arose, these enzymes evolved in a multitude of luciferases emitting different colors of light ranging from the green to the red region of the spectrum.

BIOMATERIALS

Insects, or for that matter all arthropods, classified under invertebrata, lack in backbone. However, to provide support and strength to their varied forms and sizes, insects have evolved a range of novel structural materials to protect themselves and their progenies as well as for numerous other inevitably vital functions such as shelter, foraging etc. Many of these structural solutions comprise extremely unique and fascinating materials like cuticles, which are remarkably strong mechanically, resistant to physical, chemical and bacterial degradation, and are composed of long protein chains mutually rotated to form a natural "plywood" - which could be a polysaccharide embedded in a protein matrix in adults, or protein fibers in a protein matrix as encountered in eggshells and egg-cases. Insect cuticle is a complex and variable mixture of chitin and protein laid down in layers, the exterior of which is composed of protein only with chitin/protein composites underlying it. In many insects the protein component is tanned by crosslinking of chains by aromatic compounds.

Resin, a perfect rubber, is another remarkable protein produced by hexapods such as the jumping insects. It has no regular structure, but its randomly coiled chains are crosslinked by di-trityrosine links at just the right spacing to bestow on these insects the fabulous property of elasticity needed to propel over enormous distances. Insect materials like honey, shellac and beeswax are well known for their worldwide use, also in medicine.

INSECTS IN ETHNOMEDICINE

Entomo-ethnomedicine or use of insects in traditional medicine has been in vogue for centuries both in India and elsewhere, but it is only in recent times that scientific recognition is accredited to such a practice in using insects-based lotions and remedies, even as desserts or appetizers, to cure a host of ailments, on one hand, and develop immunity, on the other. A large number of insects are known to be used in ethnomedicine. Termites, particularly the voluminous queen termite of some of the large-sized species, are on menu of Indonesians. Ants have been reported to be savoured in some south Indian areas. In the north-eastern States in India dragonflies, and even butterflies, along with several other insects, are commercially sold and relished raw as desserts (Tyagi, 1981). Seventeen arthropods, many of which being insects, and their products are widely used in south Korea against a wide range of illness, including stroke and arthritis. In China, where presently about 140 medicinal insects have been recognized and of which some are even mass-generated for the production of medicines, the crushed insects have been used for hundreds of years to treat a range of ailments including infections, inflammation and stomach complaints. There is a particular ant species, *Polyrhactus vicina*, which is believed to help immune system when a drink tonic prepared from this ant is drunk. This ant species contains a lot of zinc which has been identified for some time as a immune stimulant and an antioxidant. In United States of America ant drinks have been used as a hallucinogen, while in Britain during the Middle Ages these have been on use as a tonic for general ailments. In Thailand use of both the insects and their by-products, honey and beeswax, is common in traditional medicine as these little creatures are used singly while some others are mixed with herbs and other natural ingredients. Even sometimes they are used alive and on other times after being heated in specific fashion. In sub-Saharan Africa , clay geophagy using termite mound and mud-daubing wasp nests is practiced by pregnant women. In practice has also been an arcane and bizarre methodology of stitching the cut wounds by using the mandibles of ants and termite soldiers. Insect behaviour or the "doctrine of signatures", too, has sometimes been taken as a means to improve the human physiology (e.g., cicadas, stick insects and caterpillars).

The above remedies do not come from blues or fairytales, they exist in real life as part and parcel of day-to-day living. These are time-tested and may be further strengthened by putting them to the scientific test. Indeed, it will be a pity if this wealth of infinite wisdom on entomo-ethnomedicine do away without making a sincere look at it. Already an international conference on insect food and feed has been organized in the Netherlands in 2013 to attract the world's attention to this very important group.

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