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Medicines Derived from Insects: A Review

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Abstract: ***Insect derived products like honey, venom, silk and insect like maggots have been widely used in folklore medicine for thousands of years. Drug activities detected include powerful antimicrobials against antibiotic-resistant bacteria and HIV, as well as anti-cancer, anti-angiogenesis and anti-coagulant factors and wound healing agents. Previously, a number of overviews on insect natural products and their potential for development into drugs to treat human diseases have been published. Recently, however, there have been additional advances in this field. The present review therefore focuses on these as well as their implication for present day drug development.***

Keywords: Insect derived products, folklore medicine, honey, venom, silk, maggots

1. Introduction

In recent years, the antibiotic resistance has become a serious concern to human health, and if everyone does not act against this threat, the world is on the verge of a post-antibiotic. This phenomenon is not a regional only but also affects the poor countries as well as the rich countries. Hence, modern research sparked to explore new resources. In this context, medicines derived from insects have been widely used throughout history for medical treatment, and they are a common part of the component of Traditional Chinese Medicine [1]. Insects are considered as the most successful and diverse group of animals. They constitute about three-fourths of the total number of living organisms present on the planet [1]. From the all-known animal species, approximately 80% of them are insects [2-3]. Estimations of 200,000,000 insects per one human and 40,000.000 insects per one acre of land have been reported [2]. Tremendous biodiversity and numerous utilities of insects brought them in steady services of the mankind like other resources [2-3].

Concerning their utility, insects can be divided into 4 categories. First is the use of insects in industry which assures utilization of honeybee, silk worm, dye insect, lac insect and aesthetic insect. Second is therapeutic and nutritional utilization of insects. This includes usage of insects in traditional medicine and as food resource. Therapeutic application of honeybee products (honey, royal jelly, beeswax, bee venom, bee bread, pollens and propolis) has been reported to cure diseases like rheumatic pains, arthritis, back pains, cancers and other diseases. Third is the application of forensic entomology. By investigating the succession of insects and different stages of insect colonizers, a rough estimation of the postmortem intervals can be calculated. Fourth is the use of insects as ecofriendly component. Predators and parasites could be used as potential biocontrol agents of destructive pests. House fly larvae are used as biomass recycler. These decompose organic wastes to produce proteins and fats.

Thus, insects have been utilized by people in different ways around the world. Laboratory and clinical investigations on the honey and other bee products have increased during the past decades. Honey, royal jelly, propolis and bee venom have proven their strong antibacterial activity [3]. Previously, a number of reviews on insect derived natural products and their potential for development into drugs to treat human diseases have been published [3–5]. However, there are the significant recent advances in developing insect as potential new alternative medicinal drugs. This is an exciting and rapidly expanding new field since insects are hugely variable and have utilized an enormous range of natural products to cope up the environmental perturbations for many years.

Considering the above-mentioned facts, the present review has focused on the significant use of silk, honey, maggots and other natural products from insects with potential use in alternative medicine

2. Insect natural products in folklore medicine

Various cultures around the world, particularly in the tropics, have long histories of using insects for a wide variety of functions including production of materials such as silk, for art, in rituals, for food, and as medicines to alleviate disease and suffering [6, 7]. The use of insects in folk medicine has been particularly common in China and in the State of Bahia in Brazil [8, 9], but is also present in many other counties including Latin America, Mexico, India, Africa and South Korea [5, 6] An estimated 300 insect species are used to produce 1700 traditional Chinese medicines while 42 species have been used in Bahian Folk Medicine [8, 9]. Most medicinal uses of insects by various cultures involves some preparation of the whole insect, often the medicines are extracted from the stings of bees and wasps, or by grinding up the toasted bodies of insects or from their secretions, and then teas made for drinking or ointments for external use [5]. Sometimes the extracts from Blister beetles have been used by the Greeks for enhancing sexual libido or to increase love charms [8]. Some of the examples of Insect Folk Medicines which have subsequently proven to have great potential as an alternative medicine include:

i. Silk prescribed for flatulence, dissolving phlegm, and relieving spasms.
ii. Maggots for treating wounds to enhance healing and reduce infections.
iii. Honey products for treating wounds and infections.

iv. Bee, wasp and ant venom for cancer and all sorts of infections e.g., TB, flu, and colds.

3. Silk

Silk, a structural protein is known to exhibit an excellent combination of mechanical features, such as strength, modulus, elasticity, and toughness and it represents a distinct class of biocompatible and green polymers. It has been focused upon in biomedical research pertaining to its biodegradability, low immunogenic response and easier processability [10]. Silk can be credited as one of the most ancient materials known to man which has been documented for its use as a medical suture, as early as 131–211 A.D by Greek physician Aelius Galenus [11]. Silk has been produced for at least 5,000 years with nearly 75% now originating from China [3]. In Chinese medicine, silk has been used for a variety of human conditions including the relief of spasms and flatulence. Interestingly, silkworm larvae have also been prescribed for treating impotence [12]. Interest in the medical or industrial use of silk is not confined to the silk produced by silkworms since many other insects such as the Hymenoptera (bees, wasps, hornets, and ants) and the Trichoptera (caddis flies), as well as the Arachnida (spiders), produce silk. Scientists have been developing both kinds of spider and silkworm silk for potential uses in medicine. Silkworms silk is available in large quantities without recombinant methods necessary. However, interest persists in spider silk, despite the fact that it is impossible to develop large-scale farming of spiders, due to the fact that spider silk is extremely strong, flexible, and tough and therefore particularly promising for the production of biomaterials.

The recent work of Numata et al. [13] indicates that rapid progress is being made in the development of silk for use in medicine. They have used recombinant technology for the synthesis of spider silk in E. coli to produce silk polymers which were then used for the production of microspheres/nanoparticles and block copolymers for the targeted delivery of drugs to cancer cells or to act as gene vectors. There are also numerous recent studies of the use of silk in tissue engineering. Recent research by the same group showed that modified silk polymers can be used for the tissue engineering, vaccine production without the need for refrigerated storage, and cosmetic surgery. A number of start-up companies have been spawned and the future prospects have great potential [14]. In addition, they have looked at silk-heparin biomaterials for vascular tissue engineering, silk hydrogels for treating breast cancer. Thus, the works cited here reflect that silk based nano biomaterials hold prospects for technology translation and commercialization.

4. Maggot debridement therapy

Chronic wounds are not only a problem to their patients, but also a burden on the healthcare system due to their extensive costs. A promising alternative treatment that has re-emerged over the last 20 years is maggot therapy (MT), also known as maggot debridement therapy (MDT) or larval therapy [15]. Maggot therapy promotes wound healing by performing three key processes: deliberate utilization of live, medical-grade fly larvae for the process of wound healing, disinfection, and the debridement of wounds [16]. It can be used for the debridement of non-healing necrotic skin and soft tissue wounds, including pressure ulcers, venous stasis ulcers, neuropathic foot ulcers and non-healing traumatic of post-surgical wounds. With the increase in chronic diabetic foot wounds, maggot debridement therapy is a promising tool for health professionals dealing with difficult wounds [17].

Currently, MDT is used mostly when other conventional therapies fail or when non-surgical debridement of the wound is being considered. Currently, there are two methods of larval application. The first method is using larvae sealed within a dressing called biobag. They come in varying sizes to match different wound sizes. The larvae remain sealed inside the biobag throughout the treatment period. The other method is to use free-range larvae applied directly on the wound. Biobags can be left in place up to 4 days and free-range larvae are also left in the wound for up to 4 days per application. The number of applications required for complete wound debridement depends on the type of wound and ranges from one to several per treatment session.

Luciliasericata maggots [18] are the only species currently approved for MDT, an alternative treatment for chronic and recalcitrant wounds. The evidence for MDT is encouraging, and there is a continuous rising trend in its use. There has been a renewed interest in MDT and its role as a form of antimicrobial treatment for infected wounds. With the emergence of antimicrobial resistance, we are again likely to see its increased use in drug-resistant wound infections. Systematic reviews evaluating MDT have highlighted its successful role in treatment of Gram-positive and Gram-negative bacterial strains, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, Methicillin-resistant *Staphylococcus aureus*, and other drug-resistant pathogens. Clinical studies have confirmed a decrease in bacterial load following its use. The main mechanism of antimicrobial activity has been thought to be by the destruction of bacteria in the hind gut of the larvae. Other mechanisms include excretion of waste products like ammonia by the larvae, and secretion of other bactericides that may be responsible for combating bacterial pathogens. Medicinal maggots also have antifungal activity. However, more research is needed to demonstrate the indirect antibacterial activity observed in clinical studies, such as the possible presence of the immuno-modulatory effect of MDT [19].

In conclusion, MDT satisfies nearly all expectations for optimal wound care: fighting infection, debridement, provoking wound healing. Its low cost, non-offensive nature and absence of systemic effects make this method a good alternative of conventional wound healing treatment.

5. Bee venom therapy

Apitherapy is the use of honey bee products for medical purposes whereas; bee venom (BV) therapy is the use of live bee stings (or injectable venom) to treat various diseases. About 2, 500 years ago Hippocrates employed bee stings in his therapeutic activities. To treat different

diseases, such as arthritis, rheumatism and pain bee venom therapy have been used in traditional medicine. BV is produced by the venom gland located in the abdominal cavity and there are more than 60 identifiable components in BV, and melittin is the most biologically active peptides presents as a major component of BV. It also contains a variety of peptides including apitoxin, apamin like peptides and amines like histamine and epinephrine, sugars, minerals and nonpeptide components with a variety of pharmaceutical properties [20].

Melittin is a potent toxin found in BV. It can penetrate holes in the protective viral envelope that surrounds the human immunodeficiency virus (HIV), as well as other viruses such as herpes simplex virus and Junín virus. It is also effective against Gram-negative bacteria. Melittin causes lysis of membranes of both Gram-negative bacteria as well as the membranes of enveloped viruses such as murine retroviruses. Alternatively, melittin has anti-HIV activity well below virolytic levels and also functions to inhibit HIV gene expression [21].

The anti-arthritic properties of apitoxin present in BV have been known for epochs. The mode of action of apitoxin is thought to involve blockage of sensory nerves and, because of the presence of the enzyme hyaluronidase, increased capillary permeability. For this reason, the long-established habit of administering bee stings to heal rheumatism has a possible physiological basis: ‘‘increased capillary permeability means enhanced blood flow to afflicted areas and ganglionic blockage means reduced perception of neuralgic pain’’ [22].

Medicinal use of BV therapy wields significant *in vivo* and *in vitro* outcomes to some extent mitigate the effects of Parkinson’s disease, Alzheimer’s disease, HIV, arthritis, liver fibrosis, cancer, tumors, fibrotic diseases, Lyme disease, etc. BV uses in treating arthritis by blocking the building of the pro inflammatory substances cytokinine, PGE-2, NO, Tumor Necrosis Factor TNF-2 and Enzyme COX-2, and inhibiting the proliferation of rheumatoid synovial cells [23]. After applying different methods of venom administration like: bee stings, api-puncture, injections, electrophoresis and application with ultrasound waves (phonophoresis); good success rates lying between 60 and 90 % have been achieved [24].

BV has anti-cancer activities, due mainly to two substances that have been isolated and characterized: melittin and phospholipase A2 (PLA2). BV has different effects on the central and peripheral nervous system and used for the treatment of different neurological conditions such as Multiple Sclerosis (MS), amyotrophic lateral sclerosis (ALS) Alzheimer’s and Parkinson [25]. BV also increases coronary and peripheral blood circulation, improves the blood microcirculation, slows down heart at lower doses and stimulates it at higher ones, lowers blood pressure, antiarrhythmic against blood coagulation.

The existing evidences and the above research activities indicates that BV has therapeutic effects against allergic, autoimmune, inflammatory, neurological, skin, cancer, heart and blood system abnormalities disorders. Future studies including detailed experimental investigation of cellular and molecular mechanisms, together with well-controlled, randomized clinical trials, may eventually yield a therapeutic alternative in the treatment of various disorders using BV.

6. Honey

The use of honey as an internal and external health agent is much older than the history of medicine itself. It has been traditionally used by Egyptians, Greeks, and Romans to heal wounds and diseases of the gut, including gastric ulcers. It has also been used as a remedy for cough, sore throat, and earaches [26]. There are frequent references to honey in sacred texts. Honey has a long tradition, not only in Western medicine but also in traditional Chinese medicine and Ayurveda.

Natural honey has been reported to contain about 200 substances. Honey is composed primarily of 82.4% carbohydrates (38.5% fructose, 31% glucose and 12.9% other sugars) and 17.1% water, but also contains fructo-oligosaccharides and many amino acids, vitamins, minerals and enzymes such as glucose oxidase and catalase [26]. The composition of honey varies depending on the plants on which the bee feeds. However, almost all-natural honey contains flavonoides (such as apigenin, pinocembrin, quercetin, hesperetin etc.), phenolic acids (such as ellagic, caffeic, p-coumaric and ferulic acids), ascorbic acid, tocopherols, superoxide dismutase (SOD), reduced glutathione (GSH) and peptides. Most of those compound works together to provide a synergistic antioxidant effect [27-29].

For a long time, it has been observed that honey can be used to overcome liver, cardiovascular and gastrointestinal problems. The most remarkable discovery was antibacterial activity of honey that has been mentioned in numerous studies [30-31]. It exhibits bactericidal activity against many organisms including *Salmonella*, *Shigella*, *Escherichia coli* [31], *Helicobacter pylori* etc. Mechanisms of antimicrobial activity of honey are different from antibiotics, which destroy the bacteria’s cell wall or inhibit intracellular metabolic pathways. The antibacterial activity is related to four properties of honey. First, it draws moisture out of the environment and thus dehydrates bacteria. The sugar content of honey is also high enough to hinder the growth of microbes [32] Second, the pH of honey is between 3.2 and 4.5, and this acidity is low enough to inhibit the growth of most microorganisms. Hydrogen peroxide produced by the glucose oxidase is the third and probably the most important antibacterial component. Lastly, several phytochemical features for antibacterial activity have been identified in honey [30-31].

One of the most studied and most effective uses of honey is found in healing of wounds [33]. The Russians used honey in World War I to prevent wound infection and to accelerate wound healing. The Germans combined cod liver oil and honey to treat ulcers, burns, fistulas and boils [34-36]. Scientific documentation of the wound-healing capabilities of honey validates its efficacy as a promoter of wound repair and an antimicrobial agent [33]. Honey promotes the

activation of dormant plasminogen in the wound matrix, which results in the dynamic expression of the proteolytic enzyme. Plasmin causes blood clot retraction and fibrin destructions. It is an enzyme that breaks down fibrin clots with attached dead tissues in the wound bed [35-36]. Certain cases have shown that honey stimulates wound-healing properties even in infected wounds that do not respond to antiseptics or antibiotics and wounds that have been infected with antibiotic-resistant bacteria. Honey also aids autolytic debridement and accelerates the growth of healthy granulated wound bed.

Honey has also been reported to have inhibitory effects on fungi. Pure honey inhibits fungal growth and diluted honey appears capable of inhibiting toxin production [30]. An antifungal action has also been observed for some yeast and species of Aspergillus and Penicillium, as well as all the common *dermatophytes* [30].

Pharyngitis, commonly known as sore throat, is an acute infection induced by Streptococcus spp. Manuka honey is effective for treating sore throat with its anti-inflammatory, antiviral, and antifungal properties. Honey coats the inner lining of the throat and destroys the harmful microbes while simultaneously soothing the throat [37]. Researcher showed that honey is superior to other treatments for cough induced by upper respiratory infections, including dextromethorphan and diphenhydramine [38]. The antioxidant and antimicrobial properties of honey aided in minimizing persistent cough and ameliorated sleep for both children and adults following honey intake (2.5 ml per day).

7. Conclusion

Modern researchers pay more attention to alternative medicines with natural origin and believe that natural products may be efficient therapeutics in comparison with the synthetic drugs. Thousands of the insect derived products are one of the best natural sources as an alternative medicine. Among the several such products, the present review has focused on the medicinal uses of silk, bee venom and honey along with maggot debridement therapy. The biologically active components present in such systems are highly potent in preventing several diseases and promoting good health. Thus, these insects derived products acts as a remedy in traditional and folkloristic medicine in different cultures worldwide through the centuries. In addition to the value of medicines, these have played an almost mystical and magical role in the treatment of different forms of diseases. However, some precautions need to be taken in case of any allergens associated with these products arises and in finding the right dosage. Hence, it is necessary to conduct further studies to determine the critical mechanisms related to the pharmacological activities of these products and the appropriate amounts that can be taken in order to obtain promising health benefits.

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