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Insect natural products as potential source for alternative medicines - A Review

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ABSTRACT

Developments in bioengineering natural products from insects with potential use in modern medicines as well as in utilisation of insects as models for studying essential mammalian processes such as immune responses to pathogens are discussed in this review. The significant recent advances in developing insect derived natural products as potential new medicinal drugs and the use of medicinal plants for the treatment of human diseases has long been practised since the beginning of human civilization. To date, insects have been relatively neglected as sources of modern drugs although they have provided valuable natural products, including honey and silk, for at least 4-7000 years. The use of insect derived products as an alternative medicinal source is an exciting and rapidly expanding new field since insects are hugely variable and have a high biodiversity index. Insects products, such as silk and honey, have already been utilised commercially for thousands of years and extracts of insects used to produce for use in folk medicine around the world, nowadays several other insect products such as venoms which insects use for prey capture and defences, are also used to produce new medicinal drugs which are capable of fighting against a number of diseases like arthritis, inflammation, several cancers, neurological diseases and AIDS too. In the present decade the increasing price of biochemical medicines for the treatment of certain deadly diseases like cancer,

AIDS etc is creating a huge economical burden to the common people in the developing countries like India. The search for alternative cost effective and easily available medicines for combating the upcoming diseases is an utmost need in the present decade. The emergence of this kind of alternative medicinal sources like that from the adult insects as well as from their different life history stages or their secretions which are available in plenty in the nature will open up new vistas in the recent researches based on development of medicinal drugs for human diseases.

***Keywords*:** Insects, natural products, medicinal drugs, alternative medicine

1. INTRODUCTION

Insects and other arthropods provide ingredients that have been a staple of traditional medicine for centuries in part of East Asia, Africa and South America. Medical practitioners in more economically robust countries may refer conventional treatment it may be more result of squeamishness rather than science. In sub-Saharan Africa alone, the World Health Organization estimates that $20billion will be needed to replace the shortage of 800000 conventional health care workers by 2015. Globally ubiquitous, arthropods potentially provide a cheap, plentiful supply of healing substances in economically challenged world.
Natural products derived from insects possess medicinal value:

2. HONEY BEE PRODUCTS USED AS MEDICINE

Bee products such as honey, venom have been used in folk medicine for thousands of years for treating wounds, ulcers, inflammation, infections, pain, allergies and cancer.

2. 1. Honey bee venom

Bee venom therapy, the therapeutic application of bee venom have been used in traditional medicine to treat diseases, such as arthritis, rheumatism, pain, cancerous tumors and kin diseases. Bee venom contains a variety of peptides including melittin, apamin, adolapin, the mast – cell-degranulating peptide, enzymes (phospolipase A2), biologically active amines (i.e. histamine and epinephrine) and nonpeptide components with a variety of pharmaceutical properties.

2. 1. 1. Cancer treatment

Bee venom has been widely used in the treatment of tumors. Several cancer cells, including renal, lung, liver, prostate, mammary gland as well as leukemia cells can be targets of bee venom peptides such as melittin and phospholipase A2.

In recent study scientists reported that bee venom can induce apoptosis in cancer cells (in human leukemic U937cells) the key regulators in bee venom induced apoptosis are Bcl-2 and caspase-3 through down regulation of the ERK and Akt signal pathway (Moon *et al*., 2006). Melittin, a water soluble toxic peptide derived from bee venom of *Apis mellifera* was reported to have inhibitory effects on hepatocellular carcinoma. Melittin inhibits tumor cell metastasis by reducing motility and migration via the suppression of Rac-1 dependent

pathway, suggesting that melittin is a potent therapeutic agent for hepatocellular carcinoma (Liu *et. al.,* 2008). Melittin prevents liver cancer cells metastasis through inhibition of the Rac-1-dependent pathway.

The main target of non-steroidal anti-inflammatory drugs action is Cyclooxygenase (COX). COX-2 has been implicated in mammary carcinogenesis. The bee venom can inhibit COX-2 expression and block pro-inflammatory cytokines (TNF-alpha, IL-1 beta) production, thus prevent breast cancer (Nam *et al.,* 2003). Inhibition of COX-2 activity and proinflammatory cytokines (TNF- α and IL-1β) production by water soluble sub-fractionated parts from bee (*Apis mellifera*) venom.

2. 1. 2. Treatment for Rheumatoid arthritis

Bee venom induces apoptosis in rheumatoid synovial cells through a decrease in BCL2 expression and an increase in BAX and caspase-3 expression (Hong *et al*., 2005). Bee venom induces apoptosis through caspase-3 activation in synovial fibroblasts of patients with rheumatoid arthritis.

2. 1. 3. Controlling diabetes

Hyperglycemia in diabetes leads to increased protein glycation resulting in structural and functional alteration in proteins. Recent studies showed that bee venom prevents glycation induced increasing in beta-sheet structure decreasing in free amino groups, altering in the secondary structure and heme degradation in the hemoglobin. Hence, bee venom has the potential to be used as a natural drug to prevent diabetes complications (Behroozi *et al*., 2014). Honey bee venom decreases the complications of diabetes by preventing haemoglobin glycation.

2. 1. 4. Neurodegenerative diseases therapy

Bee venom and its major component, melittin suppress lipopolysaccharide – induced nitric oxide and inducible nitric oxide synthetase expression without causing cytotoxicity in BV2 microglia. Bee venom and melittin also exert anti-inflammatory effects by suppressing the transcription of cyclooxygenase-2 genes and proinflammatory cytokines (TNF-α, IL-6). Thus, bee venom and melittin possess a potent suppressive effect on proinflammatory responses of BV2 microglia, these compounds may also offer substantial therapeutic potential for treatment of neurodegenerative diseases that are accompanied by microglial activation (Moon *et al.*, 2007). Bee venom and melittin reduce proinflammatory mediators in lipopolysaccharide-stimulated BV2 microglia.

2. 1. 5. Antioxidant

Free radicals are ubiquitous in our body and are generated by physiological processes, including aerobic metabolism and inflammatory responses, to eliminate invading pathogenic microorganisms. Target of free radicals in inflammation include DNA, proteins, RNA and lipids. An antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules and so to prevent such changes. Oxidative stress is thought to contribute to the development of chronic and degenerative diseases such as cancer, autoimmune disorders, aging, rheumatoid arthritis, cardiovascular and neurodegenerative diseases. Propolis, pollen,

honey have the highest antioxidant activities (Carpes *et al*., 2007). Bee venom is a potent antioxidant and possesses radio protecting actions.

2. 1. 6. Treatment for HIV

Nanoparticles carrying a toxin found in bee venom can destroy Human immunodeficiency virus (HIV) while leaving surrounding cells unharmed, researchers at Washington University School of Medicine in St. Louis have shown. The finding is an important step toward developing a vaginal gel that may prevent the spread of HIV, the virus that causes AIDS. Bee venom contains a potent toxin called melittin that can poke holes in the protective envelope that surrounds HIV virus as well as other viruses. This melittin is loaded with nanoparticles which do not harm surrounding normal cells. The nanoparticles attack an essential part of the virus' structure.

Since melittin attacks double-layered membranes indiscriminately this concept is not limited to HIV. Many viruses, including hepatitis B and C rely on the same kind of protective envelope and would be vulnerable to melittin-loaded nanoparticles.

Scientists also said that these nanoparticles are easy to manufacture in large enough quantities to supply them for future clinical trials (Hood *et al*., 2013).

2. 2. Honey

Honey is a complex mixture of substances and progress is being made at the molecular level in understanding the functions of the various components on cells and the effectiveness of honey in treating a range of human ailments. For example Tonks*et al.,* 2007 (Tonks*et al.,* 2007) isolated a 5.8 kDa honey component which stimulated the production of the TNF-alpha cytokine via TLR4 in human monocytecultures. TNF- alpha is involved in the repair and regeneration of tissues. The antimicrobial activity of honey is probably due to a combination of low pH, high osmolality, and hydrogen peroxide generation together with defensin-1 and methylgly-oxal, with the latter an aldehyde generated from pyruvic acid (Ratcliffe *et al*., 2011). Interestingly, Kwakman *et al*., 2011 (Kwakman *et al*., 2011) recently showed that Revamil and Manuka honeys have different antibacterial components, with the former containing defensin-1, hydrogen peroxide, and methylglyoxal, while the latter only had methyl glyoxalate 44times the concentration of Revamil. In addition, Manuka honey was also shown to contain other unidentified antibacterial factors. Great variations in antimicrobial properties have also been discovered for a range of honeys, limiting those suitable for use in medicine (Alnaimat *et al.*, 2012).

There is great recent interest in the antimicrobial activity of honey against important antibiotic-resistant human pathogens (Seckam *et al.,* 2013).These studies showed, for example, inhibition of Gram-positive MRSA (Methicillin Resistant *Staphylococcus aureus*), of Vancomycin-Sensitive and Resistant *Enterococci* (VSE and VRE, e.g. Jenkins and Cooper, 2012) and of *Streptococcus* species isolated from wounds (Cooper *et al.,* 2011). Honey also impacts Gram-negative bacteria associated with wounds such as *Pseudomonas aeruginosa*, *Stenotrophomonas* sp. and *Acinetobacter baumannii* (Seckam *et al*., 2013). Manuka honey appears to inhibit cell division in MRSA (Henriques *et al.*, 2011) while, with *P. aeruginosa*, the cell wall is destabilised and lysis occurs (Roberts *et al.,* 2012). Bacterial DNA degradation in pathogens has also been reported with Buckwheat honey (Brudzynski *et al.,* 2012). Finally, honey can not only inhibits planktonic bacteria but also prevents the formation of biofilms (Maddocks *et al.,* 2012; Seckam and Cooper, 2013) that form, for example, on surgical

implants, thus causing prosthesis failure and additional patient distress. A review has been published of recent patents resulting from all this work on antibiotics from hives (Boukraˆaa and Sulaiman, 2009). Honey contains a number of phenols having anti-cancer properties; these are Flavonols (Quercetin, Kaempferol, Galangin, Fisetin and Myricetin), Flavones (Apigenin, Acacetin, Chrysin, Luteolin, Genkwanin, Wogonin, and Tricetin), Phenolic acids (Caffeic acids), Flavnones (Hesperidin), etc. Of these compounds, Quercetin has been shown to enhance the apoptotic ability of anti-CD95 and rTRAIL (recombinant tumor necrosis factor-related apoptosis inducing ligand) in acute lymphocytic leukemia (Spagnuolo *et al.,* 2012). Apigenin and Acacetin which not only induce caspase-dependent apoptosis in human leukemia cells in vitro but the former also produced apoptosis- mediated inhibition of U937 leukemic cell xenografts in mice (Budhraja *et al.,* 2012).

3. MAGGOT PRODUCTS

Maggot therapy is now commonly used for many types of infected wounds such as diabetic foot wounds, postoperative infections, bedsores, and leg ulcers, in the USA, Israel, and Europe (Ratcliffe *et al.,* 2011; Sherman *et al.,* 2000). The larvae of the blowfly, *Lucilia sericata*, are frequently used although other species have also been tried such as *Lucilia cuprina, Phormia regina*, and *Calliphora vicina* (Sherman *et al.,* 2000). The use of *L. sericata* larvae for treating wounds has been recognised by the U.S. Food and Drug Administration and the UK Prescription Pricing Authority. Sterile maggots can therefore be officially prescribed (http://www.medicaledu.com/maggots.htm).

Maggot therapy can be divided into 3 processes: (i) debridement of wounds; (ii) wound healing; (iii) disinfection of wounds.

Debridement of Wounds: Once maggots are applied to the wound then debridement or cleaning and removal of necrotic tissue and debris (eschar) occur so that granulation and healing can begin. Maggots clean wounds by the extra- corporeal production of enzymes that digest the debris which the maggots then feed upon (Ratcliffe *et al.,* 2011). Initially, the main enzymes identified in the maggot excretions/secretion (ES) were chymotrypsin- and trypsin-like serine proteases, an aspartyl proteinase and a metalloproteinase (Chambers *et al.,* 2003). The secretion of ammonia by the maggots increases the pH to activate the serine proteases. The most active enzymes are produced by first instar larvae (Chambers *et al.,* 2003).

Wound Healing: there is accumulating evidence that ES have an immunomodulatory role in the wound healing process (Bohoba *et al.,* 2012). In particular, neutrophils, macrophages, lymphocytes, and the complement system respond to exposure to the MS. With neutrophils, the ES inhibit elastase, the respiratory burst, hydrogen peroxide production, and migration of these cells. Elastase breaks down the extracellular matrix and delays epithelial repair, while oxygen radicals would probably have a similar effect. Concomitantly, the inhibition of neutrophil migration would help resolve the prolonged inflammatory response, to which they contribute, present in a chronic wound (Bohoba *et al.,* 2012, van der Plas *et al.,* 2007). Even more interesting is the study by Cazander *et al.,* 2012 (Cazander *et al.,* 2012) who have shown that ES could reduce complement activation by 99.99% in the sera of healthy and postoperatively immune- activated human patients. The ES break down complement components C3 and C4 which could explain, in part, the improved wound healing following maggot therapy.

Disinfection of Wounds: There is good evidence that ES can kill bacteria infecting wounds, including antibiotic- resistant strains such as MRSA (Ratcliffe *et al.,* 2011). There are reports of many different antibacterial factors in dipterans, including a range of AMPs such as Sarcotoxin 1A, a cecropin-like molecule from the flesh fly *Sarcophaga peregrine*, which is more active against Gram-negative bacteria than Gram-positive forms (Natori, 2010). Lucifensin was first purified in 2010 from an extract of the gut of *L. sericacta* larvae by Cerovsky *et al.* (2010). More recently lucifensin II was discovered and characterised from *Lucilia cuprina* and found to be identical to the *L. sercata* lucifensin except for one amino acid residue (Shazely *et al.*, 2013). Thus, lucifensins are cationic AMP (antimicrobial peptide) with main activity against Gram-positive bacteria (Andersen *et al*., 2010) so that, together with seraticin, they make an important contribution in the ES to cleaning infected wounds of MRSA and other antibiotic-resistant bacteria. The anti bacterial factors of the house fly, *Musca domestica* are also detected, because of its possible role as a vector of pathogens such as MRSA (Joyner e*t al.,* 2013; Park *et al.,* 2010). Results show that these insects also produce a defensin that is upregulated upon bacterial ingestion and that this, and probably other factors, is responsible for the anti bacterial activity against MRSA and VRE (Vancomycin-Resistant *Enterococci*) recorded for solvent extracts of maggots (Park *et al.,* 2010).

3. 1. In treatment of Bacterial infection

The well-studied medical application of arthropods is the use of maggots-the larvae of flies (most frequently the larva of *Lucilia sericata,* a blow fly) that feed on necrotic tissue (Wolff and Hansson, 2003). Fly larvae aid in wound healing via a number of mechanisms: 1) larval secretions break the adhesion molecules, fibronectin and collagen, into smaller fragments that promote fibroblasts aggregation and tissue repair (Horobin *et al.,* 2003); 2) larvae eat necrotic tissue that would otherwise form a nidus for infection, liquefying such tissues and aiding its digestion; 3) maggots release anti-bacterial substances, some of which are produced by *Proteus mirabilis* bacteria, that live naturally in the larval intestine; and 4) ingested bacteria are destroyed within the maggots (Whitaker *et al.*, 2007).

In traditional medical practice the larvae of some Diptera: Calliphoridae, notably *Lucilia illustris* (Meigen), *L. sericata* (Meigen) and *Phormia regina* (Meigen) have been employed for maggot therapy, i.e. to help clean lesions antiseptically, especially for treatment of chronic osteomyelitis. This mode of treatment remains appropriate for cases where antibiotics are ineffective and surgery impractible (Sherman and Pechter, 1988).

Zhang *et al.* (2013) isolated and purified an antibacterial protein from maggots (MAMP). MAMP demonstrated inhibitory activity against both stranded strains and clinically isolated antibiotic resistant strains of *Staphylococcus aureus in vitro.* The topically use of MAMP effectively decreased the viability of *S. aureus* and promoted wound healing in an *S. aureus* mouse skin infection model. MAMP exerted its antibacterial activity via a bactericidal mechanism based on observations using scanning electron and transmission electron microscopy. MAMP interacted with the bacterial cell membrane and disrupted the cell surface structure. MAMP exhibits potential use as a topical agent for treating bacterial infection.

Refractory bacterial infectious diseases are troublesome in the treatment. The traditional antibiotics could not be used to control bacterial infection with the indiscriminate use or abuse of drugs. Maggot therapy is a simple and highly successful method for healing of drug-resistant bacterial infected and necrotic wounds. MicroRNA from maggots down regulates the expression of pathogenic bacterial gene by binding to the 3 - untranslated regions of the

mRNA of that target gene leading to post-transcriptional gene silencing (Wang and Zhang, 2011).

4. ANT VENOM AS MEDICINE

Ants have been used as medicine, owing to their special active substances such as citral, ATP, histamine, growth hormone, superoxide dismutase etc. *Pachycondyla sennaarensis*, the samsum ant venom possesses many pharmacological effects as reducing inflammation, relieving pain, inhibition of tumor growth, hepatitis treatment, liver protection (Altman *et al.*, 1984). According to Bai *et al.*, 2003 (Bai *et al.*, 2003), solenopsin A, a primary alkaloid obtained from fire ant *Solenopsis invicta* exhibits antiangiogenic activity; this toxin has the ability to inhibit a series of kinases involving in angiogenesis mechanism.

Polyrachisla mellidens, *a* medicinal ant used in Chinese medicine, was confirmed to exert potent analgesic and anti-inflammatory actions. Its therapeutic efficacy in the treatment of various inflammatory disorders had been reported (Kou *et al*., 2005).

5. BEETLE PRODUCTS

Many of the Blister beetles (Coleoptera: Meloidae) produce toxic defensive secretions which upon contact with the skin cause blistering. One such toxin is cantharidin which has been extracted from *Mylabris caragnae*, the dried bodies of which have been used in Chinese Folk Medicine since the 13th century for the removal of warts (Galvis *et al.*, 2013) and forever 2000 years for the treatment of cancer.

Canthardin is a monoterpene derived from the bodies of several types of blister beetle, including *Mylabris phalerata* and *M. cichorii* (Chinese blister beetles) and this compound is stored in the beetle hemolymph and making up about 5% of body dry weight (Galvis *et al.*, 2013). Cantharadin has been found to inhibit the growth of human leukemic cells *in vitro* (Rauh *et al.*, 2007). In contrast to other chemotherapeutic agents, cantharadin acts as leukemia progenitor and stem cells (Dorn *et al.*, 2009). Several derivatives of cantharadin also retard the growth of prostate, oral, colon, cervical, gall bladder cancer cell lines (Efferth e*t al*., 2005; Liu and Chen, 2009; Fan *et al.*, 2007; Fan *et al*, 2004; Wang *et al.*, 2000; Peng *et al.*, 2002; Chen *et al.*, 2005; Kok *et al.*, 2005; Hill, Stewart *et al.*, 2007; Hill, *et al.*, 2007).

Research has also shown that cantharidin is an inhibitor of phosphoprotein phosphatase 1 and 2A which results in DNA damage and apoptosis (Li *et al*., 2010). Cantharidin a potent and selective PP2A inhibitor induces an oxidative stress-independent growth inhibition of pancreatic cancer cells through G2/M cell cycle arrest and apoptosis. These enzymes are involved in regulation of metabolism and the initiation of signal transduction in cells resulting in cell division. Thus, cantharidin may represent a small molecule able to switch cancer cells division and carcinogenesis off/on as well as to probe the key regulatory role of PPA2 in cell metabolism (Galvis *et al*., 2013).

Recently in the year 2007 Huang *et al.* (Huang *et al*., 2007) showed that growth inhibition and killing of human colorectal cancer cells by cantharidin was both time- and dose-dependent. The cantharidin exposure reduced CDK1 kinase activity which led to failure of the cells to progress from G2 to M phases in the cell cycle. In addition, the colorectal cells

were killed by apoptosis which was induced through the mitochondrial and death receptor pathways and activation of caspases8, 9 and 3.

Currently number of research papers has been published confirming that cantharidin, apart from inhibiting PP1 and PP2A, has multiple effects on cancer cells. Another study by Huang *et al.,* 2013 (Huang *et al.,* 2013) on metastasis of human bladder carcinoma cells, showed that exposure to cantharidin blocked the gene expression, protein levels, and activities of the matrix metalloproteinase -2 (MMP-2) and/or MMP-9. These enzymes are associated with invasive properties of many cancers so that cantharidin had an antimetastatic effect possibly by targeting the p38 and JNK1/2 MAPKs pathway of the bladder cancer cells.

Other effects of cantharidin have been studied in human breast cancer cells by Shou *et al*., (2013). They reported that cantharidin resulted in apoptosis and reduced growth, adhesion and migration of the cancer cells. The reduced adhesion resulted from repression of cell adhesion to platelets through down regulation of the α2 integrin adhesion molecule on the surface of the cancer cells. The repression of the α2 integrin occurred through the protein kinase C pathway probably due to PP2A inhibition.

Finally, most important for therapeutic use of cantharidin, Dang and Zhu 2013 (Dang and Zhu 2013) have tackled the problems of toxicity, insolubility and short half-life in circulation of this drug by designing cantharidin solid lipid nano particles as drug carriers which can be given orally.

One analogue, norcantharadine, also reduced the production of molecules that promote tumor cell adhesion and metastasis. It is believed to suppress protein phosphatase, increase oxidative stress within cancer cells, down regulate the gene STAT3 and activate the Bax genes that induce cell apoptosis by up-regulating the MAPK/ERK and p53 pathway genes (Sagawa *et al.,* 2008). Cantharadin stopped the production of P-gp, a membrane transport protein that creates chemotherapeutic drug resistance in a hepatoma cell lines (Zheng *et al.,* 2008).

6. WASP VENOM IN CANCER THERAPY

Scientists from the Institute for Biomedical Research (IRB) Barcelona have carried out successful in vitro tests using wasp venom to kill cancer cells. The peptide from wasp venom has the ability to form pores in the cell plasma membrane, penetrate into the cell and finally, cause its death either by necrosis or by triggering apoptosis. However, this powerful natural weapon can not only damage tumor cells but also affect healthy cells. As such the researchers designed a means of transporting the peptide to the tumor and making it accumulate in a specific and controlled manner. The system consists of a decorated carrier polymer with two components: a peptide that is bound to a tumor cell receptor and the cytotoxic peptide of the wasp venom.

In vitro experiments show that the substance is adequately distributed within the tumor cells and causes their death, while healthy cells, such as red blood cells, are not affected (Moreno *et al*., 2014)

Wasp venom contains Polybia MPI (from venom of the social wasp *Polybia paulista)* which shows anti tumor activity (Wang *et al*., 2008b). Polybia MPI is able to target non polar lipid cell membrane, forming ion permeable channels, leading to depolarization irreversible cytolysis and finally cell death (Matsuzaki *et al*., 1997). It has been shown that Polybia MPI

can significantly inhibit the proliferation of tumor cells and associated endothelial cells by membrane disrupting.

Fujiwara *et al*., 2008 (Fujiwara *et al*., 2008) isolated and determined the structure of anti cancer molecule from the outer envelop of the social wasp *Vespa simillima*. A biologically active quinone, 7,8-seco-para-ferruginone exhibited a growth – inhibitory effect on rat liver cancer cells. The authors suggest that the cytotoxic activity is related to the morphological changes that induce apoptosis of the cells exposed to this molecule.

NVP-(1), a 6.6 kDa protein isolated from the venom of *Nidus vespae*, inhibited proliferation of HepG2 hepatoma cells in the concentration of 6.6μg/ml. in addition NVP(1) promoted apoptosis of HepG2 cells as indicated by nuclear chromatin condensation. This protein could arrest cell cycle at G1 stage and inhibit the mRNA expression of cyclin B, cycline E, cyclin D1. NVP-(1) increased p27 and p21 protein expression but suppressed cdk2 protein expression. The extra-cellular-signal-regulated-kinase (ERK) was activated, indicating that NVP -(1) inhibits proliferation HepG2 through ERK signalling pathway, through activation of p27 and p21 and reduction of cdk2expression (Wang *et al.,* 2008a).

6. 1. Medicinal uses of caterpillar venom

There are few studies reporting antitumoral potential of caterpillar venom. Cecropins are group of peptides that were first isolated from the hemolymph of the giant silk moth *Hyalophora cecropia.* This peptide displays anti-microbial activity (Andreu *et al.,* 1985) and has been used as a potent anti-cancer agent against a variety of tumor cell lines (Chen *et al.,* 1997; Moore *et al.,* 1994; Suttmann *et al.,* 2008). The mechanism of action of this peptide against tumor cells appears to involve the formation of the pores in the membrane of these cells (Chen *et al.,* 1997).

Moore *et al.*, 1994 (Moore *et al.*, 1994) showed that cecropins are active against several mammalian lymphomas and leukemias *in vitro* and a preliminary *in vivo* study showed that cecropin B increases the survival time of mice bearing murine ascitic colon adenocarcinoma cells.

Suttmann *et al.,* 2008 (Suttmann *et al.,* 2008) showed that cecropin A and B inhibit the viability proliferation of bladder cancer cells, but with no effect on fibroblasts. The selective antitumor action mechanism of these peptides depends on disruption of target cell membrane resulting in irreversible cytolysis and cell destruction. Both peptides may offer novel strategies for the treatment of bladder cancer cells with limited cytotoxic effects on benign cells.

7. DISCUSSION

Despite the fact that insects have not been a rich source of modern drugs, they have, for thousands of years, provided many invaluable natural substances, including silk and honey products (royal jelly, beeswax, pollen, and propolis). Insect secretions and ground-up bodies have commonly been used in Folklore Medicine not only in China and Bahia but also in India, Asia, Africa, and Mexico (Dossey, 2010; Pemberton, 1999; Gomes *et al.,* 2011). Insects make up the largest and most biodiverse group of organisms on the planet. Likewise, the magnitude of the chemical diversity which they produce and utilize is also one of the most impressive in the living world. With the advent of modern technologies to analyze and assay

ever smaller amounts of material, it is important that previously neglected taxa and natural matrices are capitalized upon. Clearly, among these are insects which possess one of the richest and most unexplored reservoirs of potentially useful substances. From toxins used to defend against attack by predators and other offending opponents to peptides which help to ward off infection by various microbes and other parasites, insects and their defence chemicals hold great promise for the future of natural products drug discovery.

8. CONCLUSION

The purpose of the present review is to focus on the use of insect natural products as potential source for alternative medicine that is beneficial for curing as well as giving protection from the diseases that modern human civilization is combating for. This overview briefly describes significant recent advances in developing insect natural products as potential new alternative medicinal drugs. This is an exciting and rapidly expanding new field since insects are hugely variable and have utilised an enormous range of natural products to cope up the environmental perturbations for many years. This field of investigation provides a promising research topic due to the importance to man in various fields including ethnobiology, medicine and pharmaceutical development.

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