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Entomology, Ornithology & Herpetology: Current Research

Mini-Review

Cholesterol Uptake Targeted Growth Regulation to Control Disease Transmitting Vector Populations

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ABSTRACT

Cholesterol is one of the vital compounds required maintain principal metabolic pathways and structural material in the human and animal body. Insects are lack of the essential enzymes required for the biosynthesis of cholesterol from precursor molecules in nature and which makes them depend on dietary cholesterol. Thus the blocking of cholesterol uptake interfere the metabolic pathways of insects and effects on the survival of the them. Based on this characteristic nature, certain phytochemicals can be applied to inhibit Aegypti Sterol Carrier Protein 2 (AeSCP-2) activity via competitive binding and proven to have effective insecticidal activities against disease transmitting mosquitoes and other insect vectors. Range of candidate compounds and plant sources, that block the cholesterol uptake in insects, can effectively be used to prevent and spread of vector born disease have been discussed.

Keywords: Mosquito;Vector control;Vector borne diseases;Cholesterol digestion

INTRODUCTION

A diverse array of tropical vector borne diseases are transmitted to human through the infected arthropods. Memberes of arthropods of mosquitoes, sand flies, house fly, blackfly, tsetse fly and kissing bugs are mainly responsible for some of the most virulent vector borne diseases in the world [1]. Furthermore, mosquitoes are considered to be the most dangerous group of insects as different species of mosquitoes transmits a range of diseases to man and animal including malaria, dengue, lymphatic filariasis, dirofilariasis and Japanese encephalitis [2]. Moreover, other arthropads transmit diseases such as leishmaniasis (sand flies), enteric diseases (house flies), onchocerciasis (blackfly), trypanosomiasis (tsetse fly) and chagas disease (kissing bugs). Strategic approach to preveting and controlling of vector borne diseases are not only limited to treating patinets but also are mainly depending contol of vector population1. During the pre-dichlorodiphenyltricholoethane (DDT) era, the main vector control stratergies were environmental friendly and biological controlled methods of drainage of swamps and other mosquito breeding sites, clearing of vegetation's to remove vector resting places and various other traditional means [3,4]. However, discovery of DDT made it looks like the most relieving discovery of the history until the uncontrolled use of this chemical resulted very serious damages to the ecosystems and animals. Consequently, DDT resistant mosquitoes resulted due to mutations1. This example indicates the inability of using of chemicals as a solution to control of vector borne diseases5. Further, insecticides and other chemical resistant arthropod vectors are emerged as a result of long term usage of chemicals to control arthropod density in the environment. Therefore, it is utmost important to invent environmentally friendly and more effective novel insecticides to prevent and minimize any chance of development of a resistance among the arthropods. Insecticides target various metabolic pathways in arthropods that essential for the survival and for the maintenance of their life cycle. In addition, insects that expose to the particular insecticide become incapable of producing the cholesterol which acts as an essential compound in their body structures and as a precursor for molting hormones within their bodies. This makes them dependable on the external sources of cholesterol [5]. Therefore, if there is a process which makes them unable to uptake cholesterol, will be fatal to the target insect. A literature search was carried out in PubMed Central (PMC) looking for research articles that describe pre-clinical studies of inhibition of cholesterol uptake in arthropods. The following

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Received: September 06, 2021; **Accepted:** September 20, 2021; **Published:** September 27, 2021

Citation: Letchuman S, Premarathna AD (2021) Cholesterol Uptake Targeted Growth Regulation to Control Disease Transmitting Vector Populations. Entomol Ornithol Herpetol. 10: 245.

search terms were used: "cholesterol uptake, mosquito, vector control, vector borne diseases".

LITERATURE REVIEW

Cholesterol as a vital compound in animals

Cholesterol plays an essential role in the stability and the architecture of the plasma membrane and as a precursor for bile acids and steroid hormone synthesis in mammals [6]. Under healthy homeostatic conditions the circulating level of cholesterol is regulated by a balance between local synthesis dietary cholesterol and removal of excess cholesterol from peripheral tissues.

Cholesterol is a highly insoluble molecule and is transported through the circulatory system via endogenous transporters called lipoproteins. Lipoproteins mediate the processing and delivery of dietary cholesterol to peripheral tissues and help to maintain homeostatic balance by removing the excess cholesterol from peripheral tissue to liver [7]. Cholesterol can be synthesized by almost all the cells in the body, and the enzyme involving the catalyzing of the rate-limiting step of cholesterol synthesis is 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase. HMG-CoA reductase is inactivated when it is bound to statins and is transcriptionally reduced when intracellular cholesterol level is high [8]. It helps to generate semipermeable barriers between cellular compartments and to regulate membrane fluidity influencing several trans-membrane signaling processes. The most important pathways for net excretion of cholesterol from the body are as free cholesterol with bile or by convering it to bile acids [9,10]. Cholesterol is also accumulated in specific regions of the membrane, combine with sphingolipids, and create small compartmentalized highly stable micro domains known as lipid rafts. Lipid rafts are referred as signaling platforms because its structure and function depends on the respective lipid composition and the target proteins [11]. Lipoproteins also contain one or more apolipoproteins (apos) which provide structural stability and act as ligands for specific cell surface receptors or as activators of enzymatic reactions. Apolipoprotein decides the function and metabolic fate of lipoproteins. Circulating lipoproteins exchange their lipid and protein components between each other and as a result change their size shape and density. According to their density, lipoproteins are categorized into five main groups: chylomicrons, Very Low Density Lipoproteins (VLDL), Intermediate Density Lipoproteins (IDL), Low Density Lipoproteins (LDL), and High Density Lipoproteins (HDL) [12,13]. LDL particles provide cholesterol to the most of peripheral tissues via the LDL receptors. Endocytosis process involves in the uptake of the whole lipoprotein particles [14]. HDL particles, on the other hand play an important role in removing excess cholesterol from peripheral tissues, to initiate the reverse transport of cholesterol to liver. The HDL mediated reverse cholesterol transport process, which is essential to facilitate the unique ability of liver to process and promote the excretion of excess cholesterol from the body. The transporter facilitates this process by promoting the efflux of cholesterol from peripheral tissues for incorporation into HDL particles and removal of peripheral cholesterol via lipoprotein receptors in liver [6]. As previously discussed, cholesterol is important as a structural component in cellular membrane and also as a precursor for insect molting hormone in insects. As insects are unable to synthesize cholesterol due to lack of enzymes required for cholesterol biosynthesis pathway, they intake cholesterol from their dietary sources [15].

Sterol carrier protein mediated cholesterol uptake and its inhibition

Dietry cholesterol must be transported from mid gut to the site of action where it is used as a structural component or for biosynthesis of other molecules. A "Sterol Carrier Protein" (SCP) is required for the transportation of cholesterol from the luminal to the basal side of the midgut epithelium in insect body because cholesterol is a highly hydrophobic molecule [16]. Therefore, inhibition of these carrier molecules may have a negative effect on the rate of cholesterol uptake. Hence any compound that inhibits the production or the action of SCP can be used as an insecticide. Based on the studies on SCP isolation and characterization, insects Sterol Carrier Protein 2 (SCP-2) has been identified as a target for the insecticide production [17,18]. Moreover, mosquito SCP-2 has been isolated and characterized for the production of AeSCP-2 (Aedes aegypti SCP-2) [18]. This mosquito SCP-2 is a low-molecular-weight protein in SCP-2 gene family [19]. In addition, another insect SCP-2 such as, MsSCP-2 (Manduca sexta SCP-2) has also been isolated and characterized [17]. Attempts on identifying chemicals that inhibit the action of SCP-2 via competitive binding have revealed the ability of organic compounds to act as SCPIs17. However, SCPI-1[N-(4-{[4-(3,4-dichlorophenyl)-1,3-thiazol-2-yl]amino}-phenyl)acetamidehydrobromide] and SCPI-2[8-chloro-2-(3-methoxyphenyl)-4,4-dimethyl-4,5-dihydroisothiazolo[5,4-c]quinoline-1(2H) thione] are two of the main compounds which could be used as the insecticides and proven to be effective against mosquitoes since SCPI-1 has shown a broad toxic effects on a large number of mosquito species [20, 21]. Further, some other compounds phytochemicals have shown promising results in inhibiting AeSCP-222, 20. The compound named "quercetin" which is isolated from the plant *Saxifraga stolonifera* (creeping saxifrage) has shown promising AeSCP-2 inhibitory activity [22]. Even though quercetin had not indicated a remarkable larvicidal effect (*in-vitro*) against *Aedes aegypti*, it acts as insecticide to other insects, including some beetles and termites [23,24]. Therefore, scientists suggest a possibility of using quercetin as an effective insecticide against other species of mosquitoes as well. Another compound named "mangosteen" is also isolated from plant *Garcinia mangostana* (mangosteen) has shown more promising results as it exhibits larvicidal effect against six species of mosquitoes namely; *Stegomyia aegypti, Anopheles stephensi, Anopheles gambiae, Culex pipiens, Anopheles quadrimaculatus* and *Culex quinquefasciatus* [20]. The other compounds which exhibits evidences of having an inhibitory effect on cholesterol uptake can be listed down as, *Annona squamosa* alkaloids against *Anopheles stephensi, Tagetes minuta* flower extract against adults and larvae of *Aedes aegypti* and *Anopheles stephensi*, leaf extract of *Polyalthia longifolia* against larvae and pupae of *Culex*

quinquefasciatus and peppermint (*Mentha piperita*) oil, Camphor (*Cinamomum camphora*) oil, Clove (*Myrtus caryophyllus*) oil and Eucalyptus (*Eucalyptus globulus*) oil against third instar larvae of *Aedes aegypti, Anopheles stephensi* and *Culex quinquefasciatus* [25-28]. Other two compounds of alpha mangosteen and panthenol have been identified to have potential ability to bind with AeSCP-2 and inhibit its action. Application of these insecticides more frequently at higher doses has led to accumulation of toxic residues that contaminate the ecosystems and adversely affect non-target organisms as well [29].Therefore, it is important to focus to invent agents that are environmental friendly, less expensive and locally available materials for vector control. Thus phytochemicals can be selected over synthetic compounds in vector control which have minimum environmental disturbance and minimum risk on other living organisms.

Challenges and future perspectives

Despite the nature of the insecticide there is always a chance of developing a resistance from insects to an insecticide. Therefore, any reason for the development of such resistance must be prevented. The resistance must be managed through removing selection pressure by rotation of insecticides or by using mixture of insecticides. Use of integrated vector control approaches is also recommended in minimizing the risk of resistance and maximizing the effectiveness [30]. Furthermore, it is also vital to make sure that the insecticides have no effect on other non-targeting organisms.

DISCUSSION

Most of the compounds tested in reported studies are specific for mosquito SCP-2 indicating a less likelihood of harming non-targeted species. However, further studies are necessary to confirm that the use of these compounds is environment friendly. Although the plant derived compounds had proven to be very promising in controlling vectors, like many phytochemicals, these compounds are not photo stable and will require careful formulation such as slow release formulations combined with UV-blocking additives [31]. Moreover, plant species mentioned above might not be available in all geographical settings. Therefore, it is important to discover possible alternatives which have similar effects through further research. Use of these research findings may ensure the successful control of vector population by implementing proper control procedures with proper care on the targeting environment to control vector borne diseases [32].

CONCLUSION

Targeting SCP-2 in mosquitoes using the compounds which are able to inhibit the binding ability of cholesterol to SCP-2 is very effective in controlling mosquito vector populations in disease endemic areas if used with proper care and with integrated approaches.

ACKNOWLEDGEMENT

The authors wish to thank to technical support given by Dr. Ranjith Adhikari, Faculty of Veterinary Medicine and Animal Science, University of Peradeniya, Sri Lanka.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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