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APPEARANCE OF INSECTICIDE RESISTANCE CAPABILITY AMONG MALARIA CAUSING MOSQUITO VECTORS: AN APPREHENSION IN DEVELOPED AND DEVELOPING NATION

Jitendra Sharma [1] and Manalicha Pawe [2]

[1]PhD Scholar, RMRC (ICMR) Dibrugarh, Assam

[2]M.Sc Student, Cotton College, Guwahati, Assam

*Corresponding Author Email: jitendra.du.biotech@gmail.com

ABSTRACT

Malaria becomes a serious obstacle in developed and developing countries till at the present because of emergence of the drug resistant parasites and pesticide resistant mosquito vectors as well as non-availability of suitable and effective malaria vaccine .The present study focused a state of knowledge regarding the prevalence pattern of insecticide resistance malaria causing mosquito vectors in developed and developing countries with special reference to India. This study illustrated molecular and biochemical mechanism associated with insecticide resistance malaria causing mosquito vectors. The piece of writing point out some significant research query to the researcher's and the scientist's which helps coming generation to carry out novel works and find out apposite answer to solve the burden of malaria among the whole community.

KEY WORDS

Insecticide, drug, malaria, mosquito vector, vaccine etc

INTRODUCTION

Malaria remains a major public health problem in developed and developing countries till at the present because of emergence of the drug resistant parasites and pesticide resistant mosquito vectors as well as non-availability of suitable and effective malaria vaccine [1]. Resistance to antimalarials especially by *P.falciparum* as well as insecticides by principle malaria causing mosquito vector species is spreading throughout the world and posing a serious obstacle to malaria control program [2]. To limit the burden of malaria, government had focused on vector control strategies and implemented many programmes for control of malaria encumber by using different types of insecticides against the malarial vectors. Although different vector control measurement ware taken but still malaria becomes a serious problem across the globe. Presently insecticides belonging to different groups viz, Organochlorine, Organophosphate and synthetic pyrethroids are used for public health spray. Insecticides belonging to Carbamate group have yet not been introduced for public health spray in India. Strategy for change of insecticide has always been reactive. Successive changes in the insecticide were made after the failure of the control by the ongoing insecticide intervention. A subsequent change in the insecticides has led to the sequential selection pressure of insecticides resulting in multiple insecticide resistance malaria vectors.

Malaria vectors in India are resistance to dichloro diphenyltrichloroethane (DDT) alone or double resistance to DDT and hexachlorocyclohexane (HCH) or triple resistance to DDT,HCH and malathion and quadruple resistance to DDT,HCH, malathion and deltamethrin (Synthetic pyrethroids). India reports a wide distribution of 9 anopheline vectors transmitting 3 *Plasmodial* species, *P. falciparum, P. vivax and P. malariae* [3] of which *An. Culicifacies* and *An.stephensi*

have shown wide spread resistance in different parts of India Other vector species are mostly susceptible to these insecticides. There is a great anxiety that the major malaria vector species *An.culicifacies* has developed resistance to all group of insecticides used so far in the public health programme. This species is reported to be resistant to organochlorine insecticides-DDT and HCH, organophosphate insecticides-malathion and recently to synthetic pyrethroids also. Development of resistance to synthetic pyrethroids warrants a caution of the impending possibility of wide spread resistance to other compounds of this group that are introduced in public health programme for indoor residual spray as well as insecticide treated mosquito nets [4,5].

Despite the fact that a few reports from Indian point of view revealed that deltamethrin incorporated polyethylene long-lasting netting and Olyset nets was safe, wash-resistant, and assessed to be an operationally feasible, community-based intervention for sustainable management of disease vectors to prevent malaria transmission [15,16]. Treated nets may be considered as mosquito traps baited by the odour of the sleeper. Recent trials in Assam have shown that when a whole community is provided with treated nets, so many mosquitoes of anthropophilic species are killed by contact with the nets that the density and/or sporozoites rate of the vector population is reduced. At present only pyrethroids are used for net treatment which suggested that emergence of pyrethroid resistance would have a disastrous effect.

Biochemical mechanism:

Insecticide resistance mechanisms may have varying impact on the effectiveness of insecticide-based control programmes. Knowledge of resistance mechanisms is necessary to guide insecticide use in vector control programmes. Biochemical assays showed that the DDT resistance was caused by elevated levels of glutathione S-transferase (GST) activity leading to increased rates of metabolism of DDT to DDE. The numbers of individuals with elevated GST and DDT resistance were well correlated, suggesting that this is the only major DDT resistance mechanism among the population. The carbamate resistance is conferred by an altered acetylcholinesterase (AChE) -based resistance mechanism. Only some study revealed that the level of resistance observed in the bioassays correlates with the frequency of individuals homozygous for the altered AChE allele. This suggests that the level of resistance conferred by this mechanism in its heterozygous state is below the level of detection by the WHO carbamate discriminating dosage bioassay. The low levels of organophosphate (OP) and pyrethroids (PY) resistance could be conferred by either the elevated esterase or monooxygenase enzymes. The esterases were elevated only with the substrate *p*NPA, and are unlikely to be causing broad spectrum OP resistance. The altered AChE mechanism may also be contributing to the OP but not the pyrethroid resistance [6].Several biochemical study illustrated similar finding. Although, biochemical assay is not only the diagnostic tool to be used for detection of insecticide resistance mosquito vector, molecular study support the biochemical evidence and provided an important tool regarding molecular mechanism behind insecticide resistance.

Molecular mechanism:

Molecular studies over the past decades have identified several polymorphisms associated with the resistance phenotype; e.g. resistance against pyrethroids and DDT, known as knock-down resistance (kdr), has been linked to mutations in the Para-type, voltage-gated sodium channel (VGSC) gene. This leads to Structural modifications in insecticide binding sites, of voltage gated sodium (NaV) channel. Recent studies suggest that in addition to metabolic resistance, mutations in the sodium channel (the target of pyrethroids as well as DDT) may be playing a role in the resistance to cypermethrin and deltamethrin in mosquito populations from India. PY compounds act on the insect nervous system, targeting the NaV channel. This channel is composed of four domains (I-IV) and each domain comprises six transmembrane helices (S1-S6) [7,8,9]. Pesticides such as PY and DDT retard the activation and inactivation potential of NaV channels, triggering a series of repetitive discharges in motor and sensory axons, and resulting in paralysis ("knock-down") and death [9]. However, several insect species, including Anopheles gambiae, Culex pipiens, Culex quinquefasciatus and A. aegypti, may present a

resistance phenotype to chemicals which target the NaV, commonly called knockdown resistance [10-14]. The knock-down resistance trait (named kdr) and another kdr-related trait (super-kdr), which confers greatly elevated resistance in combination with kdr, were mapped to chromosome 3 [8]. Both traits have been associated with a lower electrophysiological sensitivity of elements from the nervous system and a reduced function of the NaV channel. Many studies have focused on finding mutations in NaV channel sequences from knock-down resistant populations. Characterization of sequences from A. gambiae and C. quinquefasciatus pyrethroid resistant strains showed that the most common mutation is a leucine to phenylalanine substitution in the S6 hydrophobic segment of domain II [11], although a leucine to serine mutation has also been reported at the same 1014 site [12,13]. However, a few reports have shown that kdr genotyping is a good predictor of susceptibility to pyrethroid and DDT, and, at the moment, it is considered the best tool for predicting the efficacy of these compounds in the field [19].

DISCUSSION

DDT and pyrethroids are neurotoxins that act on the voltage- gated sodium channels by modifying their gating kinetics, resulting in the prolonged opening of individual channels leading to paralysis and death of the insect. One of the mechanisms of pyrethroid resistance in insects is referred to as knock-down resistance (*kdr*) caused by reduced target site sensitivity. The phenotype is commonly conferred by a single point mutation (L1014F/S/ H) in the IIS6 segment of voltage gated sodium channel [8,18]. Other mutations in different regions of the gene also confer knock-down resistance in some insects [8,17], but among anopheline this is the only locus where point mutations have been reported to date conferring resistance.

There are only a limited molecular studies associated with insecticide resistance was carried out in India [20]. Information regarding resistance of malaria vectors to various insecticides has been documented in Southern part of India. A low frequency of the *kdr* allele (L1014F) mostly in heterozygous condition was observed in the resistant mosquito population from the Surat district of India. Two additional amino acid substitutions in the VGSC of an *An. culicifacies* population was reported from Malkangiri district of Orissa, India. That was the first report of the presence of L1014S (homologous to the *kdr-e* in *An. gambiae*) and a novel mutation V1010L (resulting from G-to-T or -C transversions) in the VGSC of *An. culicifacies* in addition to the previously described mutation L1014F. The V1010L substitution was tightly linked to L1014S substitution [20,21]. Resent report from National Institute of malaria Research (NIMR) regarding Insecticide resistance monitoring in different parts of India demonstrated that *An. culicifacies* was resistant to DDT and malathion in most parts of India and to synthetic pyrethroids in Chhattisgarh and Andhra Pradesh. Absence of cross resistance between DDT, malathion, deltamethrin and bendiocarb with chlorfenapyr was observed in *An. Stephensi* and *An. culicifacies*. It was found that Chlorfenapyr could be a potential option for manangement of insecticide resistance. Upregulation of AcNos (*Anopheles culicifacies* nitric oxide synthase) activity was found in refractory strain of An. culicifacies species A in comparison to susceptible strain in Real Time PCR assys at different days pBM. Bioinformatic studies on NADPH cytochrome P450 reductase gene evolution in Indian *An. minimus* showed that the population had experienced population bottle neck in the recent history and genetic drift has shaped variations in this insecticide resistant conferring gene.

But the information regarding the pattern of insecticide resistance gene polymorphism of malaria vectors like *An.minimus* and *An.dirus* widespread in the North eastern region of India are not available. Such study will facilitate us to understand detail knowledge which helps out researchers to blueprint novel insect repellent depending upon currently existing tainted target site so as to plan for suitable vector control strategies.

FUTURE STUDY NECESSITATES:

Till now no such study has been carried out regarding allelic distribution of VGSC gene mutations among malaria vectors in malaria endemic areas of Assam. Such study will explore the possibility of any polymorphism among the major potential malaria vectors prevailing in this part of country associated with insecticide resistance. The geographic

distribution of *kdr* haplotypes should reflect the interplay between the evolutionary forces of mutation, gene flow and selection. Such type of endeavour will certainly bring some outcomes which will be very much helpful for understanding the malarial vector biology in this region to underestimate the mechanisms of insecticide resistance in malaria vectors at both the molecular and biochemical levels and to suggest for suitable vector control strategies. Future study will need in this part of country which will help to understand the pattern of insecticide resistance of malaria vectors of this region and impact of the resistant allele on the efficacy of pyrethroids or other currently used insecticides so as to suggest for suitable malaria as well as other vector borne disease control strategies.

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***Corresponding Author:**
Jitendra Sharma*
*PhD Scholar, RMRC (ICMR) Dibrugarh, Assam