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REVIEW ARTICLE

INSECTICIDAL SUSCEPTIBILITY AND RESISTANCE OF PHYTOCHEMICALS OVER SYNTHETIC LARVICIDESAGAINST MOSQUITO SPECIES (DIPTERA): A REVIEW

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ABSTRACT

The diversity and proliferation of mosquitoes depends on the availability of breeding sites, sources and abiotic factors of the environment. Mosquito species serves as a vector for most of the life threatening diseases like malaria, chikungunya fever, yellow fever, dengue fever, filariasis, Japanese encephalitis, West Nile virus infection, Zika virus etc. To control the growth of these species many chemical pesticides are used like malathion, phenothrin, pyrethrins and temphos. But these insecticides are now showing less effect on the target species and are also dangerous for the non-target species. Under the Integrated Mosquito Management (IMM), alternative strategies for mosquito control were highlighted. The steady use of manmade insecticides is the origin of toxic substance bio magnification in the food chain, development of resistance in vector species and adverse effects on environmental quality and non target organisms including human health. On the contrary phytochemicals are harmless, convenient and cheap, biodegradable and manifest wide range of precise activities against different species mosquitoes. In this review, the present day knowledge onkind of mosquito species, the diseases they transmit as vectors, their life cycle and phytochemical sources have been studied. The mosquito species which are vectors of many diseases have developed resistance capacity against chemical larvicides and are showing less mortality rate. Whereas phytochemicals are a blend of chemical compounds therefore the mosquitoes are more susceptible against them with a very high mortality rate. A comparison between chemical and natural larvicides with respect to susceptibility and resistance for mosquito control have been reviewed.

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INTRODUCTION

Mosquito comprise a monophyletic taxonbelongs to the order Diptera and family Culicidae,(SINCLAIR 1992)and are a variety of 3,490 species of class insecta which are basically flies belonging to the phylum Arthropoda. According to a study some 3,490 species are presently recognized formally (Harbach and Howard 2007).The mosquitos are having a large family which occurs throughout the tropical and temperate regions of the world as well as afar the Arctic region. Mosquitoes are most diverse and least known in tropical forest environments. Some 3,490 species are currently formally recognized Mosquitoes have an attenuated segmented body, a pair of wings and a pair of halters, pair of Plumose type antennae and three pairs of legs and having the piercing and sucking type of mouthpart. Mosquitoes act as vector and can transmit more diseases as compared to any other arthropods, thus affecting millions of people throughout the world. According to WHO it is declared as the "public enemy number one".As per World Health Organization (World Health Organization 2012) mosquito borne diseases affect the every-day life of more than 50% of the human population globally and human morbidity and mortality is on the rise.

In addition, mosquito-borne diseases have a major effect on the world's economy, where the estimated annual cost of malaria alone, in 2011, was 1.66 billion USD (E.L. *et al*. 2013). As mosquitoes are cosmopolitan they are generally spread in more than 100 countries around the world and every year they are infecting 700 million people with different mosquito borne diseases out of which 40 million cases are from India solely. They are the vectors for a number of diseases like Dengue, Malaria, Yellow fever,Chikengunya, Filariasis, West Nile Fever, Encephalitis, Zika virus etc.around the world. To control the proliferation of mosquitoes the major tools used is the application of synthetic insecticides or larvicides like organophosphate and organic chlorine compounds. But because of technical,operational, human, ecological and economic factors these insecticides have not been very productive. Use of these synthetic insecticides in mosquito control program has been restricted. Due to concern of environmental sustainability, lack of novel insecticides, elevated cost of insecticides, their indestructible nature, excessive bio magnificationthrough the environment and an increase in the rate of the resistance of these insecticides by the target organism on a global scale(Brown 1986) (Russell, Kay, and Skilleter 2009), hence a category of rules and regulations have been shaped by the Environmental Protection Act in 1969 to test the efficiency of chemical pesticides in the environment(Bhatt and Khanal 2009). According to Dahmana, H., & Mediannikov, O. (2020) theRe-emergence of significant mosquito-borne diseases, including outbreaks, reported native and imported caseshave been noted around the world (Figure 1.1). Thus it has evoked the researchers to search for alternatives like eliciting the use of effective mosquito control strategies which should focus on surveillance and monitoring, public education, depletion of the source of mosquitoes and environmental friendly non-toxic larval control. Scrutinizing all these factors, the search and application of eco-friendly and biodegradable alternatives like biological control vector and phytochemicals has become the main interest of larval control program instead of chemical derivative pesticides. Exploration of floral diversity is a constructive alternative perspective for the chemical free mosquito control insecticides, thus getting involved into using more safer and biodegradable insecticides which will be a more feasible procedure for mosquito management. Moreover, contrary to the common pesticides having only one active ingredient, phytochemicals consists of a blend of different active ingredients which not only affects the physiological but also the behavioral actions of mosquitoes. As it is a blend of many chemical compounds the pests fails to become resistant to these types of compounds. Therefore to identify efficient, biodegradable and suitable bio-insecticides which can be ecologically adaptive is of vital importance for continued vector control management. Furthermore, botanicals products can in future be an alternative for the same as they have several insecticidal properties and can also be a remedy for mosquito borne diseases.

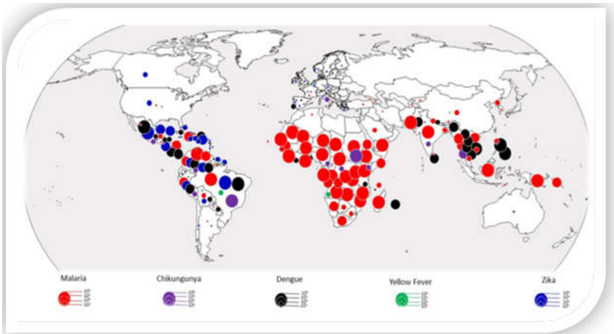
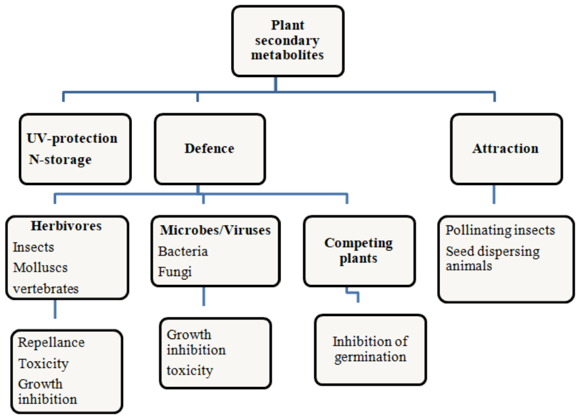


Figure 1.1. Re-emergence of significant mosquito-borne diseases, including outbreaks, reported native and imported cases (2017-2019) Reference: Dahmana, H., &Mediannikov, O. (2020)

Phytochemicals: The naturally occurring insecticides discovered from floral sources are phytochemicals.phytochemicals applications for mosquito control are studied since(Shahi *et al*. 2010), but due to the detection of DDT which is a synthetic insecticide deviated the use of natural larvicidesin mosquito control program.But with the course of time importance to phytochemicals where again given importance as the use of chemical larvicideswere confronting many difficulties due to incautious and stereotyped use of chemical insecticides in the environment, therefore phytochemicals which are not harmful to non-relevant organisms were acknowledged. Therefore from that time hunt for new bio active compounds from the plant kingdom has been initiated. Several chemicals are produced by plants and most of them have medicinal and pesticide properties. In the pest control programs More than 2000 plant species are recognized as producers of valued metabolites and chemical factors.Plant families- Asteraceae, Cladophoraceae, Miliaceae, Labiatae, Oocystaceae, Rutaceaeand Solanaceaehave various types of larval, adulticidal and repellent activities against different species of mosquitoes(Shaalan *et al*. 2005). Many groups of chemicals from plants such as alkaloids, terpenoids,steroids, essential oils and phenolicsfrom various botanics have been described earlier for their larvicidalactivities. The other plant extracts having larvicidal properties are lactones, isoflavonoids, fatty acids, alkanes, alkynes, alkenes, pterocarpans, ligans etc.(Ghosh A, 2012). Plant extracts have Insecticidal effects and differs not only togeographical varieties, mosquito species, plant species, but also due to type of solvent chosen and kind of extraction adopted.(Shaalan *et al*. 2005).The different kinds of plant secondary metabolites which are produced in the plants having different functions and can also act as potential larvicides, adulticides, ovicidesetc is represented below (Figure 1.2). Different phytochemicals have different types of mode of action, some shows contact toxity, some affect the midgut primarily and then can affect the gastric caeca and malphigian tubules as the secondary mode of action whereas some act as Insecticidal Growth Regulatory hormones(IGRs) and inhibit the growth of the larvae (Figure 1.3)



Reference: Wink, M. (2006).

Figure 1.2. Functions of plant secondary metabolites

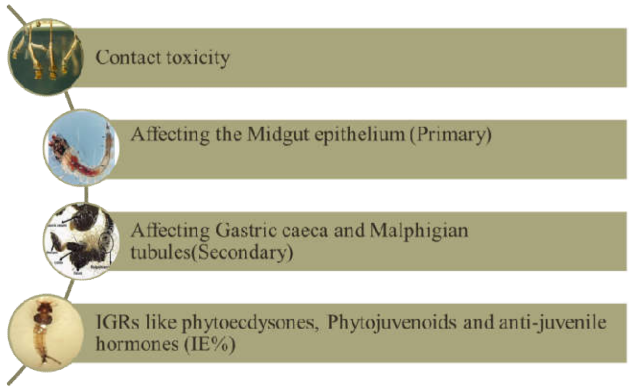


Figure 1.3. Mode of action of Phytochemicals

Susceptibility and resistance to chemical Insecticide: The Integrated Pest Management have a section to use insecticides to kill mosquitoes that spreadZika, dengue, and chikungunya viruses and as well as transmits diseases like Malaria West Nile Fever, Elephantesis etc. The insecticides can be larvicide or adulticide and can be applied by professionals as well as homeowners. The repeated use of the insecticides has made the mosquito populations resistant to it and therefore there is an overall decrease in the capability of these insecticides to eradicate the mosquitoes. If the mortality by the insecticide is left unchecked, insecticide resistant could possibly increase the growth rate of the mosquitoes. The details of case studies on susceptible/resistance chemical mosquito insecticides isdepited in (Table 1.3). The WHO global reports states that pyrethroids, organochlorines, carbamates and organophosphates are the four major insecticide which have become resistant insecticides to mosquitoes(WHO,2010-2016) From 2010 , a total of 68 countries have reported resistance to at least one class of insecticide, with 57 of those countries reporting resistance to 2 or more classes. All the chemicals like malathion, naled, phenothrin, permethrin,and pyrethrinsare mosquito adulticides which is used in the early evening through fogging and most of them are conducted by vector control districts.The only chemical insecticide Temephosan organophosphate with significant larvicidaluse isconsidered only for use by personnel of mosquito abatement districts, public health officials, personnel under contract to those agencies or similar agencies. The continuous use of chemical pesticides having the same chemical formula eventually decreases the mortality rate of the mosquitoes and slowly they become resistant to the insecticides in their next generations a diagrammatic representation of resistance from chemical insecticides is depicted in (Figure 1.4). Whereas some of the major advantages and disadvantages of space sprays or chemical larvicides are discussed below. (Table 1.2)

Table 1.2. Advantages and Disadvantages of Space sprays

Advantages of space sprays	Disadvantages of Space sprays
Immediate effect- suitable for control of disease outbreak	Effects lasts for shorter period-repeated at least once a week
Less insecticide is required for one application	Insecticide resistance monitoring and management
Kills exophillic species of mosquito	The cost of equipment, operational and maintenance high
	Needs specially trained staff for maintenance and repair
	Problems with acceptability

The use of chemical pesticides apart from being resistant to the larvae are also now being a potential risk to the non target species. The pesticides used for the mosquito control are targeting the other species like a case in U.S where the U.S. Fish and Wildlife service(FWS) put forward a plan on August 15 2013 to assign a critical habitat for the Bartram's scrub-hairstreak (*Strymonacisbartrami*),Florida Leafwing (*Anaeatroglodytafloridalis*) butterflies according to the Endangered species Act. The reason of these species becoming threatened was found to be the drift from the mosquito control pesticides application which was effecting the other non target species also. (U.S. Fish and Wildlife Service, October 2015). The *Culex*genus has the most notorious reputation for developing resistance to insecticides as observed from the history. This genus have developed resistance against insecticides like organophosphates,carbamates and pyrethroids (Mansour SA 2000, Prabhakar K 2004) (Karmegam *et al*. 1997) (Rahuman and Venkatesan 2008) (Kamaraj *et al*. 2010). If we look back into the history of mosquito resistance insecticidesin India the first case was of *Cx*. *Quinquefasciatus* which became DDT resistantfrom a village near Delhi in 1952 (Rajkumar S,2005). Far on in time, there were manyplaces like Pune,Patna, Rajahmundry and Nagpur, where *Culex* mosquitoes were observed resistance to several chemical insecticides such as fenitrothion, DDT, BHC, temephos and malathion, (Rahuman AA,2007;Maurya P,2009 (Sharma, Mohan, and Srivastava 2006)(Rahuman and Venkatesan 2008)(Rajkumar and Jebanesan 2006). Mukhopadhyay *et al*. Investigated in *Cx. quinquefasciatus* larvae a mortality rate of 3.125 and 0.125 mg/l concentration of Malathion, and DDT respectively.

An insecticide resistant study from Gorakhpur and Pune on *Cx. quinquefasciatus* based on WHO criteria(Maniafu *et al*. 2009),observed malathionresistance and absolute susceptibility to deltamethrin and entire resistance to DDT .When the results were compared of Gorakhpur and Pune it was evident that the population of *Cxquinquefasciatus* from Pune revealedlower LC_{50} value for malathionand DDT as compared to Gorakhpur population. Whereas deltamethrin exhibits no remarkable difference for both the populations of LC_{50} values of deltamethrin. Another study from Nigeria clearly exhibits the distinctive outcome of Deltamethrin, permethrin, larvicideon three Anopheles species**:** An**.** coluzzii **,**An**.** gambiae, and An**.** arabiensis**.** In one of the earlier studies (Awola TS, 2002) (Awolola *et al*. 2007), it was investigated that An**.** arabiensis population from Lagos and Niger and was entirely susceptible to deltamethrinandpermethrin. Whereas in disparity to the earlier studies the current observations in Niger and Kwara exhibits An**.** arabiensis resistance to deltamethrin. A study revealed many levels of tolerance of*Aedesaegypti to* propoxur and malathion.from different localities.Except the standard susceptible USDA strain all the other strains exhibits high resistance to DDT. But the USDA labroratory strain exhibited 100 % mortality and was thus considered susceptible to malathion. A study from SamutSongkhram, Thailand shows that the *Aedes* species RR_{50} resistance indicates that larva from all areas cannot resist against Zeolite chemical (RR < 5) with 1, 0.73, and 0.70 of SuanLuang, Jompluak, and Ladyai subdistrict, respectively. Comparing the statistic shows no difference of mosquito larva eradication ($P > 0.05$) by temephos in all areas,larvae from Jompluaksubdistrict have a highest number of LC50 of GPO-1, at 34.73, followed by mosquito larva from Ladyai and SuanLuangsubdistrict at 30.72 and 24.64 consecutively (Chaiphongpachara, 2017).

A study from Kunar, Laghman and Nangarhar provinces in Afganistan shows the *Anophelesstephensi*populations resistance to malathion, DDT, pyrethroid and bendiocarb insecticides is perceptible in various populations of the *Anopheles sp*. The results concluded that the *An. stephensi* from Laghman is more resistance to the chemical insecticides as compared to the other field populations.(Safi *et al*. 2019). The study from Mafang and Port Moresby in Papua New Guinea shows foremost tolerance to pyrethroids in *Ae. aegypti*. Whereas *Aedesalbopictus* exhibits less intensity tolerance to DDT and susceptibility to pyrotheroids.This is one of the first report of *Ae.aegypti* resistance against pyrethroid in PNG (Demok *et al*. 2019).

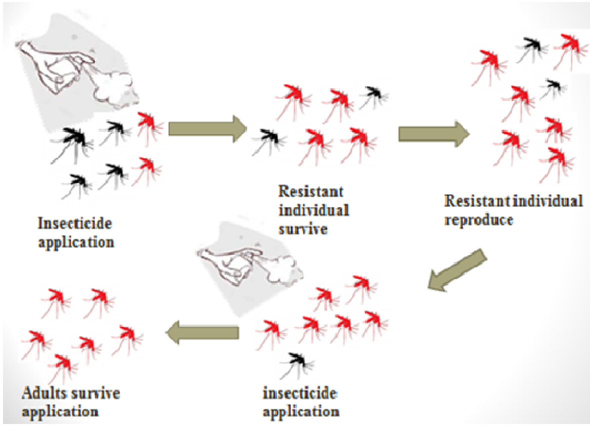


Figure 1.4. Cross resistant activity of insecticides

Susceptibility and resistance to Phytochemicals: *E.alba* when extracted with methanol exhibits LC_{50} value against early third instar larvae of *Aedesaegyptii* of 127.64ppm whereas the LC_{50} values of hexane, benzene, ethyl acetate, and chloroform extract were 151.38, 165.10, 154.88, and 146.28 ppm, respectively. Maximum larvicidal activity was observed in the methanol extract followed by chloroform, benzene, ethyl acetate and hexane extract. Therefore from the results it can be concluded the crude extract of *E. alba*has an excellent potential for controlling *Ae. aegypti* mosquito.(Govindarajan M, 2011). Studies carried out by Tennyson S. et.al. 2012, in Chennai, Tamilnadu, India exhibits the hexane extracts of the plants *Murrayakoeingii* and *Cleistanthuscollinus* reveals 100% mortality at bioassay for 24 h, which is followed by diethyl ether, dichloromethane and ethyl acetate extracts of *Hydrocotylejavanica* ,*Leucasaspera* , *C. collinus,* ,*Sphaeranthusindicus* ,*Zanthoxylumlimonella* , and *M. koeingii*after 48 h exposure.These experiments were carried only against*Cx. quinquefasciatus* and therefore further studies are needed for all the larval stages of different species of mosquitoes along with the identification of extracts and active ingredients present in the plants.

A study from Malasia exhibits *G. renghas* bark extract as the highest larvicidal activities as compared to other plant extracts, like *M. fasciculiflora* ,*Anacardiumoccidentale*and *Mangiferaindica*. It was observed that*Aedesaegypti* of both field and laboratory strains were less susceptible as compared to laboratory sand field strains of*Ae. Albopictus*. These plants were studied for the first time and exhibits high larvicidal activities against these species which are vector for dengue and is low cost, target specific and environmental friendly. (Yousaf A, 2015). *Terminaliachebula* was assayed for the larvicidal activity by the extracts of ethyl acetate, hexane,crude benzene, methanol and chloroform for their toxic activity against three principal vector mosquitoes, viz., *Aedesaegypti, Anopheles stephensi, and Culexquinquefasciatus*.The most larval death was exhibited by extracts of methanol in *T. chebula* against *Aedesaegypti*, *Anophelesstephensi*, and *Culexquinquefasciatus* having LC_{50} value of 93.24, 87.13, and 111.98 ppm, respectively.

Table 1.3. Summary of the case studies of mosquito insecticides

Sr.No.	Genus	Resistant to pesticides	Susceptible to pesticides	Place	Reference
1.	*Culex sp.* *Cx. Quinquefasciatus*	Organophosphates Carbamates Pyrethreoids; DDT	-	Delhi (1952)	Mansour SA 2000, Prabhakar K 2004 Karmegam *et al*. 1997 Rahuman and Venkatesan 2008 Kamaraj *et al*. 2010; Rajkumar S,2005
	Cx. Quinquefasciatus	fenitrothion, DDT, BHC, temephos and malathion	-	Nagpur, Pune, Rajhmundry	Rahuman AA,2007;Maurya P,2009 Sharma, Mohan, and Srivastava 2006 Rahuman and Venkatesan 2008 Rajkumar and Jebanesan 2006
	Cx. quinquefasciatus	Malathion, DDT	Deltamathrin	Pune, Gorakhpur	Maniafu *et al*. 2009
2.	**An. arabiensis**	-	Deltamethrin, permethrin	Lagos, Niger	Awola TS,2002
	An. arabiensis	Deltamethrin,	-	Lagos, Niger	Awolola *et al*. 2007
	Anophelesstephensi	-	malathion, DDT, pyrethroid and bendiocarb	Kunar, Laghman and Nangarhar provinces in Afganistan	Safi *et al*. 2019
3	*Aedesaegypti Aedesaegypti* (USDA strain)	propoxur and malathion-	DDT	US	
	Aedes species	temephos	Zeolite chemical	SuanLuang, Jompluak, and Ladyai	Chaiphongpachara, 2017
	Aedesaegypti *Aedesalbopictus*	Pyrethroids DDT	Pyrethroids	Mafang and Port Moresby in Papua New Guinea	Demok *et al*. 2019

Table 1.4. Summary of the case studies of Phytochemicals as mosquito larvicides

Sr.No.	Plant used	Mosquito species	Solvent used	Larvicidal activity/Resistance/susceptible	Reference
1.	*E.alba*	*Aedesaegyptii*	Methanol hexane, benzene, ethyl acetate, chloroform	127.64ppm 151.38 ppm 165.10 ppm 154.88 ppm 146.28 ppm	Govindarajan M, 2011
2.	*Murrayakoeingii* , *Cleistanthuscollinus Hydrocotylejavanica* ,*Leucasaspera* , *C. collinus*, ,*Sphaeranthusindicus* ,*Zanthoxylumlimonella* , and *M. koeingii*	*Cx. quinquefasciatus*	Hexane diethyl ether, dichloromethane and ethyl acetate	100% mortality(24h) 100% mortality (48h)	Tennyson S. et.al. 2012
3.	*G. renghas* *M. fasciculiflora Anacardiumoccidentale* *Mangiferaindica*	*Aedesaegypti* *Ae. Albopictus*	**-**	Highly susceptible Less susceptible	Yousaf A, 2015
4.	*Terminaliachebula*	*Aedesaegypti, Anopheles stephensi* *Culexquinquefasciatus.*	ethyl acetate, hexane, crude benzene, methanol chloroform	93.24 ppm 87.13 ppm 111.98 ppm	Veni T, 2017
5.	*Lantana camara, Hyptissuaveolens, TecomastansNerium oleander*	*Aedesaegypti* and *Culexquinquefasciatus*	methanol ,chloroform ,and petroleum ether	55.41 mg/L, LC_{50} 64.49 mg/L 10.63 mg/ L, LC_{50} 19.26 mg/L, LC_{50} 35.82 mg/L, LC_{50} 38.39 mg/L, respectively	Hari and Mathew 2018
6.	*Althaea ludwigii*	*Culexpipiens*	Ethyl acetate and Chloroform	susceptible	Abutaha N, 2018

The results shows that the plant consist promising larvicidalactivities against mosquito species and can be replaced by chemical insecticides in mosquito control programs. (Veni T, 2017). In a recent study extracts from the leaves of *Lantana camara, Hyptissuaveolens, Tecomastans* and *Nerium oleander*, with three organic solventsmethanol, chloroform, and petroleum ether were prepared. The plant extracts were screened against *Aedesaegypti* and *Culexquinquefasciatus* for larvicidal activity separately and in a blend. The maximum larvicidal activity against *Cx. Quinquefasciatus* was exhibited by petroleum ether extract of *L. camara* which was followed by petroleum ether extract of *T. stans*which was further followed by methanol extract of *N. oleander* and Petroleum Ether extract of *H. suaveolens* the values are LC_{50} 10.63 mg/ L, LC_{50} 19.26 mg/L, LC_{50} 35.82 mg/L, LC_{50} 38.39 mg/L, respectively. whereas *Ae. aegypti*, Petroleum ether extract of *T. stans* exhibits highest larvicidal activity followed by *H. suaveolens* LC_{50} value of 55.41 mg/L,LC_{50} 64.49 mg/L, respectively .A combination of these extracts against *Cx. quinquefasciatus* and *Ae. Aegypti*ensued in a weave withLC_{50} values of 4.32 and 7.19 mg/L. (Hari and Mathew 2018)

Culexpipiens larvae were tested against botanical extracts composed using various solvents discrete concentrations were tested. The effects were observed for LD_{50} and LD_{90}at 24 h and 72 h intervals and the values were determined. *Cx. pipiens* 4th instars exhibitssusceptibility to Ethyl acetate and Chloroform extracts of *Althaea ludwigii* but were highly supported byexposure time and extract concentrations.(Abutaha N, 2018)

RESULTS

From the above studies it is established that different mosquito species are vectors of different diseases and breeds on different grounds, the number of cases of Malaria, Dengue, Chikengunya etc. in India shows the need of effective larvicides which can control mosquito proliferation. The mosquito species which are vectors of many life threatening diseases have developed resistance capacity against chemical larvicides and are showing less mortality rate. Whereas phytochemicals are a blend of many chemical compounds therefore the mosquitoes are more susceptible against them with a very high mortality rate and very few are resistant. The comparison in this review concludes that green larvicides are far better and target specific with high mortality rate and can readily replace the chemical larvicides.

CONCLUSION

In today's world the preference is given to the environmental safety. An insecticide should be effective but should be eco-friendly first so that it does not affect the non-target organisms and harm other species as well as humans. As chemical insecticides are harmful for the non-target species and are now a days are becoming less effective as the mosquitoes are becoming resistant to these chemicals therefore zero mortality is observed in most of the cases thus increasing the disease rate transmitted through these insects. To overcome this situation Phytochemicals can serve as a green, safe,inexpensive,effective and readily available alternative to eradicate the mosquitoes around the world. In traditional medicines there are several plants which are being used as mosquito larvicides around the world. Many techniques are being developed for the production of new green insecticide. Many botanical products such as ornamental plants, edible crops, herbs, shrubs trees as well as marine plants exhibitlarvicidal activities on mosquitoes. The extraction strategy thrivingin solvent systems and the characteristics of larvicidesagainst various vector species can be a recommended for future studies.

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