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Surmounting the Environmental Impact Of Insecticides; Adopting A Sustainable Approach In The Fight Against Malaria- A Review

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ABSTRACT

As a notorious parasitic disease known to have continuously ravaged the human populations for centuries, malaria remains a major public health concern notably in developing countries. However, several approaches have been employed in a bid to annihilate the disease with many of such turning out to be unsustainable; causing more damage to the environment as well as the life forms in it. The use of synthetic pesticides initially portrayed an outstanding impact in curbing the anopheline vector, but was not long before their harmful effects began to manifest on non-target organisms including humans. The current work laid emphasis on dichlorodiphenyltrichloroethane (DDT) and pyrethroid. DDT usage was linked to several diseases ranging from neurological to reproductive as well as causing cancer. On the other hand, pyrethroids were initially considered to have no adverse effects, have now been observed to induce allergies, asthma and aggressive behaviors in children while impairing verbal abilities and intelligence. In order to curtail malaria disease and prevent the deleterious effects of synthetic pesticides, there is a need to prioritize the use of biopesticides; a better alternative, which is equally, or more effective and most importantly, eco-friendly with little or no harm to non-target organisms.

Keywords: Malaria, anopheline vector, DDT, pyrethroid, biopesticides.

INTRODUCTION

Aside from being the most common protozoan parasitic disease across tropical and subtropical parts of the world, malaria remains an infectious debilitating disease with significant morbidity and mortality [1, 2]. Despite various strategies to put the disease under control, it has been escalating especially in developing countries. In 2019,

229 million cases of malaria were recorded globally, leading to an estimated 409,000 deaths with 51% of these deaths occurring in African countries mostly among children below 5 years of age [3]. Malaria is commonly associated with poverty, which adversely affects economic development, with Africa losing an estimated 12 billion dollars yearly through costs of health care, lost ability to work and negative effects on tourism [4, 5].

Plasmodium falciparum, *Plasmodium malariae*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium knowlesi* cause malaria in humans and are spread via the bite of female Anopheles mosquitos [6]. *Plasmodium falciparum* is thought to be responsible for the bulk of deaths [7], however new research reveals that *P. vivax* is linked to potentially life-threatening diseases [8]. According to Castro *et al*., 2004 [9], the intensity of transmission, seasonality and geographic distribution of malaria is influenced by environmental factors as well as by human, vector and the parasites which altogether constitute the malaria system. In the quest for malaria control, altering the environment is one of the oldest approaches, but the complex interactions of the malaria system further pose a great challenge toward eradication. However, focusing more on the environmental components as a result of its encompassing interactions with other elements in the system is vital in the goal of eradicating malaria [9].

A major tool for efficient control and prevention of malaria is the attack of the anopheline mosquito vectors [10, 11]. This is reflected in the use of long-lasting insecticide treated nets (LLINs) and indoor residual sprayings (IRS) which are prevalent in Africa [12, 13]. The use of synthetic chemical insecticides in controlling malaria vector has had a significant impact, however, there are cases of insecticide resistance

coupled with its unaffordability by individuals [13, 14], and the potential harmful effects caused to non-target organisms including human and the environment [15]. Recently, synthetic chemical insecticides are being discouraged owing to their environmental pollution, deleterious consequences on human health and other non-target population and the continuous global surge in insecticide resistance [15]. Hence, due to the toxic and adverse effects of these compounds, there is a need to search elsewhere for alternatives that will be equally or of higher efficacy and most importantly environment-friendly in the control of malaria. The possible candidate in this regard is biopesticides with biologically active chemicals which are easily decomposed and are not toxic to other species [16], and effectively suitable for controlling mosquitoes [17].

This review focuses on the detrimental health effects of two mostly used insecticides [(DDT), and pyrethroid] against malaria vector and the eco-friendly alternatives that could be explored in lieu of the former.

INSECTICIDES

Varieties of insecticides are used in controlling a number of insect borne diseases and were found to be effective [18]. However, these compounds were later discovered to pollute the air, lakes, oceans, fishes and aquatic birds that feed on such fishes [19]. Some of these chemicals after entering the animal body became endocrine disruptors, and operate by mimicking and acting contrary to natural hormone [20], with their long-term effect associated to negative health effects in humans such as suppression of immunity, hormone disruption, reproductive anomalies, decreased intelligence and cancer [19, 20]. There are different types of pesticides a broader term which include insecticides, fungicides, herbicides, rodenticides and

others. They are classified in various ways, but based on their chemical compositions; they are grouped into organochlorine, organophosphate and carbamate pesticides/insecticides [21].

Organochlorine Pesticides

The most common organochlorine insecticide is dichlorodiphenyltrichloroethane (DDT) with others like dieldrin, endosulfan, heptachlor, dicofol and methoxychlor which are known to cause many environmental and human health problems [22, 23]. DDT will be extensively discussed below.

Organophosphate Pesticides

This group of pesticides were believed to be better than organochlorines environment-wise [24], with the most common ones; glyphosate and others such as malathion (used against mosquito), parathion and dimethoate [25, 26]. Many of these chemicals known to disrupt the endocrine system, affect the activity of cholinesterase, reduce secretion of insulin, alter protein, carbohydrate and fat metabolism, causing oxidative stress and affecting the nervous system [24, 27, 28]. Studies revealed exposure to these chemicals have serious health effects ranging from cardiovascular diseases [29], adversely affect the male reproductive system [30], and causing dementia and other neurological problems in children [31, 32].

Carbamate Pesticides

These include aldicarb, carbofuran and ziram, they are linked with affecting endocrine activity [33, 26] and causing reproductive disorders [24, 33]. They are also known to suppress the immune system by causing necrosis and apoptosis of natural killer cells [34] and T lymphocytes [35].

In this review, more emphasis is given to DDT and pyrethroid, because though, DDT is banned, it is still used in some places,

while pyrethroid is recommended by WHO because they were initially thought to be harmless.

Dichlorodiphenyltrichloroethane (DDT)

DDT is an organochlorine insecticide that was globally used to control malaria vector. Although, it has been banned for over thirty years, it is still in use to control malaria in regions like Africa [36]. Following the successful use of DDT to destroy insect vectors like mosquito that spread epidemic diseases such as malaria, it became tagged as the "wonder pesticide" that saved the lives of millions of people, but this glory became upturned upon the publication of "silent spring" in 1962 by Rachel Carson, an American marine biologist [37]. The book revealed the hazardous effects of DDT to humans and wildlife and paved the way for banning the compound. About the same time, it was discovered that some insects that used to be susceptible to DDT started developing resistance [37].

A position statement given by the World Health Organization (WHO) in 2006, promoted DDT usage in indoor residual spraying (IRS) to combat malaria vector [22]. However, indoor residual spraying of DDT has been shown by many studies to increase the level of human exposure [38] resulting in toxic effects including developmental abnormalities [39], neurological diseases [40], reproductive diseases [41] and cancer [42]. Moreover, DDE (dichlorodiphenyldichloroethane), a metabolite of DDT has been implicated in causing childhood diabetes and obesity [43]. DDT played a principal role in the near elimination of malaria in the world, with the exception of tropical countries where the continuous life cycle of mosquitoes and poor infrastructure persist [37]. The compound mimics estrogen thereby altering hormonal balance as well as increasing the risk of breast cancer in women [37]. Due to its solubility in fat, it enters into membrane

causing the leakage of potassium and sodium ion from neurons, thus, resulting in death by convulsion and paralysis [37]. A great environmental impact of DDT is its toxic effects on aquatic life such as crayfish, daphnids, sea shrimps, fishes and other fish-eating birds [37]. In birds, the insecticide interferes with calcium deposition in eggshells, with less calcium culminating in weaker eggshells that easily crack while on incubation. This phenomenon was linked to the decline in the population of bald eagle [44].

PYRETHROIDS

Pyrethroids are synthetic derivatives of pyrethrum, a natural insecticide derived from *Chrysanthemum cinerariaefolium* [45]. Insects are about 2250 times more susceptible to pyrethroids than vertebrates, which could be due to the insects' small size, lower body temperature, and more sensitive sodium channel [45]. Due to the rapid decomposition of pyrethrum in sunlight, it was substituted with pyrethroids which were initially considered safe for humans and higher animals [46]. Based on this earlier notion, pyrethroids were recommended to be used as insecticides in the control of malaria majorly as constituents of insecticide treated nets [47]. Pyrethroids act by interacting with sodium channels and causing extended depolarization of neurons and are of two types- type I and type II based on the structure of the compound and their mechanism of action and the undesirable symptom they elicit [45]. By causing a change in sodium channels during opening and closing of membranes of neurons, type I pyrethroids induce tremors of the whole body, aggressive behavior, hypersensitivity and ataxia [48, 46]. Type II pyrethroids affect both sodium and chloride channel and causes salivation and motor dysfunction in mammals [49].

The neuronal membrane ion channel as well as mitochondrial membranes of crayfish,

lobster and fishes such as *Danio renio*, carp, and rainbow trout have been found to be affected arising from pyrethroid toxicity in aquatic ecosystem [50, 51]. This insecticide mainly gain entrance into the body via skin contact, however, other points of entry include through inhalation, or food and water ingestion [52, 53]. Owing to the lipophilic features of pyrethroids, they are able to move through the blood-brain barrier at concentrations considered to be neurotoxic [54]. Though, repellents composed of this compound are recommended by Center for Disease Control for pregnant women to protect against mosquito-vectored diseases [55], children are the most vulnerable to the toxic effects of the insecticide [55, 56]. They three pyrethroids; permethrin, deltamethrin and α-cypermethrin, recommended by WHO to be used in the prevention and control of malaria and other insect-borne diseases have been found to have various adverse effects on humans [57].

Permethrin

It's a type I pyrethroid that comes in yellow-brown and brown crystals as well as a liquid that's soluble in organic solvents [50]. It is used to prevent mosquitoes and other insect vectors in homes and applied to pets and clothing for treatment of scabies [58]. It causes harm to insect neurons by boosting impulse conduction, resulting in insect paralysis and death [45]. Permethrin poisoning causes epidermal sores, sore throat, nausea, vomiting, stomach pain, gastrointestinal mucosa irritation, salivation, respiratory distress, and headaches in humans and animals [59, 51]. According to Dohlman *et al.*, (2016)[60] endocrine issues caused by pyrethroid may influence male fertility by lowering sperm quality. This finding was corroborated by Omotoso *et al.*, (2014) [61], by assessing the testes of rats exposed to 500 and 1000 mg/kg doses of

permethrin for two weeks. Morphological change in testis, decreased population of mature sperm cells, indicating dysfunction in male fertility was observed.

Long-term exposure to permethrin causes oxidative stress which leads to damage of heart cells [61] Household use of permethrin is often associated with allergies and asthma notably in children [45]. Prolonged exposure to the compound results in an increased level of permethrin metabolites in urine, as well as increase in aggressive behaviors [62]. Furthermore, consumption of food containing the insecticide accidentally has been linked to short-term memory and concentration [63].

Deltamethrin

It is a type II pyrethroid, lipophilic, insoluble in water, but soluble in acetone and alcohol while existing as colorless or white crystals [64]. Mosquito nets are soaked in it due to its effectiveness against *Anopheles gambiae* and *Aedes aegyptii* [65]. Its neurotoxic action causing synaptic disturbances leading to death of insect is associated to prolonged opening of sodium channel in the membrane [48]. Similarly, it enters into animals through digestive, respiratory system and skin [66].

Human exposure for lengthy period to deltamethrin arising from insecticide-soaked mosquito net is associated with symptoms such as headaches, abdominal pain, lacrimation, nausea, diarrhea, vomiting, apathy, weakness, ataxia, convulsions, allergic reactions, hypersensitivity to sound and touch and facial edema. Skin exposure often results in paresthesia with tingling, itching, burning and numbness of skin [45]. Khalatbary and Ghaffari (2015) [67], reported additional symptoms of blurred vision, tremor of arms and legs, sensitivity to sun and unconsciousness. Its intoxication through oral route and skin is reported to accumulate in brain neurons [68], while

pregnancy exposure could result in fetal central nervous system change, with sleep disorders, impaired memory, poor verbal abilities and decreased intelligence associated to children exposure [69]. Chances of Parkinson's diseases increase due to deltamethrin action on neuronal dopamine transport [70].

α-cypermethrin

It belongs to type II pyrethroids, existing as a dense yellow powder and stable in acidic and neutral environment. It is seen at elevated concentrations in adipose tissue, skin, ovaries, kidneys, adrenal glands and liver due to its lipophilic nature [71]. Poisoning with this compound causes symptoms ranging from nausea, vomiting, diarrhea, mucosal irritation, and motor coordination disorders to tremor [71]. Long-term exposure of this insecticide especially in production workers led to them having skin lesions on face and neck [72]. Singh *et al.* (2012) [49], observed no carcinogenic, mutagenic, teratogenic effects and reproductive toxicity due to α-cypermethrin exposure. According to El Okda *et al.* (2017) [73], the compound significantly lowers CD4/CD8 concentrations, meaning it suppress the immune system in the workers tested.

On the overall, pyrethroids have low toxicity in humans, are rapidly metabolized in adults and excreted in urine, but children are the most vulnerable group, since the insecticide is likely present in breast milk, and accumulation in tissues may be as a result of lactation [55, 56]. Acute poisoning with pyrethroid in 573 cases in the 1980s, resulted in deaths of seven (7) persons [74]. Dizziness, headaches, anorexia, fatigue, nausea, vomiting, convulsion, pulmonary oedema, coma and death have been linked to oral exposure to pyrethroids [74, 72].

WAY FORWARD

The integrated vector management (IVM) strategies canvassed for by the WHO aims at targeting different stages of the mosquitoes both in indoor and outdoor settings for an efficacious, environment-suitable, sustainable control and elimination of malaria [75]. However, the overwhelming evidences of the health as well as the environmental impacts of many insecticides and the emerging adverse effects of contemporary insecticides that were initially thought to be harmless poses a new challenge, and necessitating the search for effective, harmless and eco-friendly alternatives for prevention and control in malaria endemic regions.

BIOPESTICIDES

These are naturally existing life forms like animals, plants and microbes used in the control of insect vectors of different diseases and crop damaging pests [76]. By virtue of their non-toxic and eco-friendly mechanism of action, they are being recognized globally [77]. As opposed to synthetic insecticides/pesticides, biopesticides are target specific does not affect beneficial insects, does not impair environmental quality and most importantly, are not resisted by the target organisms [78].

Microbial Pesticides

Bacteria

Bacillus thuringiensis israelensis (Bti) and *Bacillus sphaericus* (Bs) are bacteria found to be quite effective against mosquitoes [79]. Bti and Bs produce toxic crystal proteins which when ingested by mosquito larvae, damage the gut tissues, causing paralysis of the gut and consequently preventing the larvae from feeding, and finally making it to die of starvation [80, 81].

These bacterial are potent larvicidal strains used to effectively control mosquitos. Apart from bacillus strains ease of manufacture and handling as compared to chemical insecticides, they have abilities to spread

faster [82]. All the larvae of the three genera (*Anopheles*, *Aedes* and *Culex*) of mosquitoes are found to be sensitive to Bti and Bs application with *Anopheles gambiae* having the most susceptibility to the bacteria strains [83]. Recombinant bacterial strains are being developed following the endotoxin protein properties of the bacteria strains and are found to be ten (10) times potent than the strains [84].

Another strategy is to use mosquito-bacterial symbionts like Wolbachia strains, which drastically lower *Plasmodium falciparum* oocyst population in *Anopheles gambiae* [52]. Bacterial agents directly target the vector or disturb and alter the development of the pathogen within the mosquito [82].

Entomopathogenic Fungi

The use of these fungi is viewed as a very promising alternative to chemical insecticides, with species in genera Coelomomyces, Culicinomyces, Beauveria, Metarhizium, Langenidium are the mostly considered candidates [85]. Quite different from other infectious agents against vectors, fungi do not need to be ingested; external contact with the cuticle of the insect causes infection which resembles most chemical insecticides mode of application [82]. Spores of fungi can be applied to odor traps, indoor house surfaces, bed nets, curtains and remain for months [85, 86].

Though fungal mechanism of action as anti-malarial agent is not well explained, numerous studies indicate fungi as altering and disrupting nutritional balance, increasing immune response and the production of secondary metabolites in mosquito hemolymph [86]. Genetically engineered Metarhizium produce peptides that inhibits the transmission of the pathogen from its vector [82].

Parasites

Vavraia culicis and *Edhazardia aedis* parasites have been discovered to stop the development of other parasites like Plasmodium and target the vector [82]. These parasites efficacy can be seen in their ability to give combine effects on a number of epidemiological traits of the vector. Microsporidia cause a decrease in the survival rates of the larvae, hence, reducing the population of adult mosquitoes [87]. They also affect the adult longevity, altering parasite development in the vector and reducing the rates by which the mosquito bites [88]. Microsporidia like *Nosema* spp. produces spores which when ingested by the mosquito, develop in the midgut and spread to other tissues where it destroys organs and tissue [88].

Virus

Densonucleosis viruses (single-stranded DNA viruses that are non-enveloped) (DNVs) belonging to the family Parvoviridae are known to infect mosquitoes [89]. Larval stages of *Anopheles gambiae* are found to be highly susceptible to *A. gambiae* denso virus (AgDNV) with the virus able to circulate in the tissue of adult mosquitoes and can be transmitted to their offspring [89]. The toxin produced by the virus causes paratransgenesis (genetic manipulation of symbiotic microbes in mosquito) to alter the vector abilities to become infected, transmit the parasites, or to reduce the vector birth rate or lifespan [90].

Larvivorus fish

Predatory fishes such as the *Gambusia affinis*, a freshwater fish that feed on mosquito larva have been used for long in the control of mosquitoes. This fish compared to chemical insecticides is more effective, harmless to wildlife and humans, cheap to manage and little or no risk of mosquito resistance [91]. In order to reduce the loss of native species by the introduction of exotic species, native larvivorus species could be encouraged as seen in Kutch

district (India) where *Alphanus dispar* was used [92]. Likewise, some of these fish apart from achieving the main goal of controlling malaria, could be harvested and sold to generate income as seen in Kenya, Tanzania and Gambia where *Oreochromis niloticus* was used to attain about 94% reduction in population of *A. gambiae* and *A. funestus* while harvesting parts for consumption and income purposes [93, 94].

Botanical insecticides

A number of secondary metabolites are produced by plants which are toxic to insect [95]. Neem plant (*Azadirachta indica*) is one of such plants that has been greatly studied with its leaf and seed containing azadirachtin, which is a potent antifeedants and insect growth regulator that is biodegradable and non-toxic to non-target organisms [77]. Apart from being eco-friendly, neem extracts have the capacity to be efficacious against mosquitoes [96].

UZIMAX is a newly developed plant-based biopesticide for malaria vector control with a potential of killing 100% of Anopheles larva within the span of 48 h [75]. It contains a mixture of compounds that synergistically deactivate behavioral and physiological processes of mosquito. Having blends of chemicals that are greatly effective larvicides, it is eco-friendly, posing no threat to the environment, humans and other non-target organisms including fish, tadpoles, beetles and bees [97].

CONCLUSION

A number of approaches have been used in a bid to annihilate the scourge of malaria and stamp out its devastating consequences. Some of these strategies include altering the development of the parasite and controlling the population of mosquitoes majorly through decimating the larval stages. However, over-reliance on the use of conventional chemicals- insecticides, though indicated an ephemeral success, is currently

found to be unsustainable partly due to the development of resistance strains of mosquito and chiefly by the numerous side effects posed to non-target organisms including humans. The various adverse effects on humans resulting from the use of these chemicals have however, spurred the search for better alternatives which are equally or more effective, environment-friendly and cause little or no harm to non-target organisms.

Embracing the use of biopesticides in the race to overcome malaria with its huge benefits and negligible adverse effect on wildlife, humans and the environment seems to be in tandem with not only the IVM strategies, but also the principle of sustainability.

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