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Commentary

Azadirachta indica as a public health tool for the control of malaria & other vector-borne diseases

Neem-based products from *Azadirachta indica* have been successfully used for pest control in agriculture and gardening since long in India and more recently in European countries and in the USA[1]. The seed kernels, particularly rich in bioactive azadirachtin and other limonoids (tetranortriterpenoids), are the main source for a large number of products used for the control of pest insects, mites, fungi and soil-borne nematodic root parasites[1].

Surprisingly, registered neem products for the control of pathogens, ectoparasites or disease vectors affecting human and animal health are few. The moderate interest of chemical and pharmaceutical industries for developing neem-based products for human health stands in sharp contrast to the wide traditional use of neem preparations by populations of different cultures, in India, in other Asian countries and in Africa. Leaves, seeds, roots, bark and the flowers of the plant are used to cure different ailments, such as jaundice and stomach ulcers and to combat a variety of infectious and parasitic diseases, ranging from leprosy, to chicken pox, to malaria[2].

A large amount of scientific evidence is available on the potential of *A. indica* as a source for the development of human and animal health products. For example, neem seed oil and essential oils from leaves and bark have been shown to inhibit the growth of various genera of pathogenic bacteria, such as *Mycobacterium* and *Streptococcus*[3]. Antiviral activity of neem leaf extracts has been evidenced against dengue virus[4] and HIV[5]. Moreover, several important parasitic protozoa, including *Trypanosoma*[6], *Leishmania*[7] and *Plasmodium*[8], have been shown to be susceptible to neem extracts and purified limonoids. Antifilarial activity has been demonstrated with an alcoholic extract of neem flowers against *Setaria cervi*, a parasitic nematode of the water buffalo (*Bubalis bubalis*)[9]. Further, many arthropod ectoparasites are susceptible to both the insecticidal, growth regulatory and repellent activity of neem extracts[10]: for example, lice[11] and ticks[12] can be successfully controlled by neem extracts, and many species of mosquitoes, including important vectors of parasitic diseases, have been shown to be susceptible to neem products[13].

In this issue, K. Gunasekaran and colleagues[14] present evidence on the potential of the commercial product NeemAzal T/S 1.2 per cent EC for the control of *Anopheles stephensi*, *Culex quinquefasciatus* and *Aedes aegypti*, vectors of important infectious and parasitic diseases. Less than 1 ppm of the product, added to larval basins, was adequate to interfere with larval development, inhibiting the emergence of adults by 50 per cent. Thus, NeemAzal T/S 1.2 per cent EC can be considered a promising insecticide to complement currently used biological larvae control tools, such as *Bacillus thuringiensis* var. *israelensis* and *B. sphaericus* formulations, insect growth regulators and larvivourous fish[15]. As neem trees are very common in most countries with mosquito-borne diseases, neem based larvicides can be produced locally. In areas where commercial larvicides are not accessible or not affordable to the population, the local preparation of neem extracts or the use of unprocessed plant parts like crushed seeds or wood chippings may represent a valid alternative. Evidence supporting such a community-based approach has been recently published by scientists from a Kenyan research institution, showing that neem wood chippings added at 0.4 g/l to water basins containing *An. gambiae* s.s. larvae inhibited adult emergence by 50 per cent[16].

Currently, malaria control strategies in endemic areas focus on vector control targeted to the adult mosquito stage. In several African countries, the intensity of transmission and the disease burden have been successfully reduced by the wide use of insecticide treated bed nets (ITN) and indoor residual spraying (IRS)[17]. Targeting adults has the advantage that, under sufficient coverage conditions, an impact not only on mosquito densities but also on mosquito longevity is achieved, resulting in a reduction in the number of infective mosquitoes. The recent encouraging results have raised renewed confidence that malaria elimination or at least a major reduction of transmission is feasible, even in African settings. To reach this goal, however, integrated vector control needs to be adopted as a strategy, supplementing ITN and IRS with larval control measures tailored to the eco-epidemiological settings. Larviciding is suitable for urban and peri-urban areas, where permanent and semi-permanent breeding sites are identifiable, and has a potential also in settings characterized by a markedly seasonal vector activity, where it allows the transmission season to be shortened by treating breeding sites[15]. Biological larvicides, such as neem based products, have a valuable role to play in such integrated vector control endeavours.

The insecticides of choice for treating bednets and mosquito netting are synthetic pyrethroids such as permethrin, deltamethrin and alpha-cypermethrin. However, the emergence of pyrethroid-resistant vector species in many endemic areas and the threat of losing these effective insecticides for malaria control, urge for the development of alternatives. May *Azadirachta indica* be a potential resource for the development of new insecticides for the treatment of netting or housing? Neem based insecticides act on target organisms mainly after oral uptake. However, contact activity has been described in some species. For example, the topical application of neem oil or azadirachtin rich neem seed kernel extract on *Glossina* specimens, reduced fecundity and survival of the treated females[18] and exposure of *An. stephensi* and *An. culicifacies* females to volatile neem compounds was found to impair vitellogenesis[19]. On the basis of these evidences, studies aimed at elucidating absorption mechanisms of neem molecules trough the cuticle of adult mosquitoes and at identifying bioactive compounds acting on mosquito tissues should be encouraged and may help to pave the way to the development of neem based adulticides.

The use of neem to combat mosquito nuisance makes part of the traditional knowledge 'backpack' of many Asian and African populations. Studies are now available that confirm the repellent efficacy of neem oil when applied on exposed skin parts[20] and that support the use of neem oil in kerosene lamps to expel blood seeking mosquitoes from houses[21]. A recent entomological study conducted in experimental houses in an area of Tanzania shows that the traditional custom of burning *Azadirachta* leaves and other plant species (*e.g.*, *Ocimum* sps.) reduces human biting and indoor resting of mosquitoes[22]. Such validation studies on traditional vector and disease control measures should be encouraged to provide a rational basis for integrated disease control, 'integrated' not only in terms of combining different measures but also in terms of exploiting both, modern science and traditional medicine knowledge.

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