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Invited review

Green synthesized nanoparticles in the fight against mosquito-borne diseases and cancer—a brief review

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ABSTRACT

Nanobiomedicine and parasitology are facing a number of key challenges, which mostly deal with the paucity of effective preventive and curative tools against mosquito-borne diseases and cancer. In this scenario, the employ of botanical and invertebrate extracts as reducing, stabilizing and capping agents for the synthesis of nanoparticles is advantageous over chemical and physical methods, since it is one-pot, cheap, and does not require high pressure, energy, temperature, or the use of highly toxic chemicals. Considering the overlooked connection between mosquito vector activity and the spread of cancer in USA, this review focused on the current knowledge available about green synthesized nanoparticles with efficacy against mosquito-borne diseases and cancer. Green fabricated metal nanoparticles showed antiplasmodial activity that often encompasses the efficacy of currently marked drugs for malaria treatment. They have been also reported as growth inhibitors against dengue virus (serotype DEN-2), with moderate cytotoxicity on mammalian cells. However, this feature is strongly dependent to the botanical agents employed during nanosynthesis. In addition, green nanoparticles have been successfully used to reduce mosquito young instar populations in the field. The final section focuses on some issues for future research, with special reference to the chemical standardization of the botanical extracts used for nanosynthesis and the potential effects on green fabricated nanoparticles on non-target organisms.

1. Mosquito-borne diseases: prevention is the cure

Arthropods are extremely dangerous vectors of pathogens and parasites, which may hit as epidemics or pandemics in the increasing world population of humans and animals [68,21]. Among them, mosquitoes (Diptera: Culicidae) represent a huge threat for millions of people worldwide, vectoring important diseases, including malaria (Fig. 1a–b), dengue, Zika virus (Fig. 1b–c), yellow fever, Japanese encephalitis, St. Louis encephalitis, and filariasis (Fig. 1e–f) [52,93,25,59,16,20,85,96]. Furthermore, Culicidae transmit key pathogens and parasites that dogs and horses are very susceptible to, including dog heartworm, West Nile virus, and Eastern equine encephalitis [111,66]. Unfortunately, no treatment is available for most of the arboviruses vectored by mosquitoes, with special reference to dengue. In addition, even for other mosquito-borne diseases, such as malaria, there are significant challenges that still preclude their successful management [20].

1.1. News from the malaria front

Anopheles mosquitoes (Fig. 1a) vector *Plasmodium* parasites (Fig. 1b) to people and animals, biting them mainly between dusk and dawn [52,110]. According to the latest estimates, there were about 198 million cases of malaria in 2013 and an estimated 584,000 deaths. Most deaths occur among children living in Africa, where a child dies every minute from malaria [112]. Notably, 2015 was an extraordinary year for malaria control, due to three hot news: the Nobel Prize to Y. Tu for the discovery of artemisinin [107,29], the development of the first vaccine against *Plasmodium falciparum* malaria [i.e. RTS,S/AS01 (RTS,S)] [35], and the fall of malaria infection rates worldwide, with special reference to sub-Saharan Africa [20]. However, there are major challenges that still deserve attention, in order to boost malaria prevention and control. Indeed, parasite strains resistant to artemisinin have been detected [113], the RTS,S vaccine does not offer protection against *Plasmodium vivax* malaria [30,31], which predominates in many countries outside of Africa and a number of malaria prevention and control tools currently available are quite expensive, thus not readily available for poor and marginalized populations in tropical and sub-tropical areas worldwide [20].

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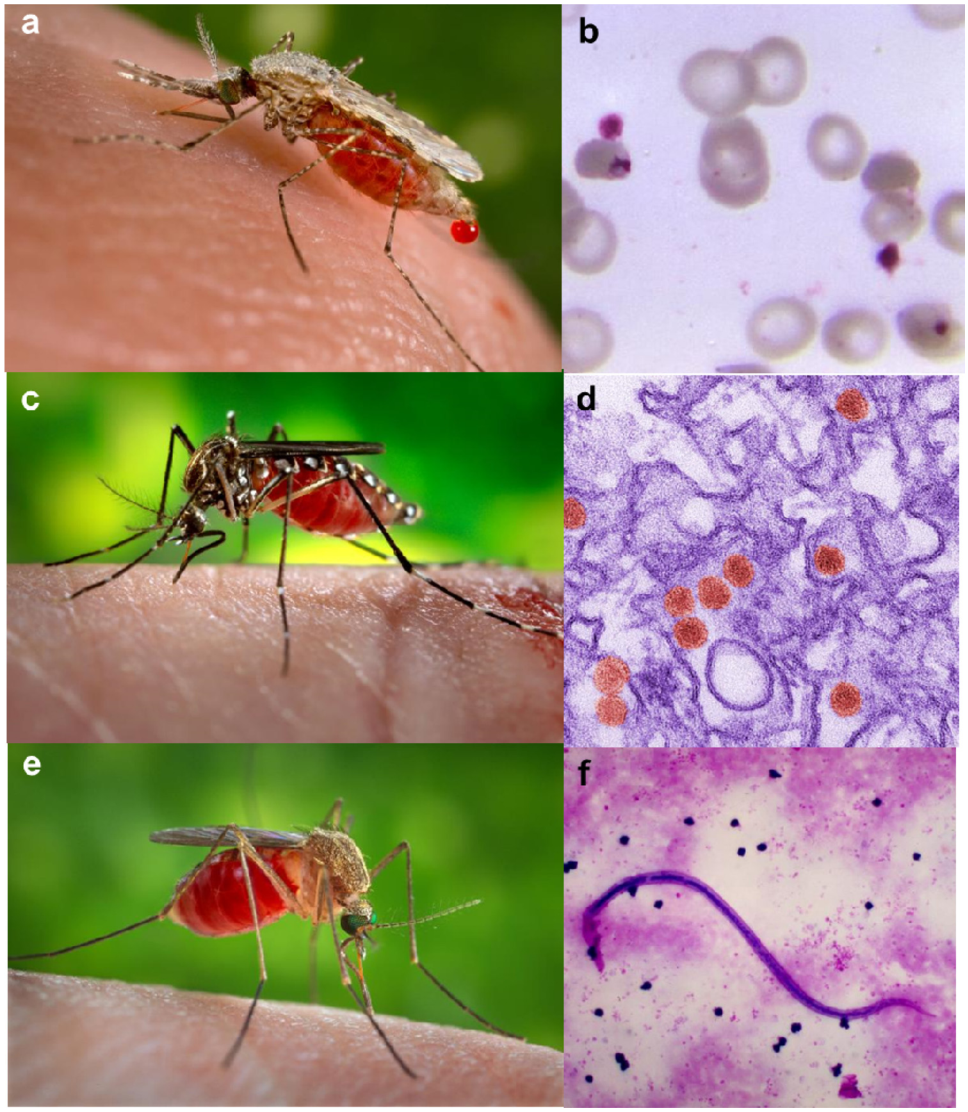

Fig. 1. Green-synthesized metal nanoparticles are effective at few μg/ml against important mosquito vectors, including *Anopheles stephensi* (a), as vector of *Plasmodium falciparum* parasites (b) causing malaria, *Aedes aegypti* (c), a vector of dengue and Zika virus (d), and *Culex quinquefasciatus* (e), a vector of many arbovirus (e.g. West Nile and St. Louis encephalitis virus) and filarial parasites, such as *Wuchereria bancrofti* (f) (photo credits: Centers for Disease Control and Prevention, USA).

1.2. Anopheles *and* Aedes *mosquitoes as vectors of cancer?*

Interestingly, a significant association of malaria incidence with all cancer mortality in 50 USA states was recently highlighted [60,61]. In detail, the evidence of an association of *Anopheles* bites with brain tumors was outlined in the relationship between malaria outbreaks in United States [99] and reports of brain tumor incidence [28]. Highly significant correlations between malaria and malignant brain tumors, as well as malaria and benign brain tumors, have been also observed [60,61] argued that this may be explained by the ability of *Plasmodium* to induce suppression of the immune system. However, it has been also hypothesized that *Anopheles* vectors may transmit obscure viruses linked with cancer development [60,61]. It should be also noted that [103] reported analogies at the cellular level for the two diseases, while [109] observed no relationship between malaria rates and primary liver cancer. Further research on this issue is needed since, if the mosquito-transmitted brain tumor viruses will be identified, the development of a brain tumor vaccine might be possible [60,22].

Furthermore, the hamster reticulum cell sarcoma can be transmitted through the mosquito vector *Aedes aegypti* (Fig. 1c) by the transfer of tumor cells [9,10]. Tumor cells remained viable up to eight hours after the ingestion by *Ae. aegypti* adults, and feeding on or off the tumor did not influence the rate of transmission [10]. On the other hand, there is no evidence of multiplication in *Ae. aegypti* of an agent from hamster reticulum cell sarcoma or of the Rauscher virus leukemia [54,10]. Moreover, mosquito bites may influence human metabolic pathways following different mechanisms, leading to other viral infections and/or oncogenesis [108]. Hypersensitivity to mosquito bites is guided by a unique pathogenic mechanism linking Epstein-Barr virus infection, allergy and oncogenesis [106,53,105,3]. During dengue virus infection, high viral titers, macrophage infiltration, and tumor necrosis factor alpha production in the local tissues are the three key important events that lead to hemorrhage [34], see also [39] and [116]. Recently, it has been highlighted [22] that basic epidemiological knowledge on the relationships occurring between mosquito vector activity and the spread of cancer is needed, as well as detailed information about the ability of Culicidae to transfer viruses or tumor cells among hosts over time.

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