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Beyond mosquitoes—Essential oil toxicity and repellency against bloodsucking insects

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ABSTRACT

The control of insect pests and vectors is a timely challenge for public health. The prevention of bites from bloodsucking insect species is based to a large extent on the use of chemical repellents and pesticides. However, their effectiveness is currently endangered, due to the fast-growing resistance levels in the targeted vectors, besides their negative impact on human health and the environment. Therefore, natural product research has been claimed as a helpful tool to develop effective green pesticides and repellents. Among them, essential oils (EOs) extracted from plants received peculiar attention for applications in "the real world", since they showed high efficacy, multiple mechanisms of action and low toxicity on non-target vertebrates. However, the large majority of research items published on the topic studied the potential of EOs in the fight against mosquitoes (668 research items) and ticks (155), while only a relatively limited amount (< 110) focused on bloodsucking insects different from mosquitoes. This knowledge is, however, of high importance for public health, since it offers new perspectives to control important arthropod vectors, including those directly linked with the spread of neglected tropical diseases (e.g., Triatominae bugs vectoring Chagas disease) or negatively affecting the productivity of livestock worldwide (e.g., biting midges, horse flies, horn flies and stable flies). Herein, the current knowledge available on the toxic and repellent potential of EOs and selected constituents against bloodsucker insects was reviewed. Major emphasis has been devoted to the control of Diptera, covering biting midges (*Culicoides*, Ceratopogonidae), black flies (Simulidae), horse and deer flies (Tabanidae), horn fly (*Haematobia irritans*, Muscidae), stable fly (*Stomoxys calcitrans*, Muscidae), sandflies (Psychodidae) and tsetse flies (Glossinidae), discussing both laboratory and field evidences. Furthermore, successful attempts aimed at the control of fleas (Siphonaptera), head, body and pubic lice (Phthiraptera) as well as bed bugs (Hemiptera, Cimicidae) and kissing bugs (Hemiptera, Reduviidae, Triatominae) have been examined. In the final section, outlooks and challenges for future research have been outlined, comparing them with what has been done in mosquito and tick control science.

1. Introduction

Bloodsucking arthropods act as vectors of an extremely wide number of pathogens and parasites (Benelli and Duggan, 2018). Mosquito-borne diseases play a key role, since 3.3 billion people still live in areas where malaria is a constant threat (WHO, 2013, see also Benelli and Beier, 2017) and 3900 million people are at risk of dengue virus infection (Brady et al., 2012; Bhatt et al., 2013; Messina et al., 2014), along with new arbovirus outbreaks, among which chikungunya and Zika virus recently received major emphasis (Benelli and Mehlhorn, 2016). Ticks transmit more pathogen species than any other group of blood-feeding arthropods worldwide, including anaplasmosis, babesiosis, borreliosis, and ehrlichiosis (Loscher and Burchard, 2010; Dantas-Torres et al., 2012; Deplazes et al., 2013; Pfäffle et al., 2013; Guglielmone et al., 2014).

Moreover, the diversity of diseases vectored by bloodsucking arthropods is astonishing. Kissing bugs (Heteroptera, Reduvidae, Triatominae) vector the Chagas disease in areas from the southern United States to northern Argentina (Klotz et al., 2014; Dujardin et al., 2015), tsetse flies (Diptera, Glossinidae) are responsible of transmitting the African sleeping sickness caused by *Trypanosoma* parasites (Keating et al., 2015; Sutherland et al., 2015; Meyer et al., 2016), and the biting midges (Diptera, Ceratopogonidae, *Culicoides*) feeding activity has been linked with several bluetongue outbreaks in the Mediterranean regions

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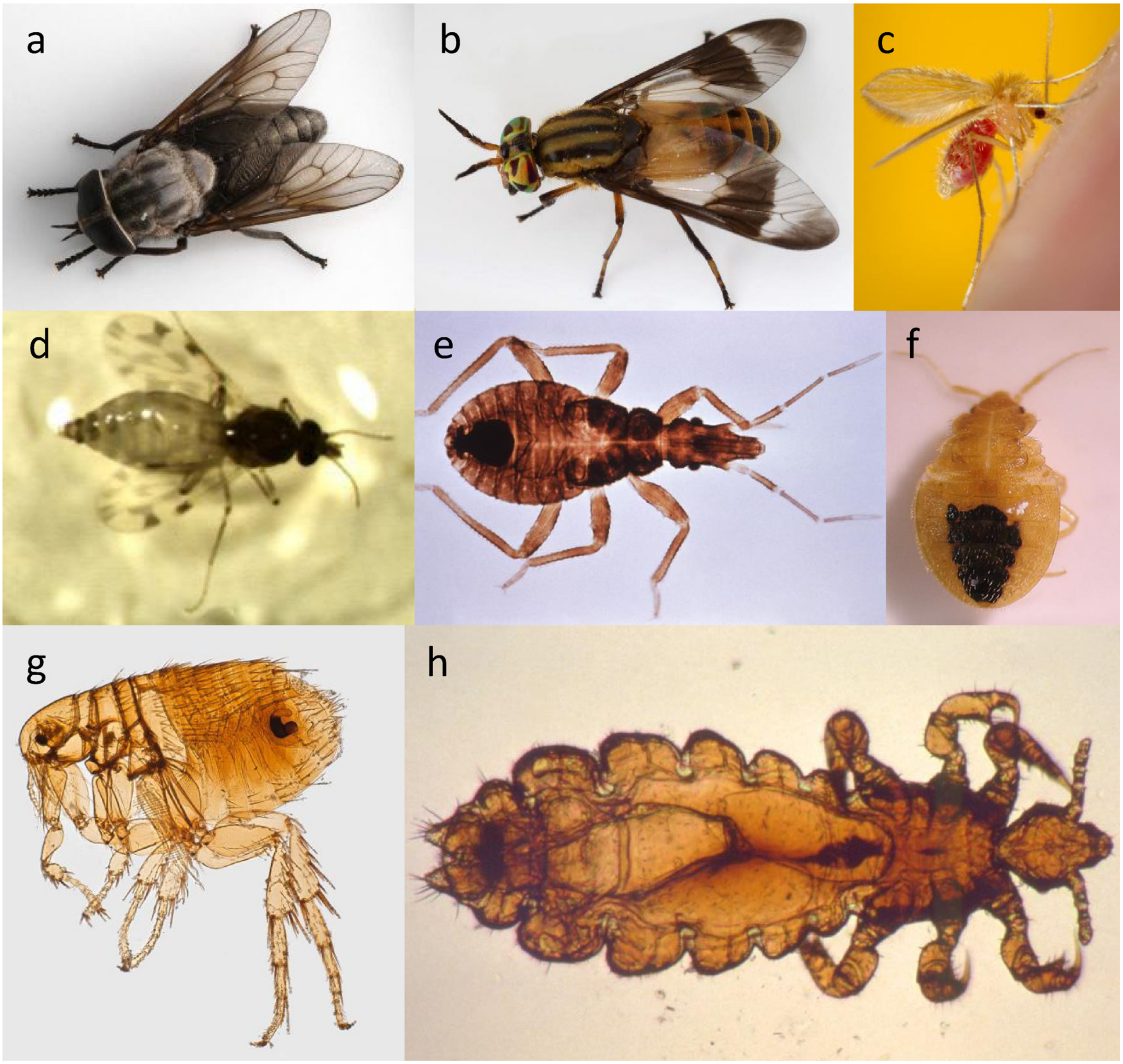

Fig. 1. Natural product research mostly focused on the toxicity and repellent potential of essential oils on mosquitoes and ticks; this review covers current knowledge about essential oil toxicity and repellence on other bloodsucking insects, including **(a)** horse flies and **(b)** deer flies (Diptera, Tabanidae), **(c)** drain flies (Diptera, Psychodidae), **(d)** *Culicoides* biting midges (Diptera, Ceratopogonidae), **(e)** kissing bugs (Hemiptera, Reduviidae, Trianomiinae), **(f)** bed bugs (Hemiptera, Cimicidae, *Cimex lectularius*), **(g)** fleas (Siphonaptera) and **(h)** head lice (Phthiraptera).

(Benelli et al., 2017a), just to cite few examples (Fig. 1).

Notably, most arthropod-borne diseases are difficult to treat. For instance, antimalarial drugs – as many other drugs currently employed in the fight against parasites – are experiencing a serious lack of effectiveness due to the fast-growing resistance development in *Plasmodium* parasites (Ashley et al., 2014; Benelli et al., 2017b), while the recently developed *Plasmodium falciparum* vaccine (RTS,S/AS01, also known as Mosquirix) showed only transient protection, with special reference to infants (Gosling and von Seidlein, 2016). Most importantly, no drugs or vaccines are currently available against arboviruses, such as dengue, chikungunya and Zika virus (Benelli, 2015a), even if very a dengue vaccine is under development (Capeding et al., 2014; Villar et al., 2015) and some green synthesized nanoparticles recently showed promising antiviral activity against dengue virus serotype 2, acting as envelope protein inhibitors (Sujitha et al., 2015; Murugan et al., 2016). In other cases – as for Chagas disease – the treatments available (benznidazole and nifurtimox) are highly effective (Bern et al., 2007), however a prompt diagnosis is essential, since the efficacy of these drugs diminishes the longer a person has been infected (Pérez-Molina et al., 2009).

To face this challenging scenario, the control of vector populations is of timely importance nowadays. Integrated Vector Management supports the development of effective, locally adapted and sustainable vector control strategies, which do not rely to a single control tool to reduce vector populations (Nájera et al., 2011; Benelli and Beier, 2017; WHO, 2017a,b). The prevention of bites from bloodsucking arthropods is based to a large extent on the use of chemical repellents and pesticides (Xue et al., 2014). However, they have a negative impact on human health and the environment (Hicks et al., 2017; Silver et al., 2017). In addition, their effectiveness is currently endangered, due to the fast-growing resistance levels in the targeted vectors (Hemingway and Ranson, 2000; Ranson et al., 2011; Naqqash et al., 2016).

Therefore, the so-called "green chemistry", based on the employ of natural products and eco-friendly processes, has been claimed as a research field helpful in developing novel and effective green pesticides and repellents (Isman, 2008; Martínez-de la Puente et al. 2009; Semmler et al., 2009; Khater et al., 2011,2013; Khater, 2014; Benelli et al., 2016; Pavela and Benelli, 2016a). Microbial and plant products,