INSECT REPELLENTS – PAST, PRESENT AND FUTURE[1]

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Introduction

Insect repellents are an alternative to the use of insecticides. They may be applied to the skin to protect an individual from the bites of mosquitoes, mites, ticks and lice or, less commonly, may be used to exclude insects from an area, such as in packaging to prevent infestation of stored products. In our opinion, these latter uses are under-exploited at the current time. With increasing problems of insecticide resistance and increasing public concerns regarding pesticide safety, new, safer active ingredients are becoming necessary to replace existing compounds on the market. Furthermore, the use of repellents in an integrated pest management program has been ignored to a large extent. This article comprises a review of insect repellents, followed by some new research conducted in our laboratory on plant-derived insect repellents. Much of the current work is condensed from Peterson (2001).

History of insect repellents

The use of insect repellent compounds dates back to antiquity, when various plant oils, smokes, tars, etc. were used to displace or kill insects. Before the Second World War, there were only four principal repellents: oil of citronella, sometimes used as a hair dressing for head lice, dimethyl phthalate, discovered in 1929, Indalone®, which was patented in 1937 and Rutgers 612, which became available in 1939. At the outbreak of World War II, the latter three components were combined into a formulation for use by the military known as 6-2-2; six parts dimethyl phthalate, two parts Indalone and two parts Rutgers 612. Other military repellent formulae for use on clothing were developed during the war, but they all failed to provide desired protection of military personnel deployed around the world. As a result, by 1956 the United States government had screened over 20,000 potential mosquito repellent compounds. In 1953, the insect repellent properties of *N*,*N*-diethyl-*m*-toluamide (DEET, Figure 1) were discovered and the first DEET product was introduced in 1956. DEET is still the most widely used mosquito repellent. It has generally been regarded as safe, but toxic effects have been recorded, including encephalopathy in children, urticaria syndrome, anaphylaxis, hypotension and decreased heart rate.

Several other compounds have been evaluated for repellent activity, but none have had the commercial success of DEET. For example, *N*,*N*-diethylphenyl acetamide (DEPA) is licensed for use as a cockroach repellent in India (Prakash *et al*., 1990) and Colgate-Palmolive has released in Europe a cockroach repellent floor cleaner, Ajax Expel®, the active ingredient of which is *N*-methyl neodecanamide. This product has been shown to cause cockroaches to leave their harborages and cockroaches are less likely to re-infest previously occupied areas after treatment with the cleaner (Brenner *et al*., 1998). Bayer AG plans to market a mosquito repellent with the name BayRepel®, the active ingredient of which is 1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester (KBR 3023) (Yap *et al*., 2000). Active ingredients for some insect repellents are shown in Figure 1.

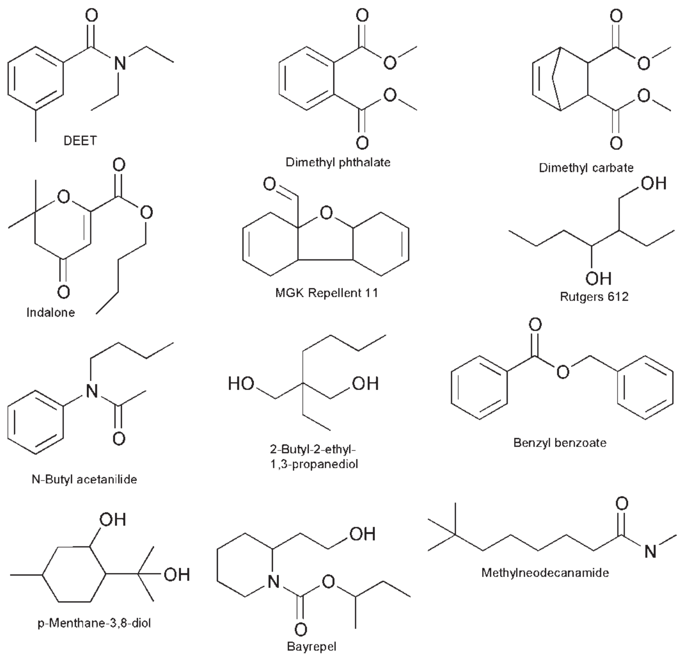

Figure 1. **Structures of several insect repellents.**

Insect repellents of natural origin

Natural ingredients are included in some formulations of insect repellents. Of 65 formulations of non-US-produced insect repellents, 33 contained DEET and the remainder contained natural oils (Schreck and Leonhardt, 1991). Of 901 substances (872 synthetics and 29 botanical oils) tested

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for repellency to four species of domiciliary cockroaches by the US Department of Agriculture (USDA) between 1953 and 1974, 127 repelled 94% or more of the German cockroaches, 61 repelled 100% and 13 repelled 100% of all four species tested. None of those 13 was a botanical extract, but many were analogs of natural products. 1,4-Naphthoquinone has many substituted forms that occur in nature (such as vitamin K). Klun *et al.* (2000) found that *Anopheles* mosquitoes were differentially repelled by isomers of some piperidines.

In the United States, citronella is a popular botanical ingredient in insect repellent formulations. Candles and incense containing oil of citronella are sold as insect repellents. The insecticidal properties of this oil were discovered in 1901, and it was used for a time as a hair dressing for the control of fleas and lice. Few studies have been undertaken to evaluate the efficacy of such products. Despite popular conception, Lindsay *et al.* (1996) reported that citronella candles or incense were ineffective for reducing the biting pressure of mosquitoes. It was found that burning an unscented candle had the same effects on reducing the biting rate of mosquitoes in the field as a citronella candle.

Three commercial products were recently evaluated for repellency in a laboratory olfactometer against *Aedes aegypti*. Buzz Away® (containing citronella, cedarwood, eucalyptus and lemongrass oils), Green Ban® (containing citronella, cajuput, lavender, safrole-free sassafras, peppermint and bergaptene-free bergamot oils) and Skin-So-Soft (containing various “oils and stearates”) failed to cause any repellency in the olfactometer, though DEET formulations were effective (Chou *et al.*, 1997).

Neem oil, from *Azadirachta indica*, when formulated as 2% in coconut oil, provided complete protection (*i.e.* no confirmed bites) for 12 hours from *Anopheles* mosquitoes (Sharma *et al.*, 1993). A neem extract proprietary product, AG1000, has been shown to be repellent to the biting midge *Culicoides imicola*, which can spread cattle diseases (Braverman *et al.*, 1999).

Quwenling, a popular *Eucalyptus*-based repellent product, contains a mixture of *p*-menthane-3,8-diol (PMD), isopulegone and citronellol. Quwenling has largely replaced dimethyl phthalate as the insect repellent of choice in China (Trigg, 1996). *Eucalyptus* oil itself, the principal ingredient of which is PMD, provided protection comparable to DEET in repelling *Anopheles* mosquitoes in field studies (Trigg, 1996). Although repellent to *Culicoides impunctatus*, *Eucalyptus* oil was attractive to *C. imicola* (Braverman *et al.*, 1999).

A common practice is to place red cedar blocks or sachets in closets to repel clothing moths. This is probably why many hope chests are made of red cedar for protection of heirloom clothing. Milled red cedar flake boards were found to be repellent to the German cockroach, but not to American or brown-banded cockroaches (Appel and Mack, 1989).

Insect repellent mode of action

In many cases, it has been found that behavior that can be labelled as repellency may be the result of any number of physiological or biochemical events. Mosquito repellency caused by DEET is thought to be due to the blocking of lactic acid receptors, abolishing upwind flight, resulting in the insect “losing” the host (Davis and Sokolove, 1976). Oleic and linoleic acids have been indicated in death recognition and death aversion (repellency) in cockroaches, and the term “necromone” has been proposed to describe a compound responsible for this type of behavior (Rollo et al., 1995).

Lactic acid is present in warm-blooded animal body odor and sweat, and is attractive to female mosquitoes. In behavioral studies lactic acid is essential to attraction of *Aedes aegypti*, but lactic acid by itself is only mildly attractive, indicating synergism with other unidentified human odor components (Geier *et al.,* 1996). Further evidence for the role of lactic acid in host seeking comes from studies examining mosquito physiology following a blood meal. Host-seeking behavior in *Aedes aegypti* stops after taking a blood meal. It has been found that following a blood meal, the sensitivity of lactic acid sensitive neurons drops, and this drop is co-incident with the cessation of host-seeking behavior. Lactic acid sensitivity returns to normal after oviposition (Davis, 1984). This serves to support the hypothesis that host seeking behavior may be modified by affecting the lactic acid receptor mechanisms of a mosquito.

It is unclear if repellents work by common mechanisms in different arthropods, and conflicting evidence exists in the literature. On the one hand, DEET is effective against many other Diptera of medical importance, as well as hematophagous Hemiptera, Siphonaptera, Hymenoptera, Acarina and Gnathobdellidae (an annelid family), suggesting that DEET operates on a fundamental physiological basis common to members of the arthropod-annelid evolutionary line (Rutledge *et al.*, 1978, and references therein). Ticks detect repellents on the tarsi of the first pair of legs (Haller’s organ) and insects detect the same substances on the antennae. These structures are thought to be serially homologous between the two classes. Furthermore, the differences in sensitivity to repellents between different classes, orders and families are differences of degree only; no fundamental differences in the type of response are observed (Rutledge *et al.*, 1997). On the other hand, virtually no sequence homology was found between genes coding for the olfactory receptors of *Drosophila* and *Caenorhabiditis elegans* (Vosshall *et al.*, 1999). Furthermore, there is not yet any comparison of olfactory gene sequence among the various arthropods, and there is no record of the response of *C. elegans* to DEET or other arthropod repellents.

Different insects differ in their sensitivity to insect repellents. Differences are loosely related to the taxonomic distance between the groups compared. Among mosquitoes, observed ED_{50} values for DEET differed by as much as 1.75 times between different strains of *Aedes aegypti*, as much as 3.45 times among species of the same genus (observed in *Anopheles*) and as much as 7 times between different genera. The most sensitive species of *Culex*, *Cx. pipiens*, is 6.9 times more sensitive than the most tolerant species of *Anopheles*, *An. albimanus*; *An. quadrimaculatus*, however, is not significantly more tolerant than *Cx. tarsalis*. Differences in sensitivity were stable over several generations, indicating a genetic, heritable basis of tolerance (Rutledge *et al.*, 1978). DEET tolerance was found to be incompletely dominant (Rutledge *et al.*, 1994).

Structure-activity relationships of repellents are unclear, and little definitive work has been done. Visual examination of Figure 1 shows that when an insect repellent incorporates a ring structure, there is often a carbonyl group immediately removed from the ring. Davis (1985) mentions other sources that report that an oxygen functional group is necessary for activity. In one study, patterns of sensitivity were similar among some chemicals of unrelated structure, but some differences existed between the sensitivity to compounds of similar structure. Observed non-correlation of structure with activity suggests that repellent tolerances may be non-adaptive; *i.e.* evolved by random drift of selectively neutral mutations (Rutledge *et al.*, 1997). Although effective topical mosquito repellents fall in a range of molecular weights of 150–250 (Taylor *et al.*, 1996), vapor pressure is the only parameter significantly related to mosquito repellent activity (Davis, 1985). Partition coefficient, molecular weight, infrared absorption, viscosity, surface tension, molecular polarizability, and Hammett substituent constants have all failed to be correlated to repellent activity (Davis, 1985).

Current research in insect repellents

Over the past several years, our laboratory has conducted research investigating insect repellents of natural origin. Insect repellents for protection of humans from biting arthropods, principally mosquitoes, make up the lion's share of insect repellents sold in the United States. As mentioned earlier, we believe that many applications of insect repellent technology are under-utilized at this time. The use of repellent barrier strips to prevent entry of insects into sensitive areas is a largely untried approach. Pyrethroid insecticides are sometimes used in this manner, but the acute toxicity of these compounds to the insects is the principal mode of action of these compounds. Also, impregnation of repellents into packaging to prevent insect infestation of stored or shipped products is also not commonly used. Our work addresses some of the methods and materials that may be employed in screening potential new active repellents in novel applications.

Our work has focussed on insect repellents derived from two plant species, the Osage orange (hedgeapple) (*Maclura pomifera*) and catnip (*Nepeta cataria)*.

Osage orange

The fruit of the osage orange has been utilized as an insect repellent for many years. Pioneers in the American West placed the ripe fruit of this tree in cupboards to repel cockroaches and other insects (Sand, 1991). The scientific validity of this well-popularized practice has been little studied. Karr and Coats (1991) found that fragments of Osage orange fruit, as well as its hexane and methanol extracts, were significantly repellent to the German cockroach *Blattella germanica*. Later research in our laboratory demonstrated that the dichloromethane extracts of Osage orange fruit were also repellent to the maize weevil *Sitophilus zeamais*. We examined the extracts and found that they contained two isoflavones, osajin and pomiferin (Figure 2) (Peterson *et al.*, 2000).

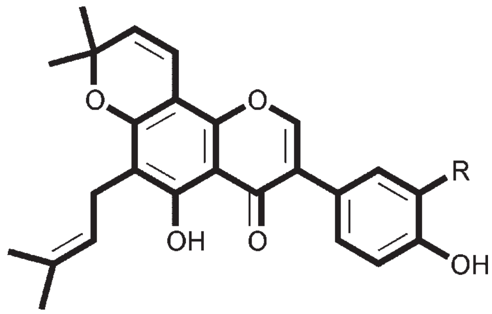


Figure 2. **Chemical structures of osajin (R = H) and pomiferin (R = OH).**

The previous study made no attempt to determine volatile components of the Osage orange extracts. Volatility is viewed by many as being essential to repellent activity, although a compound irritating to the feet of an insect will cause that insect to spend less time in a treated area. Our next study employed gas chromatography and mass spectroscopy (GC-MS) to identify volatile components of Osage orange essential oil and test the oil and its constituents in repellency trials. Numerous sesquiterpenoids were determined to be present in the oil, and many of them were repellent to the German cockroach (Figure 3) (Peterson *et al.,* accepted). To our knowledge, this was the first examination of volatile components of Osage orange oil. Because all of the compounds identified are well-known and some are available from other sources, and because there is only a small quantity of essential oil in an Osage orange, it may be more economical to extract active compounds from other sources. Whether these compounds are synergistically enhanced in mixture or if the compounds would be effective singly is currently under investigation.

Catnip

Catnip has been noted for many years for its intoxicating effect on cats. Nepetalactone has been isolated as the active component of catnip, with two isomers being present in the plant's essential oil: *Z,E* (*cis, trans*) and *E,Z* (*trans, cis*), with *Z,E*-nepetalactone predominating (Figure 4). Modern nomenclature denotes the *cis, trans* isomer as *Z,E* and the trans-cis isomer as *E,Z*. Catnip has folk uses as an insect repellent, some of which have been confirmed scientifically. Hot water extracts of catnip deterred flea beetles in one study, and fresh catnip repelled black ants (Riotte, 1975), and it was found to be repellent to members of 13 families of insects (Eisner, 1964).

Nepetalactone is also an important component of the defensive secretions of the coconut stick insect (Smith *et al.*, 1979) and the lubber grasshopper (Snook *et al.*, 1993). We isolated and purified the individual isomers of nepatalactone and compared their activities to DEET. It was found that the *E,Z*- isomer was more active than the *Z,E*- isomer and DEET at both concentrations tested (Figure 5) (Peterson *et*

Osage orange (hedgeapple) (left) and catnip (right), two plant species from which insect repellents have been extracted.

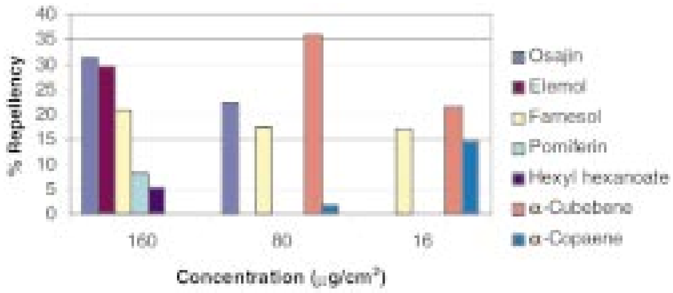
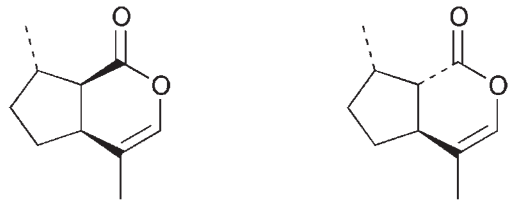


Figure 3. **Repellency of Osage orange constitutents to the German cockroach.**



Z,*E*- nepetalactone

E,*Z*- nepetalactone

Figure 4. **Structures of nepetalactone isomers from catnip.**

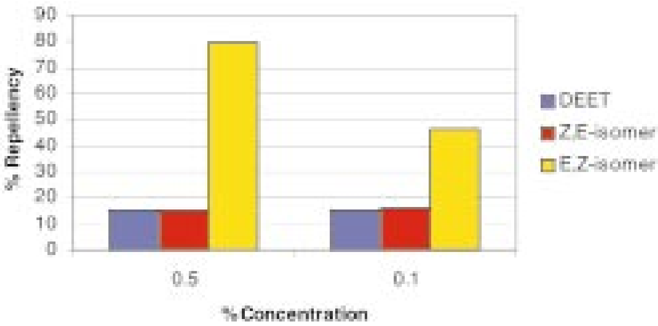


Figure 5. **Repellency of *Z,E*- and *E,Z*-nepetalactone isomers compared to DEET.**

al., submitted). The structures of the nepetalactone isomers (Figure 4) differ only in the orientation of a single chemical bond. Why this difference results in higher repellency is unknown. Obviously the *E,Z*- isomer has greater action than the *Z,E*- isomer at some receptor. Very little is known, however, about the receptors responsible for the repellent response in cockroaches; it is not known if receptors specific for repellents even exist. In all likelihood, the receptors involved are specific for other compounds, and the action of repellents at these receptors is secondary (such as the proposed mode of action of DEET mentioned in this article).

Future outlook

Much more work needs to be done before it can confidently be stated if insect repellents work in integrated pest management systems. The safety of many of these compounds still needs to be evaluated and field efficacy trials are also required. It is hoped that repellent compounds may be applied at levels lower than those compounds that are acutely toxic, thereby lowering the pesticide load on the urban environment, but this hope is purely conjectural at this point.

The use of repellents by travellers (civilian and military) may reduce the occurrence of local disease incidences in temperate areas. In countries such as Kenya, where tourism is a major source of national income, the use of repellents can increase the pleasure and comfort of tourists. In military operations, they may reduce the incidence of illness and reduce annoyance to personnel, who can then complete their operations more efficiently. Repellents can therefore be viewed as a tool with a specific role in protecting people from insect-borne illnesses. More traditional pest management operations (larval control treatments for mosquitoes, poisoned baits for cockroaches *etc*.) need to be used in conjunction with repellent technology. Repellents may have an increasingly important role in eliminating insects from certain environments (such as schools, hospitals and food preparation areas), and we believe that natural products, such as essential oils, could play a major role in new repellent technology.

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