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(54) **Title**: COMPOSITION WITH PEST RESISTANT PROPERTIES

(57) **Abstract**: A composition for topical administration containing particles and a pharmaceutically acceptable carrier. The particles may be composed of a metal oxide such as titanium oxide or zinc oxide, and may be coated with an external coating. The composition may also contain one or more organic components that are either bound or unbound to the particles. The composition may be used to prevent mosquitoes from extracting blood from a host and/or from infecting a host with a mosquito-borne disease or infection, or to protect a host from blood extraction and/or infection by a mosquito.

TITLE OF THE INVENTION

Composition with Pest Resistant Properties

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. non-provisional application Serial No. 15/179,379, filed on June 10, 2016; U.S. provisional application Serial No. 62/256,534, filed on November 17, 2015; and U.S. provisional application Serial No. 62/256,553, filed on November 17, 2015. The contents of the non-provisional application and both provisional applications are incorporated by reference herein, in their entireties and for all purposes.

FIELD OF INVENTION

This invention relates generally to the field of mosquito-borne disease control but may be applicable to other pest-related vector control. In the case of mosquito vector control, the invention relates to a topical composition which prevents the mosquito from both feeding and—as a consequence—infecting humans and possibly other mammals with mosquito-borne diseases.

BACKGROUND OF THE INVENTION

Mosquitoes at their most benign are annoying and bothersome to humans and animals. The bite of the female mosquito as it seeks blood usually causes an adverse reaction that results in itching, swelling, or sores. Of greater concern, mosquitoes are considered one of the most dangerous creatures on the planet because of their ability to spread deadly diseases. The U.S. Centers for Disease Control report that these insects kill more than one million people a year just through the transmission of malaria. Add to that the number of those sickened and killed by other mosquito-borne diseases such as dengue fever, yellow fever, and West Nile virus, and it is easy to see how they earned their dangerous reputation. In recent years the rate of infection has risen dramatically, and a growing number of scientists are now concerned that global warming will translate into an explosive growth of mosquito-borne diseases worldwide.

Mosquitoes inhabit our globe in two distinct environments. The immature stages of the mosquito (larva and pupa) live, feed, and metamorphose in aqueous settings until emerging in the winged adult stage, when the mosquito is capable of flight. After hatching from the egg there are four identifiable larval stages, in which the mosquito is designated as being a first, second, third, and fourth instar larva. The larvae actively feed and shed their exoskeletons with each transition between instars, each instar lasts approximately 1 to 2 days. The larvae then enter the pupae stage, a non-feeding stage during which the pupae undergo an energy-demanding metamorphosis into the adult mosquito.

Female mosquitoes are the only mosquitoes to feed on blood, although they do not need blood to survive. They do, however, need blood, or actually the protein in blood, for their eggs to develop. They must take a blood meal as part of their reproductive cycle. If they do not, the eggs that they lay will not be viable.

When preparing to bite its prey, a mosquito uses heat sensors on its antennae and around its mouthparts to locate capillaries near the prey's skin surface. The mosquito has a proboscis, which is a long, pointed mouthpart that is inserted to tap the capillary. There are two tubes in the proboscis. The mosquito uses one tube to inject saliva, while the other draws in blood. The saliva contains enzymes that serve two purposes: (1) to act as a mild painkiller, so the prey does not notice, and (2) to thin the blood so that it does not clot and continues to flow. It is through the saliva that the mosquito infects humans with disease. When the saliva enters the capillary, it brings with it the disease vectors with which it is infected. In addition, the mosquito may become infected with a disease from the prey via the blood it ingests.

Known methodologies for addressing this mosquito problem include physical abatement, entrapment systems using attractants, mosquitocidal bacteria, larvicides, adulticides, placement of larval predators in water bodies, adhesive traps, citronella candles, mosquito magnets, etc. Many of the methodologies are only successful against a small number of mosquitoes, while others require the introduction into the general environment of potentially harmful or toxic chemicals, such as petroleum-based oils or phenols.

One of the most effective chemical repellents is *N,N*-Diethyl-*meta*-toluamide—commonly referred to as DEET. It is hypothesized that DEET repels mosquitos by interfering with the mosquitos' odor receptors. However, DEET, like other chemical repellants, are volatile and are easily absorbed through skin , where it eventually enters the blood stream and the liver. Thus, there is an ongoing debate about the safety in using DEET, especially for children. Additionally, DEET is costly to manufacture and is not environmentally-friendly.

Thus, there is a need for a more effective and safe solution to combat the growing presence of mosquitoes and the diseases they carry.

SUMMARY OF THE INVENTION

An aspect of the invention relates to a composition comprising particles that interrupt feeding of the mosquito, and a pharmaceutically acceptable carrier.

The particles may comprise one or more metal oxides, for example, titanium dioxide, zinc oxide, or a combination thereof. In some embodiments, the particles are titanium dioxide, either rutile or anatase.

The particles may also comprise an external coating. The external coating may comprise, for example, a hydrophilic polymer, propylene, propylene glycol phospholipid derivative such as lecithin, or a combination thereof.

The composition may comprise one or more organic components. In certain embodiments, the organic components may have an effect on mosquitoes, such as to deter, repel, and/or irritate the mosquitos. Examples of such organic components may include, but are not limited to, pure forms or derivatives of lemongrass, citronella, picaridin (ir3535), chrysanthemum, cedar, soybean, and a combination thereof.

The one or more organic components may be bound or unbound to the particles. In some embodiments, more than one organic component may be bound to a single particle.

In certain embodiments, one or more organic components may be bound to a particle by being infused in an external coating on the particle.

The composition of the invention may be for use in a method of preventing mosquitoes from extracting blood from a host and/or from infecting a host with a mosquito-borne disease or infection, or a method of protecting a host from blood extraction and/or infection by a mosquito.

Another aspect of the invention is a method of preventing mosquitoes from extracting blood from a host and/or from infecting a host with a mosquito-borne disease or infection, or a method of protecting a host from blood extraction and/or infection by a mosquito. The method may comprise applying a composition of the invention to the dermis.

Yet another aspect of the invention is a method of preparing a composition of the invention. The method may comprise admixing the components of the composition.

A further aspect of the invention is a use of the composition of the invention in the preparation of a medicament for preventing mosquitoes from extracting blood from a host and/or from infecting a host with a mosquito-borne disease or infection, or for protecting a host from blood extraction and/or infection by a mosquito. This protection and/or prevention may be achieved by applying the medicament to the dermis of the host.

BRIEF DESCRIPTION OF THE DRAWINGS

For a better understanding of the present invention, reference is made to the following description of an exemplary embodiment thereof, and to the accompanying drawings, wherein:

Figure 1 shows scanning electron microscopy images (30000x) of uncoated 10% dimethicone titanium dioxide particles in a pharmaceutically acceptable carrier and 10% titanium dioxide particles coated with lecithin.

Figure 2 shows scanning electron microscopy images (3000x) of uncoated 10% dimethicone titanium dioxide particles in a pharmaceutically acceptable carrier and 10% titanium dioxide particles coated with lecithin.

Figure 3 shows an assembly of Petri dishes for a study described in Example 1.

Figure 4 shows the Petri dishes from Figure 3 through a thermal imaging apparatus.

Figure 5 shows a visual comparison of the mosquito feeding activity for Petri dishes (i) serving as a control, (ii) covered with a pharmaceutically-acceptable carrier, (iii) covered with a composition containing 10% titanium dioxide coated with lecithin; and (iv) covered with a composition containing 15% titanium dioxide coated with lecithin.

Figure 6 shows a scanning electron microscopy image (250x) of the sheathed proboscis of a mosquito exposed to titanium dioxide particles according to embodiments of the invention.

Figure 7 shows a scanning electron microscopy image (700x) of the front of the proboscis of a mosquito exposed to titanium dioxide particles according to embodiments of the invention.

Figure 8 shows a scanning electron microscopy image (5480x) of an area of mouth/proboscis of a mosquito exposed to titanium dioxide particles according to embodiments of the invention.

Figure 9 shows a scanning electron microscopy image (3030x) of an area near the entry of the proboscis of a mosquito exposed to titanium dioxide particles according to embodiments of the invention.

Figure 10 shows a scanning electron microscopy image (8480x) of an area of mouth/proboscis of a mosquito exposed to titanium dioxide particles according to embodiments of the invention.

Figure 11 shows a scanning electron microscopy image (2073x) of an area of the mouth/proboscis of a mosquito exposed to titanium dioxide particles according to embodiments of the invention.

Figure 12 shows a magnified image of Figure 11 (4400x).

Figure 13 shows a scanning electron microscopy image (7410x) of an area of mouth/proboscis of a mosquito exposed to titanium dioxide particles according to embodiments of the invention.

Figure 14 shows a scanning electron microscopy image (9310x) of an area of mouth/proboscis of a mosquito exposed to titanium dioxide particles according to embodiments of the invention.

Figure 15 shows a magnified image of Figure 16 (26330x).

Figure 16 shows mean feeding rates of the controls, pharmaceutically-acceptable carriers, compositions containing 10% titanium dioxide particles, and compositions containing 15% titanium dioxide particles presented in the studies listed in Example 1. .

Figure 17 shows mean decrease in feeding rate (i.e., percent change in mosquitos engorged compared to control) pharmaceutically-acceptable carriers, compositions containing 10% titanium dioxide particles, and compositions containing 15% titanium dioxide particles presented in the studies listed in Example 1.

Figure 18 shows feeding rate of a control and a composition containing 10% rutile titanium dioxide particles coated with lecithin, 1% lemongrass, and a base cream as a pharmaceutically-acceptable carrier that underwent heating for four hours.

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DETAILED DESCRIPTION

The present invention relates to a composition comprising particles, or the use thereof, for preventing mosquitoes from extracting blood from a host and/or from infecting a host with a mosquito-borne disease or infection, or for protecting a host from blood extraction and/or infection by a mosquito.

An average mosquito has a hollow proboscis which it employs to extract blood and inject saliva into its host. If a mosquito lands on an area of the dermis on which the composition of the invention has been applied, the mosquito and its proboscis will come into contact with the particles in the composition. Without being bound by theory, the composition may have desired effects which hinder the mosquito's efforts to feed. For instance, (i) the particles may present a physical barrier through which the proboscis must penetrate; (ii) the particles may be considerably smaller than the inside diameter of the proboscis but may cling together, resulting in an obstruction or irritant; (iii) the particles may cause irritation to the mosquito; or (iv) the composition may reduce the thermal signature of the host—on which mosquitos rely to search for capillaries—and thus assist in shielding capillaries and blinding the mosquito to its desired feeding target. Alternatively, in embodiments in which the composition comprises one or more organic components, the composition causes an airborne irritant/obfuscation effect where the organic components are irritating and or block sensor receptors that the mosquitoes employ for feeding.

Composition

The composition of the invention comprises particles and a pharmaceutically acceptable carrier. The particles may comprise one or more metal oxides, such as titantium dioxide, zinc oxide, or a combination thereof.

In some embodiments, the particles are titanium dioxide, which is the naturally occurring oxide of titanium, having a chemical formula of TiO_2. It is a low cost, naturally occurring mineral. The two most common forms of titanium dioxide are rutile and anatase, and the particle in the composition of the invention may be of either form.

The particles may be micro-scale, nano-scale, or a combination of these sizes. In certain embodiments, the particles are between about 1 and about 100nm.

The particles may be present in the composition in an amount of about 1 to about 25% by volume, or about 5 to about 15% by volume, in relation to the pharmaceutically acceptable carrier.

The particles may comprise an external coating. The external coating may comprise, for example, a hydrophilic polymer, propylene, propylene glycol phospholipid derivative such as lecithin, or a combination thereof. The ratio of the external coating to the particles may be about 0.1 to about 10% of the total weight of the particles, or about 0.5 to about 4 % of the total weight of the particles.

In certain embodiments, the external coating is lecithin. Lecithin is a generic term to designate any group of yellow-brownish fatty substances occurring in animal and plant tissues composed of phosphoric acid, choline, fatty acids, glycerol, glycolipids, triglycerides, and phospholipids. Glycerophospholipids in lecithin include phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, and phosphatidic acid. Particles coated with lecithin may have hydrophilic properties, which may facilitate a uniform dispersal of the particles throughout the composition in which the particles are stacked at the nano-scale level. This stacking effect may present a layer of protection on the surface of the dermis.

Without being bound by theory, the use of coated particles may present a uniform physical barrier to prevent or inhibit mosquitos from drawing blood from the host. This is illustrated in Figures 1 and 2, which are scanning electron microscopy images of a test membrane containing uncoated dimethicone titanium dioxide particles and titanium dioxide particles coated with lecithin, respectively. These images show that the coated particles may present a uniform barrier.

The composition may comprise one or more organic components. Examples of an organic component include, but are not limited to, pure forms or derivatives of lemongrass, citronella, picaridin (ir3535), chrysanthemum, cedar, and soybean. The organic components may be present in an amount of about 0.1 to about 5%, or about 1%, by volume of the composition.

The one or more organic components may be bound to the particles. In certain embodiments, the organic components may be infused into an external coating on the particles. The ratio of the organic components to the external coating may vary from about 1 to about 99%, depending on the absorbency of the particle and the level of effect of the organic component desired.

The one or more organic components may also be unbound to the particles. In other words, the organic components may be in the pharmaceutically acceptable carrier of the composition along with the particles.

The composition may be in the form of a cream, gel, lotion, suspension, spray or ointment. The composition may be suitable for topical administration to the dermis, and may form a substance that remains adherent to the surface of the dermis.

The pharmaceutically acceptable carrier may comprise one or more excipients known in the art for preparation of a cream, gel, lotion, suspension, spray, or ointment, including but not limited to emollients or softening agents, emulsifying or thickening agents, humectants and/or moisturizers, gelling agents, preservatives, oils, waxes, solvents, fragrances, dyes, antioxidants, antifoaming agents, stabilizing agents, pH adjusters, and the like.

Examples of suitable oily phases include, but are not limited to, hydrocarbons such as soft white paraffin, liquid paraffin, mineral oils, and the like. In some embodiments, an oily phase may be present in the composition in an amount of about 0.5 to about 20% by weight of the composition, or about 1 to about 15% by weight.

Examples of emulsifiers and thickeners include, but are not limited to, ethers of polyethylene glycol and fatty alcohols, cetyl alcohol, stearyl alcohol, sorbitol and other non-ionic emulsifying waxes, polyoxyethylene stearyl or cetyl alcohol ethers, glyceryl monostearate, polyoxyethylene sorbitan palmitate, Tween 20, 21, 40, 60, 65, 80, 81 or 85, polyoxyethylene glycol ethers of fatty alcohols such as cetearyl alcohol (Ceteareth-20), monoglycerides and fatty alcohols, fatty acid esters of alcohols having 3-21 carbon atoms, such as glyceryl monostearate and glyceryl monopalmitate. In certain embodiments, emulsifier-thickeners are present in an amount of about 2 to about 15%, or about 2 to about 12%, by weight of the composition.

Examples of emollients or softening agents include, but are not limited to, cetyl esters, wax and natural spermaceti wax, petrolatum, glyceryl monooleate, myristyl alcohol, and isopropyl palmitate. In some embodiments, emollients are present in an amount of up to about 10% by weight of the composition.

Examples of a humectant or moisturizer include, but are not limited to, glycerin, which may also be considered an emollient. In certain embodiments, glycerin is present in the formulation up to about 20% by weight, such as about 2 to about 12% by weight.

Examples of preservatives include, but are not limited to, methyl paraben, propyl paraben, quaternium-15, and chlorocresol. In some embodiments, preservatives are present in an amount of up to about 0.5% by weight of the composition.

Examples of suitable solvents include, but are not limited to, water and ethanol.

Examples of gelling agents include, but are not limited to, polysaccharides and gums, such as carboxymethylcellulose, alginic acid, agar, xanthan gum, gum arabic and the like.

Examples of antioxidants include, but are not limited to, vitamin E (tocopherol). In some embodiments, tocopherol salts such as tocopherol acetate are included in the composition.

In certain embodiments, the composition of the invention comprises the formulation shown in Table 1 below:

Table 1. Composition according to embodiments of the invention.

Ingredient	**Percentage by weight**
Water	65.30%
Hydroxyethylcellulose	1.80%
Zemea Select Propanediol	2.00%
SD alcohol 40-B (200 proof)	10.00%
Syntran PC776	10.00%
Phenoxetol	0.40%
Treated Titanium Dioxide	10.00%
Lemongrass	0.25%
KF-6011	0.25%
	100.00%

One of ordinary skill in the art would understand how to adjust the percentages by weight of the exemplified composition in order to accommodate different amounts of titanium dioxide and lemongrass, and to accommodate different organic components other than lemongrass.

The composition of the invention may be for use in a method of preventing mosquitoes from extracting blood from a host and/or from infecting a host with a mosquito-borne disease or infection, or a method of protecting a host from blood extraction and/or infection by a mosquito. This method is further described below.

Method of Prevention and/or Protection

The invention also relates to a method of preventing mosquitoes from extracting blood from a host and/or from infecting a host with a mosquito-borne disease or infection, or a method of protecting a host from blood extraction and/or infection by a mosquito. The method may comprise applying a composition of the invention to the dermis.

The composition may be applied onto the dermis through various means including, but not limited to, by hand, using a dispenser or applicator (such as a wipe into which the composition is infused), spraying the composition onto the dermis, etc.

The host may be a mammal, including humans, primates, livestock animals (such as sheep, pigs, cattle, horses, donkeys), laboratory test animals (such as mice, rabbits, rats, guinea pigs), and companion animals (such as dogs, cats).

The impact of applying the composition of the invention to the dermis may also include (i) reducing the available source of blood with which the female mosquito utilizes in the reproductive process and thus reducing the mosquito population near host-populated areas; and (ii) facilitating the death of the mosquito as a result of its interaction with the composition of the invention.

In some embodiments, the composition may prevent mosquitoes from extracting blood from a host and/or from infecting a host with a mosquito-borne disease or infection, or may protect a host from blood extraction and/or infection by a mosquito by forming a physical barrier.

The method of the invention prevent mosquitoes from infecting a host with a mosquito-borne disease or infection. Examples of mosquitoes include, but are not limited to, Ades egypti, Anopheles, Aedes albopictus, asian tiger, and the like. Examples of mosquito-borne diseases or infections may include, but are not limited to, malaria, yellow fever, Chikungunya, West Nile virus, dengue fever, filariasis, and Zika virus.

Method of Preparation

The invention relates to a method of preparing a composition of the invention. The method may comprise admixing the particles and the pharmaceutically acceptable carrier. In certain embodiments, the method may also comprise admixing the particles with one or more organic components, either separately or together with the pharmaceutically-acceptable carrier.

In some embodiments, the particles may be homogenized within the pharmaceutically acceptable carrier. In certain embodiments, the particles may be spun in a centrifuge.

The particles may be coated with an external coating using techniques known in the art. In certain embodiments, the external coating may be combined with one or more organic components before the external coating is coated onto the particles. Alternatively, one or more organic components may be admixed with the particles after the particles are coated with the external coating.

The invention also relates to the use of the composition of the invention in the preparation of a medicament for preventing mosquitoes from extracting blood from a host and/or from infecting a host with a mosquito-borne disease or infection, or a for protecting a host from blood extraction and/or infection by a mosquito. This protection and/or prevention may be achieved by applying the medicament to the dermis of the host.

EXAMPLES

Example 1

Studies were performed to evaluate the efficacy of compositions according to embodiments of the invention.

Petri dishes (35 mm) were covered with stretched lamb skin, and bovine blood with anti-coagulant (0.3% sodium citrate) was injected into each Petri dish. The lamb skin on each Petri dish was (i) covered with a composition according to embodiments of the invention, (ii) covered with a pharmaceutically-acceptable carrier (e.g., a base cream) containing no particles, or (iii) absent any pharmaceutically-acceptable carrier or particles to serve as a control. Each Petri dish was heated and the temperature of the blood was maintained at 35-37 degrees Celsius using an infrared thermometer to monitor the temperature.

The Petri dishes were then exposed to approximately 450-650 female mosquitoes. The mosquitoes were allowed to feed for about one hour, and were then harvested and visually examined with an optical microscope to find evidence of blood ingestion (e.g., engorgement of blood). The mosquitos were scored as either no blood ingestion or engorged based on the microscopic examination.

Figure 3 provides an example of how Petri dishes were assembled for a study. In this case, the study involved a composition comprising 10% titanium dioxide coated with lecithin, a composition comprising 15% titanium dioxide coated with lecithin, and a control.

Figure 4 shows how the temperature of the blood in the Petri dishes were monitored and maintained. Notably, the Petri dishes covered with either the composition containing 10% titanium dioxide coated with lecithin or the composition containing 15% titanium dioxide coated with lecithin exhibited a substantial decrease in the thermal signature. Figure 5 demonstrates the behavior of the mosquitos during a study. Here, fewer mosquitos were on the Petri dishes covered with either the composition containing 10% titanium dioxide coated with lecithin or the composition containing 15% titanium dioxide coated with lecithin, as compared to Petri dishes covered with the pharmaceutically-acceptable carrier (base cream) or serving as the control

The impact on the mosquitos of titanium dioxide particles according to embodiments of the invention was further shown using scanning electron microscopy. Figures 6 and 7 are images of the proboscis of a mosquito and shows particles of titanium dioxide particles coated with lecithin embedded in the surface of the proboscis. Figure 7 also shows the pharmaceutically-acceptable carrier fouling the hair structures on the perimeter of the mouth. Figures 8-10 are images of an area of the mouth/proboscis of a mosquito and shows particles of titanium dioxide particles coated with lecithin embedded in the surface of the proboscis as well as the pharmaceutically-acceptable carrier fouling the hair structures. Figures 11 and 12 are images of an area of the mouth/proboscis of a mosquito and shows particles of titanium dioxide particles coated with lecithin attached to a hair structure on the mosquito. Figure is an image of an area of the mouth/proboscis of a mosquito and shows particles of titanium dioxide particles coated with lecithin (bright area) inside the pharmaceutically-acceptable carrier cream fouling a scale-like feature on the surface of the proboscis. Figures 14 and 15 are images of an area of the mouth/proboscis of a mosquito and shows particles of titanium dioxide particles coated with lecithin inside the carrier of the invention fouling a scale-like feature on the surface of the proboscis.

The following studies were performed:

March 17, 2015 Study

The Petri dish assembly and methodology described above was used in a study comparing (a) a composition containing 15% titanium dioxide particles and a water-based gel as a pharmaceutically-acceptable carrier, (b) the water-based gel (without particles), and (c) a control.

These results, shown in Table 2 below, indicate that the Petri dish covered by the composition exhibited a lower feeding rate of the mosquitos as compared to the control.

Table 2. Results of the March 17, 2015 Study

	# of Mosquitos Tested	# of Mosquitos Engorged	% of Mosquitos Engorged
15% titanium dioxide particles and a water-based gel	299	16	5.4%
Water-based gel	350	72	20.6%
Control	327	126	38.5%

These results indicate that the presence of the 15% titanium dioxide particles reduced the feeding rate of the mosquitos.

March 31, 2015 Study

The Petri dish assembly and methodology described above was used in another study comparing (a) a composition containing 15% titanium dioxide particles and a water-based gel as a pharmaceutically-acceptable carrier, (b) the water-based gel (without particles), and (c) a control.

The results, shown in Table 3 below, indicate that the Petri dish covered by the composition exhibited a lower feeding rate of the mosquitos as compared to the control.

Table 3. Results of the March 31, 2015 Study

	# of Mosquitos Tested	# of Mosquitos Engorged	% of Mosquitos Engorged
15% titanium dioxide particles and a water-based gel	280	6	2.1%
Water-based gel	292	34	11.6%
Control	301	55	18.3%

These results further indicate that the presence of the 15% titanium dioxide particles reduced the feeding rate of the mosquitos.

April 3, 2015 Study

The Petri dish assembly and methodology described above was used in another study comparing (a) a composition containing 15% titanium dioxide particles and a water-based gel as a pharmaceutically-acceptable carrier, (b) a composition containing 25% titanium dioxide particles and a water-based gel as a pharmaceutically-acceptable carrier, (c) the water-based gel (without particles), and (d) a control.

The results, shown in Table 4 below, indicate that the Petri dishes covered by compositions containing the titanium dioxide particles exhibited a lower feeding rate of the mosquitos as compared to the control.

Table 4. Results of the April 3, 2015 Study

	# of Mosquitos Tested	# of Mosquitos Engorged	% of Mosquitos Engorged
15% titanium dioxide particles and a water-based gel	318	8	2.5%
25% titanium dioxide particles and a water-based gel	265	7	2.7%
Water-based gel	270	8	3.0%
Control	262	12	4.5%

These results indicate that the presence of the titanium dioxide particles reduced the feeding rate of the mosquitos.

May 1, 2015 Study

The Petri dish assembly and methodology described above was used in another study comparing (a) a composition containing 10% titanium dioxide particles and a water-based gel as a pharmaceutically-acceptable carrier, (b) a composition containing 15% titanium dioxide particles and a water-based gel as a pharmaceutically-acceptable carrier, (c) a control.

The results, shown in Table 5 below, indicate that the Petri dishes covered by compositions containing the titanium dioxide particles exhibited a lower feeding rate of the mosquitos as compared to the control.

Table 5. Results of the May 1, 2015 Study

	% of Mosquitos Engorged	**% Change in Mosquitos Engorged Compared to Control**
10% titanium dioxide particles and a water-based gel	13.53%	-64.06%
15% titanium dioxide particles and a water-based gel	5.45%	-85.52%
Control	37.64%	N/A

These results indicate that the presence of the titanium dioxide particles reduced the feeding rate of the mosquitos.

May 8, 2015 Study

The Petri dish assembly and methodology described above was used in another study comparing (a) a composition containing 5% titanium dioxide particles and a water-based gel as a pharmaceutically-acceptable carrier, (b) a composition containing 15% titanium dioxide particles and a water-based gel as a pharmaceutically-acceptable carrier, and (c) a control.

The results, shown in Table 6 below, indicate that the Petri dishes covered by compositions containing the titanium dioxide particles exhibited a lower feeding rate of the mosquitos as compared to the control.

Table 6. Results of the May 8, 2015 Study

	# of Mosquitos Tested	# of Mosquitos Engorged	% of Mosquitos Engorged
5% titanium dioxide particles and a water-based gel	377	48	12.73%
15% titanium dioxide particles and a water-based gel	466	39	8.37%
Control	342	117	34.21%

These results indicate that the presence of the titanium dioxide particles reduced the feeding rate of the mosquitos.

June 19, 2015 Study

The Petri dish assembly and methodology described above was used in another study comparing (a) a composition containing 15% anatase titanium dioxide particles and a base cream as a pharmaceutically-acceptable carrier, (b) a composition containing 15% rutile titanium dioxide particles and a base cream as a pharmaceutically-acceptable carrier, and (c) a control.

The results, shown in Table 7 below, indicate that the Petri dishes covered by compositions containing the titanium dioxide particles exhibited a lower feeding rate of the mosquitos as compared to the control. Further, the Petri dish covered by the composition containing the rutile titanium dioxide particles exhibited a lower feeding rate of the mosquitos as compared to the Petri dish covered by the composition containing the anatase titanium dioxide particles.

Table 7. Results of the June 19, 2015 Study

	# of Mosquitos Tested	# of Mosquitos Engorged	% of Mosquitos Engorged
15% anatase titanium dioxide particles and a base cream	274	34	12.4%
15% rutile titanium dioxide particles and a base cream	300	21	7.0%
Control	363	101	27.8%

These results indicate that the presence of the titanium dioxide particles reduced the feeding rate of the mosquitos, and that rutile titanium dioxide particles may be more effective in reducing the feeding rate of mosquitos.

June 26, 2015 Study

The Petri dish assembly and methodology described above was used in another study comparing (a) a composition containing 15% anatase titanium dioxide particles and a base cream as a pharmaceutically-acceptable carrier, (b) a composition containing 15% rutile titanium dioxide particles and a base cream as a pharmaceutically-acceptable carrier, and (c) a control.

The results, shown in Table 8 below, indicate that the Petri dishes covered by compositions containing the titanium dioxide particles exhibited a lower feeding rate of the mosquitos as compared to the control. Further, the Petri dish covered by the composition containing the antase titanium dioxide particles and the Petri dish covered by the composition containing the rutile titanium dioxide particles exhibited nearly the same feeding rate of the mosquitos.

Table 8. Results of the June 26, 2015 Study

	# of Mosquitos Tested	# of Mosquitos Engorged	% of Mosquitos Engorged
15% anatase titanium dioxide particles and a base cream	289	27	9.3%
15% rutile titanium dioxide particles and a base cream	350	34	9.7%
Control	393	121	30.8%

These results indicate that the presence of the titanium dioxide particles reduced the feeding rate of the mosquitos, and that anatase titanium dioxide particles and rutile titanium dioxide particles may have the same efficacy in reducing the feeding rate of mosquitos.

July 17, 2015 Study

The Petri dish assembly and methodology described above was used in another study comparing (a) a composition containing 10% anatase titanium dioxide particles coated with lecithin and a base cream as a pharmaceutically-acceptable carrier, (b) a composition containing 15% anatase titanium dioxide particles coated with lecithin and a base cream as a pharmaceutically-acceptable carrier, and (c) a control.

The results, shown in Table 9 below, indicate that the Petri dishes covered by compositions containing the titanium dioxide particles exhibited a lower feeding rate of the mosquitos as compared to the control. Further, the Petri dish covered by the composition containing the 10% antase titanium dioxide particles and the Petri dish covered by the composition containing the 15% antase titanium dioxide particles exhibited nearly the same feeding rate of the mosquitos.

Table 9. Results of the July 17, 2015 Study

	# of Mosquitos Tested	# of Mosquitos Engorged	% of Mosquitos Engorged
10% anatase titanium dioxide particles coated with lecithin and a base cream	274	3	1.1%
15% anatase titanium dioxide particles coated with lecithin and a base cream	213	3	1.4%
Control	310	45	14.5%

These results indicate that the presence of the titanium dioxide particles coated with lecithin reduced the feeding rate of the mosquitos, and that 10% anatase titanium dioxide particles and 15% anatase titanium dioxide particles may have the same efficacy in reducing the feeding rate of mosquitos.

July 24, 2015 Study

The Petri dish assembly and methodology described above was used in another study comparing (a) a composition containing 10% rutile titanium dioxide particles coated with lecithin and a base cream as a pharmaceutically-acceptable carrier, (b) a composition containing 15% rutile titanium dioxide particles coated with lecithin and a base cream as a pharmaceutically-acceptable carrier, and (c) a control.

The results, shown in Table 10 below, indicate that the Petri dishes covered by compositions containing the titanium dioxide particles exhibited a lower feeding rate of the mosquitos as compared to the control. Further, the Petri dish covered by the composition containing the 10% rutile titanium dioxide particles and Petri dish covered by the composition containing the 15% rutile titanium dioxide particles exhibited nearly the same feeding rate of the mosquitos.

Table 10. Results of the July 24, 2015 Study

	# of Mosquitos Tested	# of Mosquitos Engorged	% of Mosquitos Engorged
10% rutile titanium dioxide particles coated with lecithin and a base cream	240	263	239
15% rutile titanium dioxide particles coated with lecithin and a base cream	38	12	9
Control	15.8%	4.6%	3.8%

These results indicate that the presence of the titanium dioxide particles coated with lecithin reduced the feeding rate of the mosquitos, and that 10% rutile titanium dioxide particles and 15% rutile titanium dioxide particles may have the same efficacy in reducing the feeding rate of mosquitos.

July 31, 2015 Study

The Petri dish assembly and methodology described above was used in another study comparing (a) a composition containing 10% rutile titanium dioxide particles coated with lecithin, a pigment, and a base cream as a pharmaceutically-acceptable carrier, (b) a composition containing 15% rutile titanium dioxide particles coated with lecithin, a pigment, and a base cream as a pharmaceutically-acceptable carrier, and (c) a control.

The results, shown in Table 11 below, indicate that the Petri dishes covered by compositions containing the titanium dioxide particles exhibited a lower feeding rate of the mosquitos as compared to the control. Further, the Petri dish covered by the composition containing the 15% rutile titanium dioxide particles with pigment exhibited a lower feeding rate of the mosquitos as compared to the Petri dish covered by the composition containing the 10% rutile titanium dioxide particles with pigment.

Table 11. Results of the July 31, 2015 Study

	% of Mosquitos Engorged	% Change in Mosquitos Engorged Compared to Control
10% rutile titanium dioxide particles coated with lecithin, a pigment, and a base cream	31.6%	-32.0%
15% rutile titanium dioxide particles coated with lecithin, a pigment, and a base cream	25.7%	-44.7%
Control	46.5%	N/A

These results indicate that the presence of the titanium dioxide particles coated with lecithin reduced the feeding rate of the mosquitos, and that 15% rutile titanium dioxide particles with a pigment may be more effective in reducing the feeding rate of mosquitos than 10% rutile titanium dioxide particles with a pigment.

August 7, 2015 Study

The Petri dish assembly and methodology described above was used in another study comparing (a) a composition containing 10% anatase titanium dioxide particles coated with lecithin, a pigment, and a base cream as a pharmaceutically-acceptable carrier, (b) a composition containing 15% anatase titanium dioxide particles coated with lecithin, a pigment, and a base cream as a pharmaceutically-acceptable carrier, and (c) a control.

The results, shown in Table 12 below, indicate that the Petri dishes covered by compositions containing the titanium dioxide particles exhibited a lower feeding rate of the mosquitos as compared to the control. Further, the Petri dish covered by the composition containing the 10% anatase titanium dioxide particles with pigment and the Petri dish covered by the composition containing the 15% anatase titanium dioxide particles with pigment exhibited nearly the same feeding rate of the mosquitos.

Table 12. Results of the August 7, 2015 Study

	# of Mosquitos Tested	# of Mosquitos Engorged	% of Mosquitos Engorged
10% anatase titanium dioxide particles coated with lecithin, a pigment, and a base cream	311	20	6.4%

15% anatase titanium dioxide particles coated with lecithin, a pigment, and a base cream	269	16	6.0%
Control	245	19	7.8%

These results indicate that the presence of the titanium dioxide particles coated with lecithin reduced the feeding rate of the mosquitos, and that 10% anatase titanium dioxide particles with a pigment and 15% anatase titanium dioxide particles with a pigment may have the same efficacy in reducing the feeding rate of mosquitos.

Figure 16 shows the mean feeding rates (i.e., percent of mosquitoes engorged) of the controls, pharmaceutically-acceptable carriers, compositions containing 10% titanium dioxide particles, and compositions containing 15% titanium dioxide particles presented in the studies listed in Example 1. Figure 17 shows the mean decrease in feeding rate (i.e., percent change in mosquitos engorged compared to control) pharmaceutically-acceptable carriers, compositions containing 10% titanium dioxide particles, and compositions containing 15% titanium dioxide particles presented in the studies listed in Example 1. Based on these data, the presence of the titanium dioxide particles reduced the feeding rate of the mosquitos, and 15% titanium dioxide particles may be more effective in reducing the feeding rate of mosquitos than 10% titanium dioxide particles.

Example 2

Studies were performed to evaluate the efficacy of compositions according to embodiments of the invention.

Petri dishes (35 mm) were covered with stretched lamb skin, and bovine blood with anti-coagulant (0.3% sodium citrate) was injected into each Petri dish. The lamb skin on each Petri dish was (i) covered with a composition according to embodiments of the invention, (ii) covered with Off!, (iii) covered with a pharmaceutically-acceptable carrier and lemongrass, or (iv) absent any pharmaceutically-acceptable carrier or particles to serve as a control. Each Petri dish was heated and the temperature of the blood was maintained at 35-37 degrees Celsius using an infrared thermometer to monitor the temperature.

The Petri dishes were then exposed to approximately 450-650 female mosquitoes. The mosquitoes were allowed to feed for about one hour, and were then harvested and visually examined with an optical microscope to find evidence of blood ingestion (e.g., engorgement of blood). The mosquitos were scored as either no blood ingestion or engorged based on the microscopic examination.

The following studies were performed:

October 9, 2015 Study

The Petri dish assembly and methodology described above was used in a study comparing (a) a composition containing 10% titanium dioxide particles coated with lecithin, 1% lemongrass, and a base cream as a pharmaceutically-acceptable carrier, and (b) a control.

The results, shown in Table 13 below, indicate that the Petri dish covered by the compositions containing the titanium dioxide particles with lemongrass exhibited a lower feeding rate of the mosquitos as compared to the control.

Table 13. Results of the October 9, 2015 Study

	% of Mosquitos Engorged	% Change in Mosquitos Engorged Compared to Control
10% titanium dioxide particles coated with lecithin, 1% lemongrass, and a base cream	0.34%	-99%
Control	34.0%	N/A

These results indicate that the presence of the titanium dioxide particles coated with lecithin and lemongrass reduced the feeding rate of the mosquitos.

October 23, 2015 Study

The Petri dish assembly and methodology described above was used in another study comparing (a) a composition containing 10% rutile titanium dioxide particles coated with lecithin, 1% lemongrass, and a base cream as a pharmaceutically-acceptable carrier, (b) Off!, and (c) a control.

The results, shown in Table 14 below, indicate that the Petri dish covered by the composition containing the titanium dioxide particles with lemongrass exhibited a lower feeding rate of the mosquitos as compared to the control. Further, the Petri dish covered by the composition containing the titanium dioxide particles with lemongrass and the Petri dish covered by Off! exhibited nearly the same feeding rate of the mosquitos.

Table 14. Results of the October 23, 2015 Study

	# of Mosquitos Tested	# of Mosquitos Engorged	% of Mosquitos Engorged
10% titanium dioxide particles coated with lecithin, 1% lemongrass, and a base cream	285	1	0.35%
Off!	319	0	0%
Control	367	132	36.0%

These results indicate that the presence of the titanium dioxide particles coated with lecithin and lemongrass reduced the feeding rate of the mosquitos, and that 10% titanium dioxide particles with lemongrass and Off! may have the same efficacy in reducing the feeding rate of mosquitos.

November 13, 2015 Study

The Petri dish assembly and methodology described above was used in another study comparing (a) a composition containing 10% rutile titanium dioxide particles coated with lecithin and a base cream as a pharmaceutically-acceptable carrier, (b) a base cream as a pharmaceutically-acceptable carrier and 1% lemongrass, and (c) a control.

The results, shown in Table 15 below, indicate that the Petri dish covered by the composition containing the titanium dioxide particles exhibited a lower feeding rate of the mosquitos as compared to the control. Further, the Petri dish covered by the composition containing base cream with lemongrass exhibited a lower feeding rate of the mosquitos as compared to the Petri dish covered by the composition containing titanium dioxide particles.

Table 15. Results of the November 13, 2015 Study

	# of Mosquitos Tested	# of Mosquitos Engorged	% of Mosquitos Engorged
10% rutile titanium dioxide particles coated with lecithin, and a base cream	348	17	4.9%
base cream and 1% lemongrass	402	2	0.5%
Control	330	34	10.3%

These results indicate that the presence of the titanium dioxide particles coated with lecithin reduced the feeding rate of the mosquitos, and that the presence of lemongrass is effective in reducing the feeding rate of mosquitos.

March 18, 2016 Study

The Petri dish assembly and methodology described above was used in another study comparing (a) a composition containing 10% rutile titanium dioxide particles coated with lecithin and a base cream as a pharmaceutically-acceptable carrier, (b) a composition containing 10% rutile titanium dioxide particles coated with lecithin and a base cream as a pharmaceutically-acceptable carrier that underwent heating for four hours, and (c) a control.

The results, shown in Table 16 below, indicate that the Petri dish covered by the composition containing the titanium dioxide particles exhibited a lower feeding rate of the mosquitos as compared to the control. Further, the Petri dish covered by the composition containing the titanium dioxide particles coated with lecithin and the Petri dish covered by the composition containing the titanium dioxide particles coated with lecithin and was heated for four hours exhibited nearly the same feeding rate of the mosquitos.

Table 16. Results of the March 18, 2016 Study

	# of Mosquitos Tested	# of Mosquitos Engorged	% of Mosquitos Engorged
10% rutile titanium dioxide particles coated with lecithin, and a base cream	271	321	287

10% rutile titanium dioxide particles coated with lecithin, and a base cream and heated for four hours	113	20	17
Control	41.7%	6.2%	5.9%

These results indicate that the presence of the titanium dioxide particles coated with lecithin reduced the feeding rate of the mosquitos, and that heating the composition did not impact the efficacy of the composition.

April 22, 2016 Study

The Petri dish assembly and methodology described above was used in another study comparing (a) a composition containing 10% rutile titanium dioxide particles coated with lecithin, 1% lemongrass, and a base cream as a pharmaceutically-acceptable carrier that underwent heating for four hours, and (b) a control.

The results, shown in Table 17 below, indicate that the Petri dish covered by the composition containing the titanium dioxide particles exhibited a lower feeding rate of the mosquitos as compared to the control.

Table 17. Results of the April 22, 2016 Study

	# of Mosquitos Tested	# of Mosquitos Engorged	% of Mosquitos Engorged
10% rutile titanium dioxide particles coated with lecithin, 1% lemongrass, and a base cream and heated for four hours	272	10	3.7%
Control	347	112	32.3%

These results indicate that the presence of the titanium dioxide particles coated with lecithin reduced the feeding rate of the mosquitos. These results are further illustrated in Figure 18.

* * *

Those of ordinary skill in the art will recognize that many modifications and variations of the present invention may be implemented without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modification and variations of this invention provided they come within the scope of the appended claims and their equivalents.

WHAT IS CLAIMED IS:

1. A composition for topical administration comprising particles and a pharmaceutically acceptable carrier, wherein the particles comprise a metal oxide.

2. The composition of claim 1, wherein the metal oxide is selected from the group consisting of titanium oxide, zinc oxide, and a combination thereof.

3. The composition of claim 2, wherein the metal oxide is titanium oxide.

4. The composition of claim 1, wherein the particles are present in an amount of about 1 to about 25% by volume of the composition.

5. The composition of claim 1, wherein the particle is coated with an external coating.

6. The composition of claim 5, wherein the external coating comprises a hydrophilic polymer, propylene, propylene glycol phospholipid derivative, or a combination thereof.

7. The composition of claim 6, wherein the external coating comprises lecithin.

8. The composition of claim 5, wherein the external coating is present in an amount of about 0.1 to about 10% of the total weight of the particles.

9. The composition of claim 1, further comprising one or more organic components.

10. The composition of claim 9, wherein the organic components are selected from the group consisting of lemongrass, citronella, picaridin (ir3535), chrysanthemum, cedar, soybean, and a combination thereof.

11. The composition of claim 9, wherein the organic components are not bound to the particles.

12. The composition of claim 9, wherein the organic components are bound to the particles.

13. The composition of claim 10, wherein the organic components are infused an external coating on the particles.

14. The composition of claim 10, wherein the organic components are present in an amount of about 0.1 to about 5% by volume of the composition.

15. The composition of claim 1, wherein the composition is in a form of a cream, gel, lotion, suspension, spray, or ointment.

16. The composition of claim 1, wherein the composition is for use in a method of preventing mosquitoes from extracting blood from a host or from infecting a host with a mosquito-borne disease or infection, or a method of protecting a host from blood extraction or infection by a mosquito.

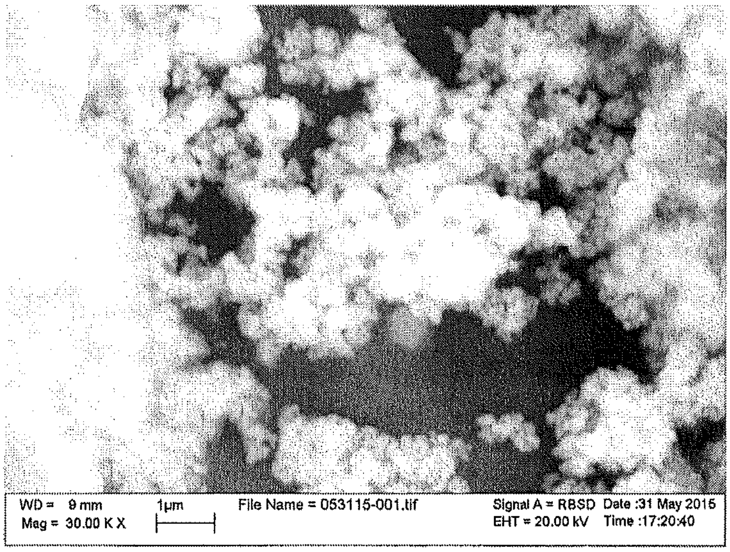
17. A method of preventing mosquitoes from extracting blood from a host or from infecting a host with a mosquito-borne disease or infection, said method comprising applying to the dermis of the host a composition comprising particles and a pharmaceutically acceptable carrier, wherein the particles comprise a metal oxide.

18. The method of claim 17, wherein the composition is applied to the dermis by hand, using a dispenser or applicator, or spraying the composition onto the dermis.

19. A method of protecting a host from blood extraction and/or infection by a mosquito, said method comprising applying to the dermis of the host a composition comprising particles and a pharmaceutically acceptable carrier, wherein the particles comprise a metal oxide.

20. The method of claim 19, wherein the composition is applied to the dermis by hand, using a dispenser or applicator, or spraying the composition onto the dermis.

UNCOATED
Dimethicone TiO_2 (10%)



COATED
Lecithin TiO_2 (10%) (anatase)

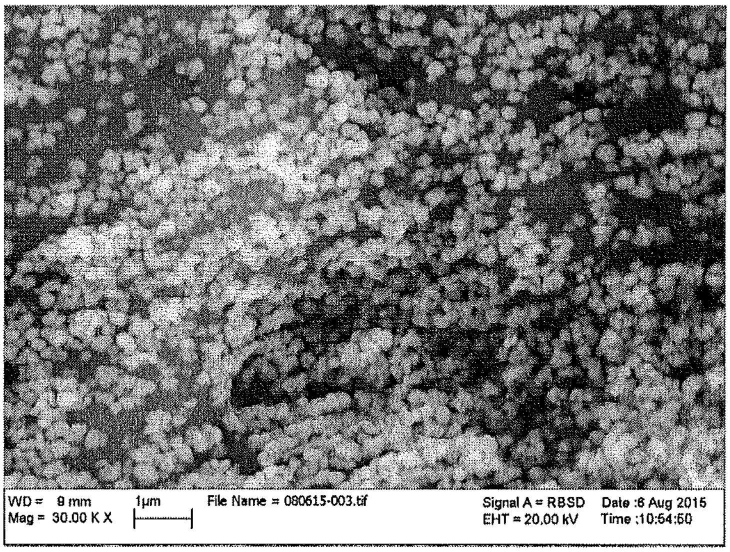
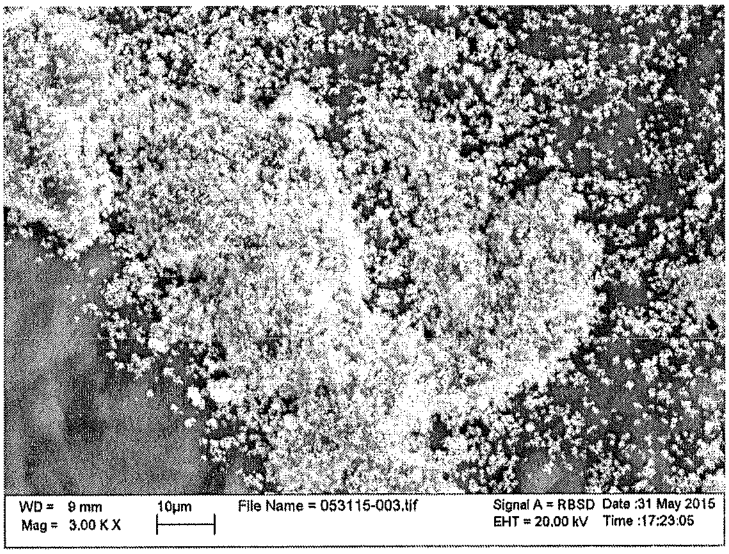


FIG. 1

UNCOATED
Dimethicone TiO_2 (10%)



COATED
Lecithin TiO_2 (10%) (anatase)

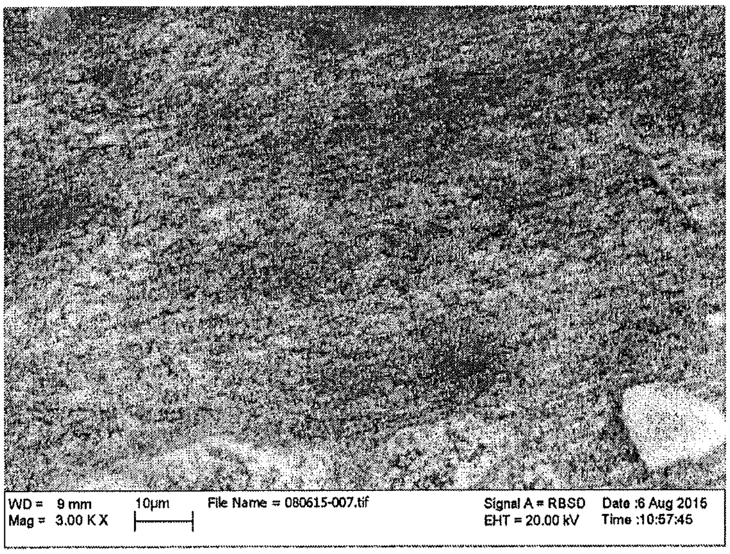


FIG. 2

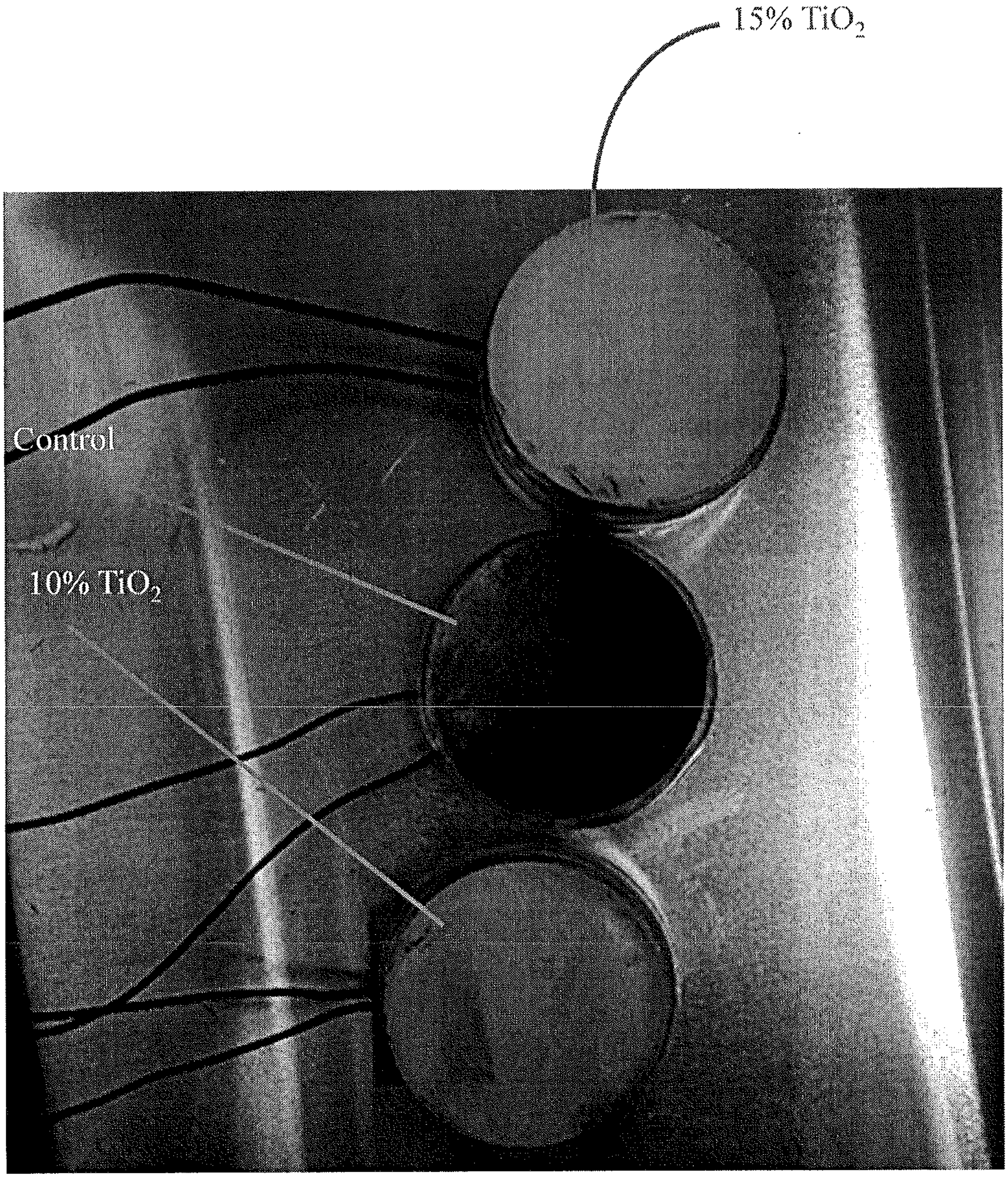


FIG. 3

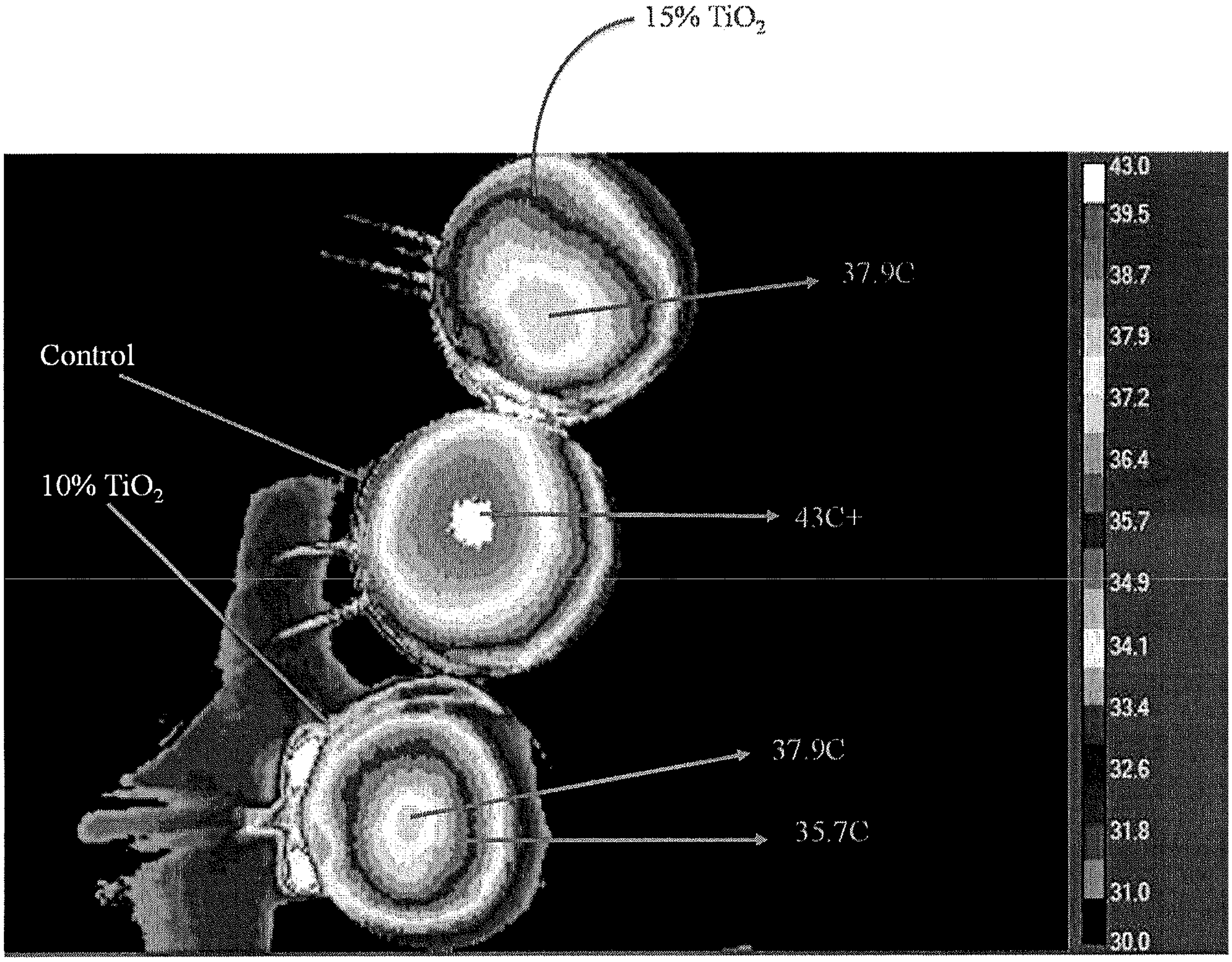
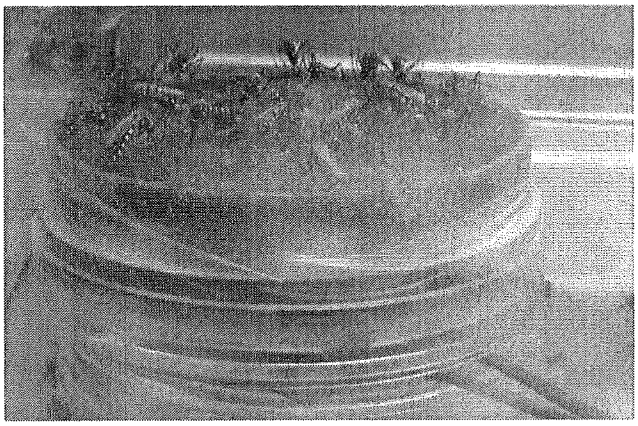
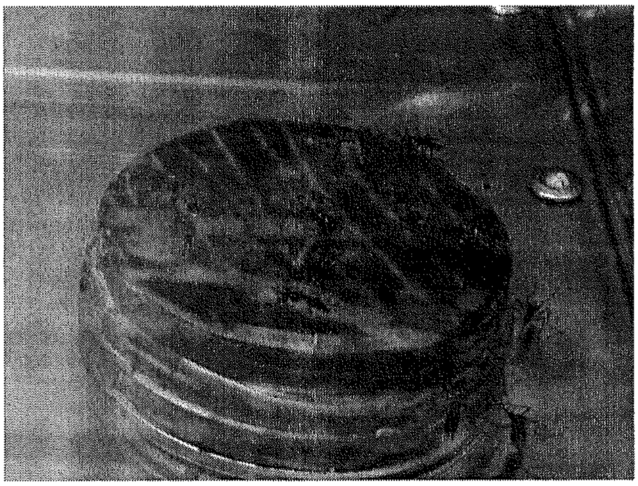

15% TiO_2
Control
10% TiO_2
37.9C
43C+
37.9C
35.7C
43.0
39.5
38.7
37.9
37.2
36.4
35.7
34.9
34.1
33.4
32.6
31.8
31.0
30.0

FIG. 4

Visual Comparison of Mosquito Feeding

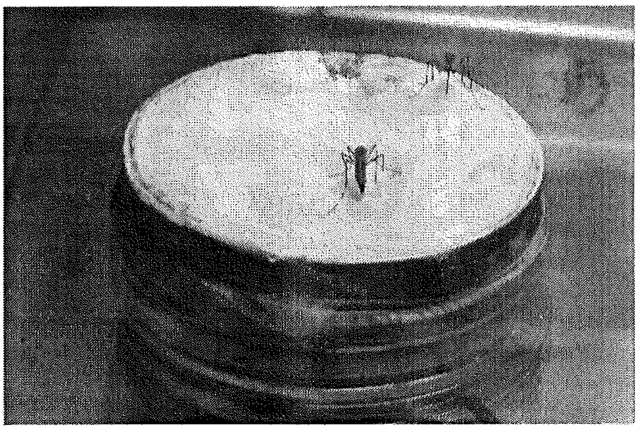


Control group – no cream of any kind



Carrier Cream with no particles for Mosquito feeding test

10% TiO_2 for Mosquito feeding test



15% TiO_2 for Mosquito feeding test

FIG. 5

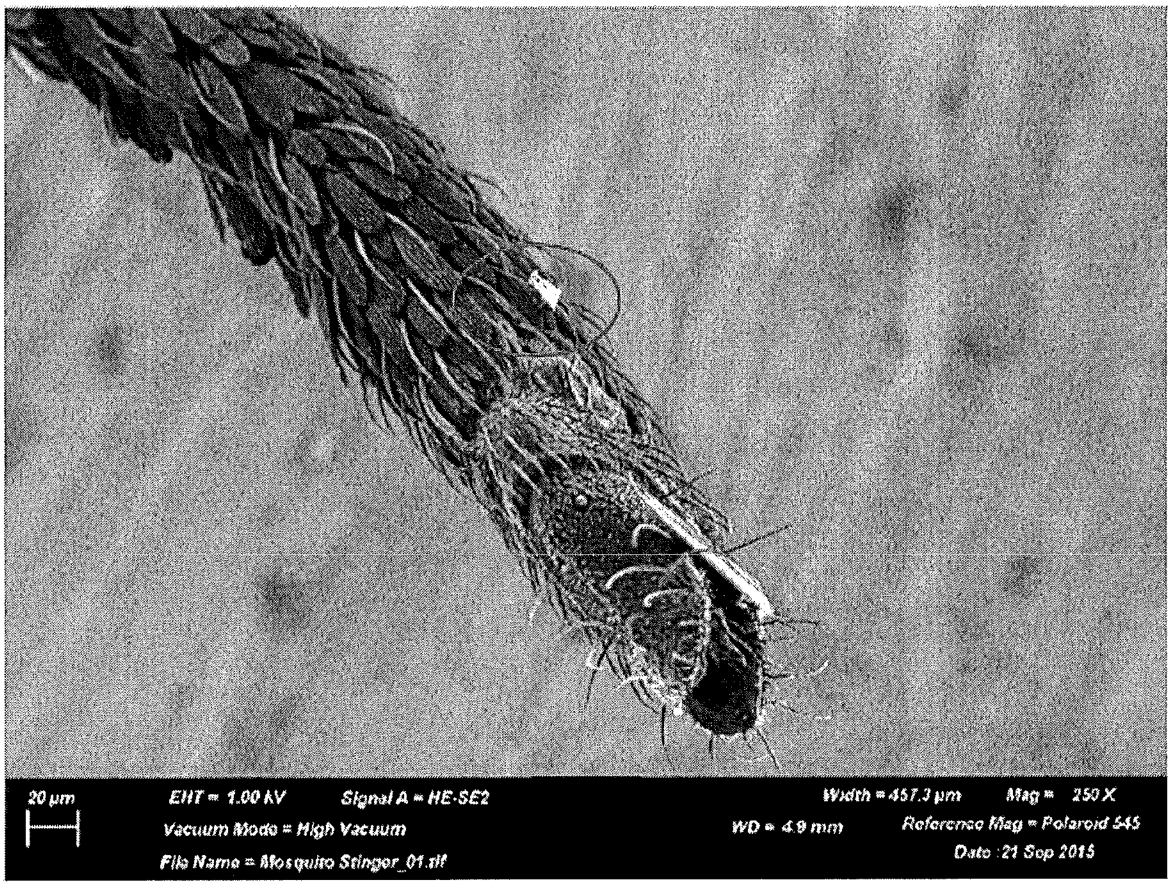

20 µm
EHT = 1.00 kV
Signal A = HE-SE2
Width = 457.3 µm
Mag = 250 X
Vacuum Mode = High Vacuum
WD = 4.9 mm
Reference Mag = Polaroid 545
File Name = Mosquito Stinger_01.tif
Date :21 Sep 2015

FIG. 6

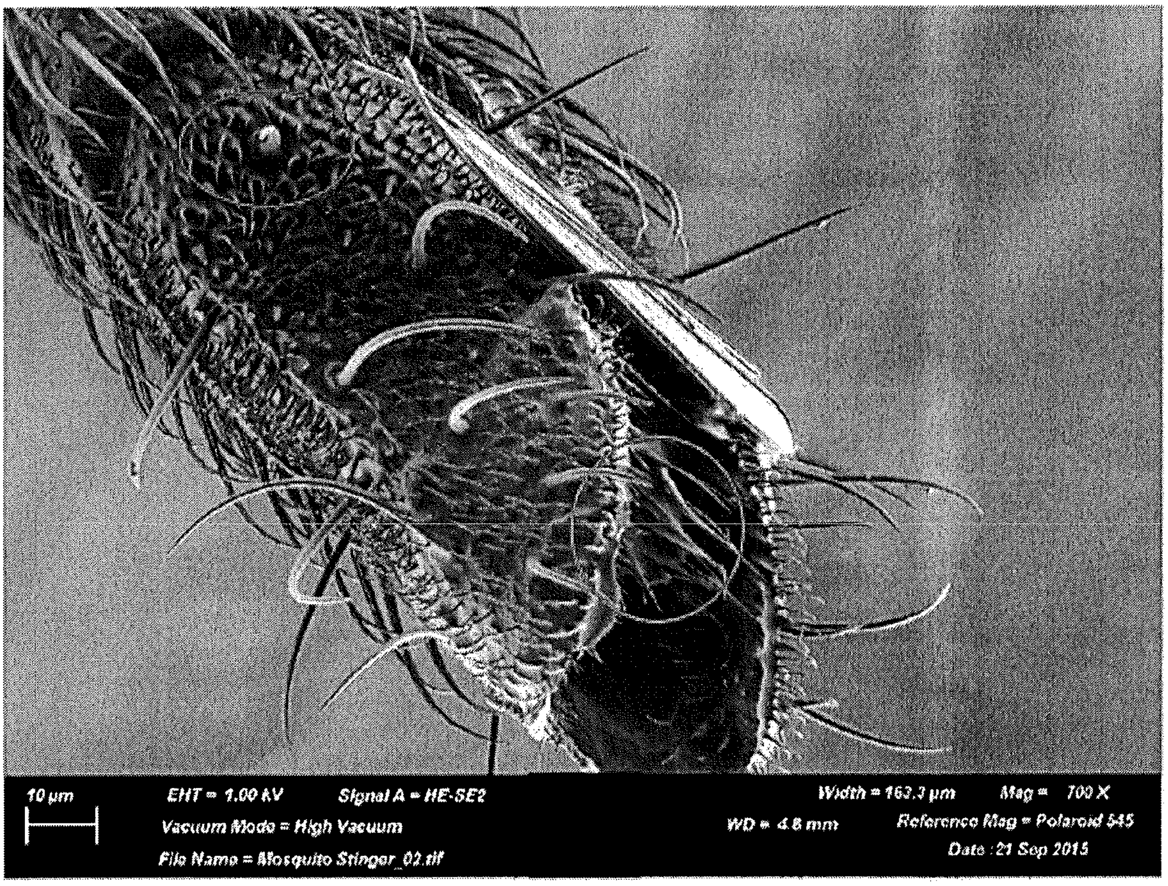
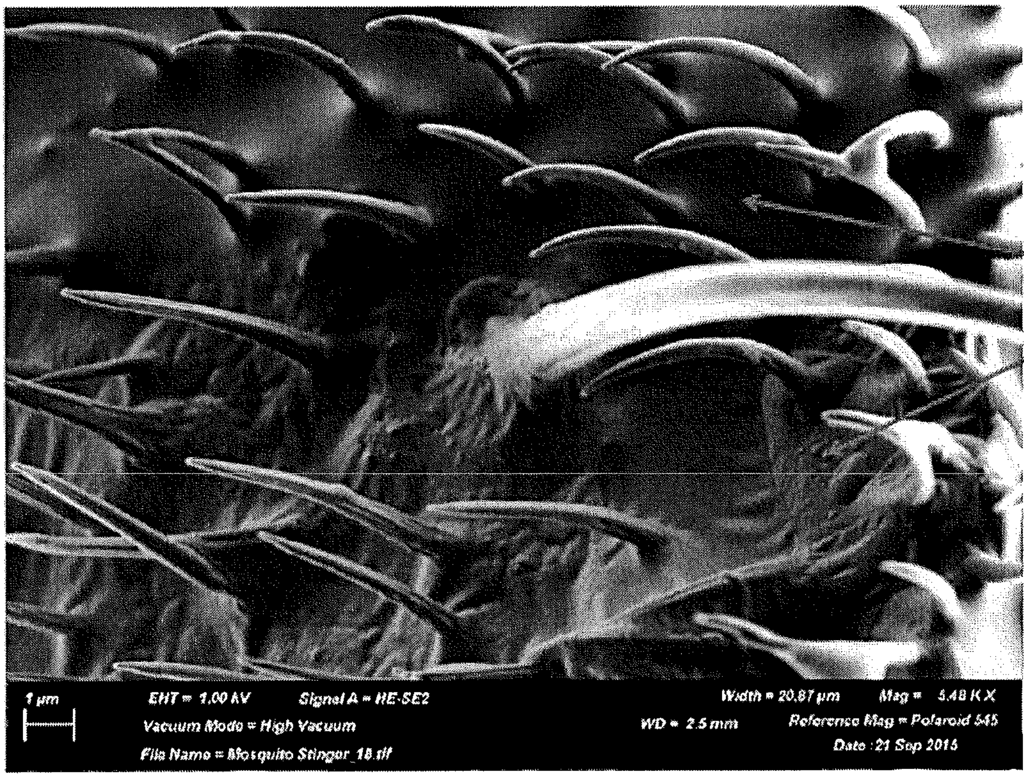

10 µm
EHT = 1.00 kV
Signal A = HE-SE2
Vacuum Mode = High Vacuum
File Name = Mosquito Stinger_02.tif
Width = 163.3 µm
Mag = 700 X
WD = 4.8 mm
Reference Mag = Polaroid 545
Date :21 Sep 2015

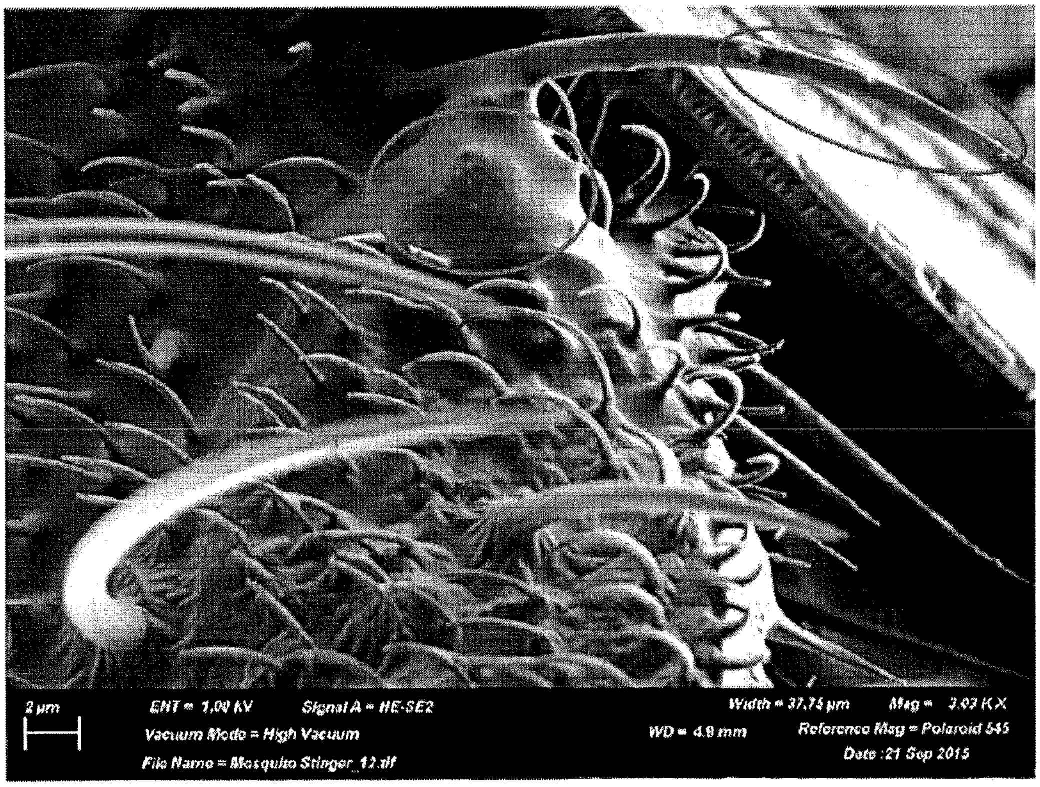
FIG. 7



5.5 kX image the mouth region of the mosquito. The nano-powder is contained in a smooth substance that covers the surface of the mouth

The image was taken at 1 kV using the SESI Detector.

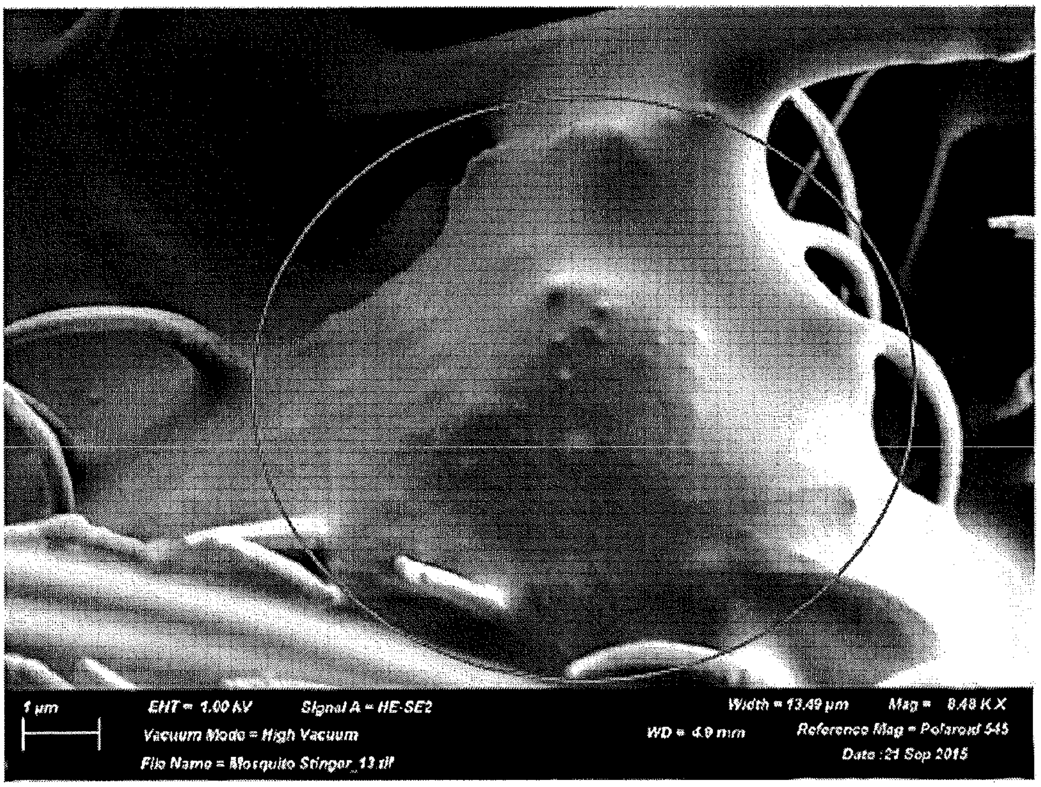
FIG. 8



3 kX image of the mouth region. Particles can be seen on a large hair and inside the "binder" substance.

The image was taken at 1 kV using the SESI Detector.

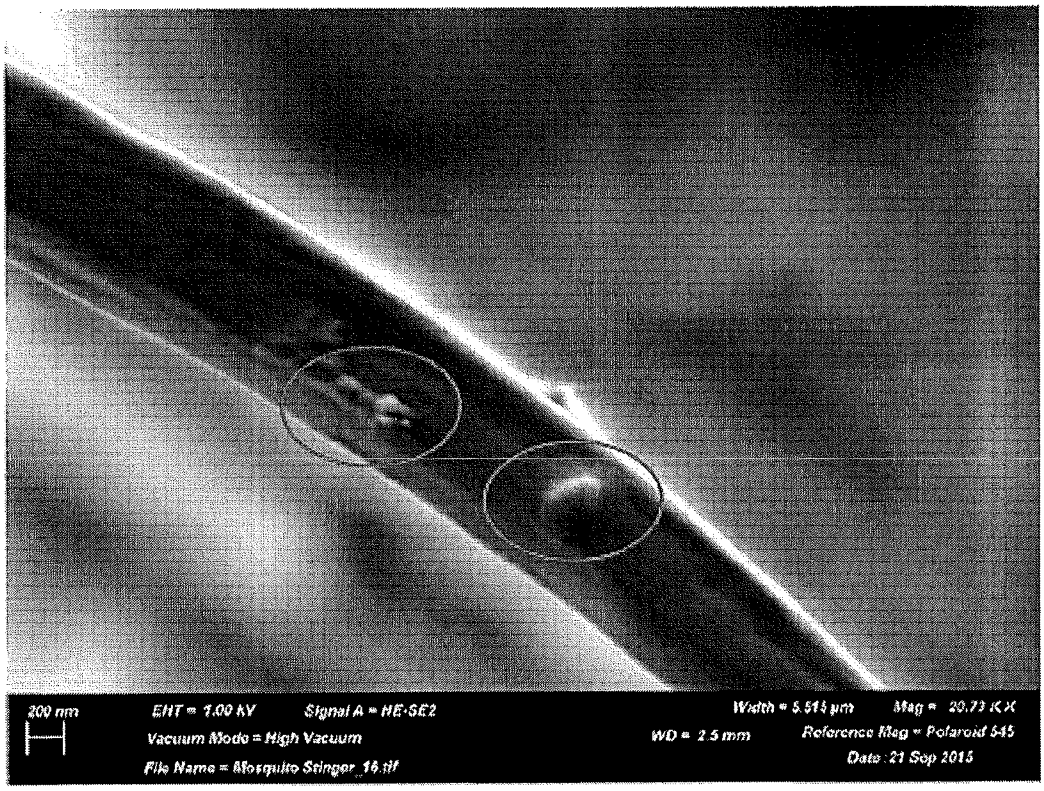
FIG. 9



8.5 kX image of particles inside the "binder" substance.

The image was taken at 1 kV using the SESI Detector.

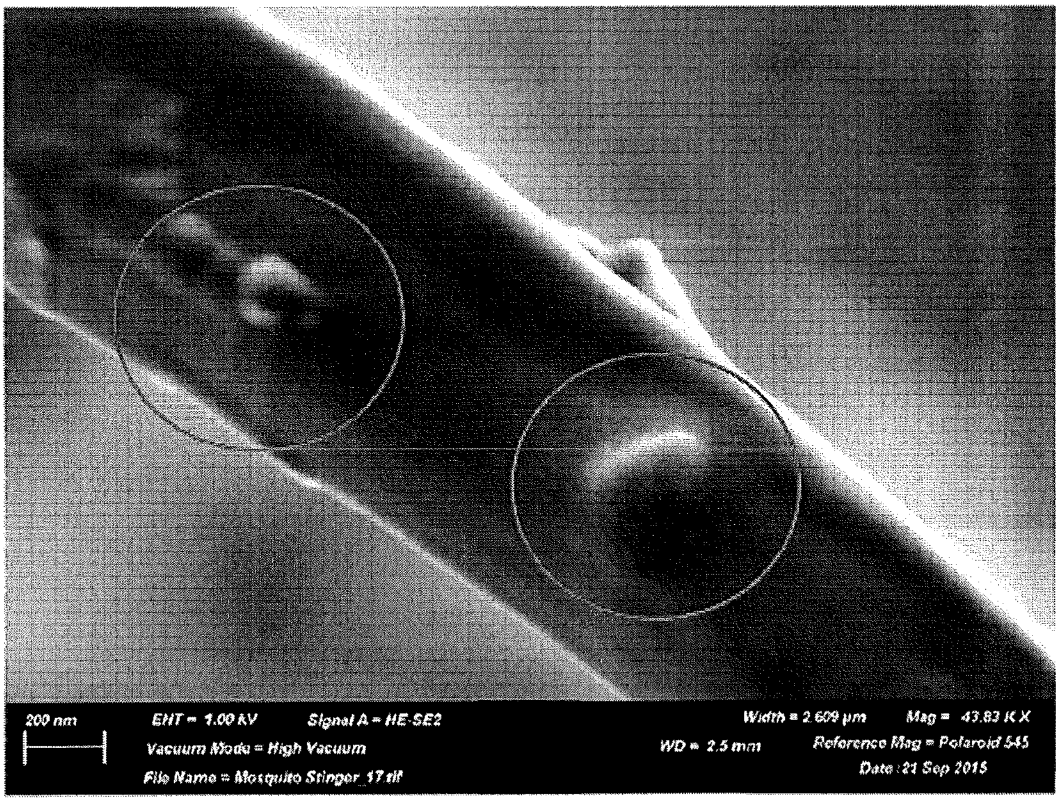
FIG. 10



21 kX image of particles on a hair

The image was taken at 1 kV using the SESI Detector.

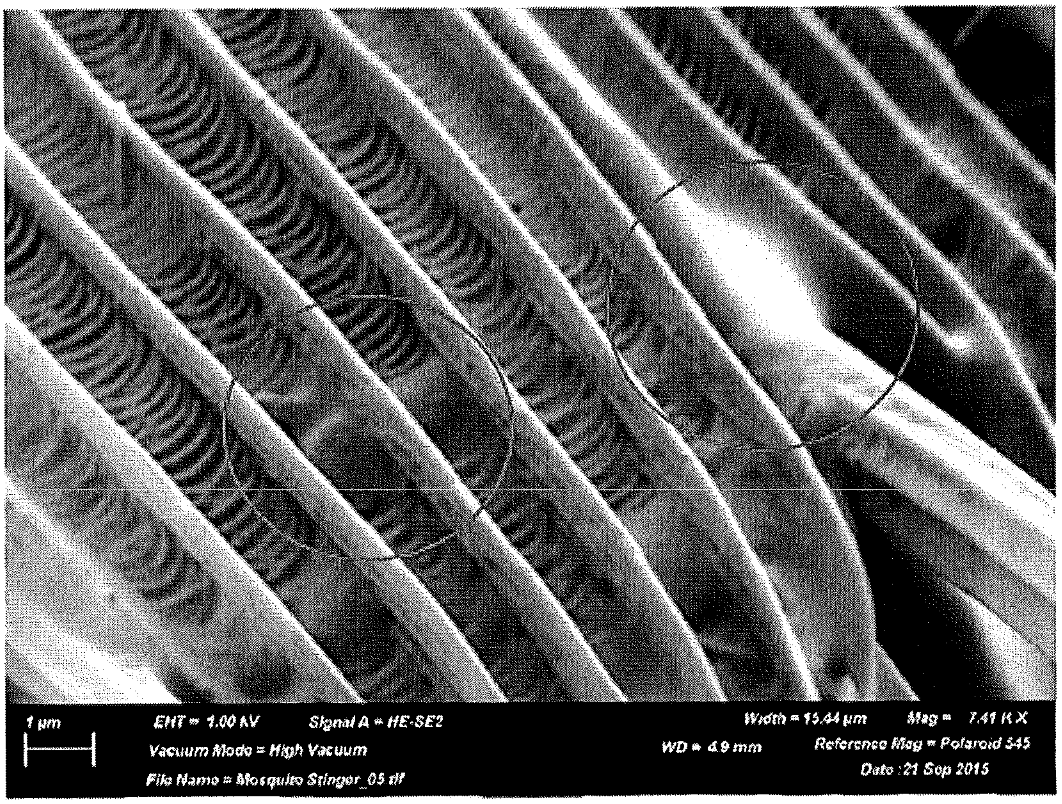
FIG. 11



44 kX image of particles on a hair

The image was taken at 1 kV using the SESI Detector.

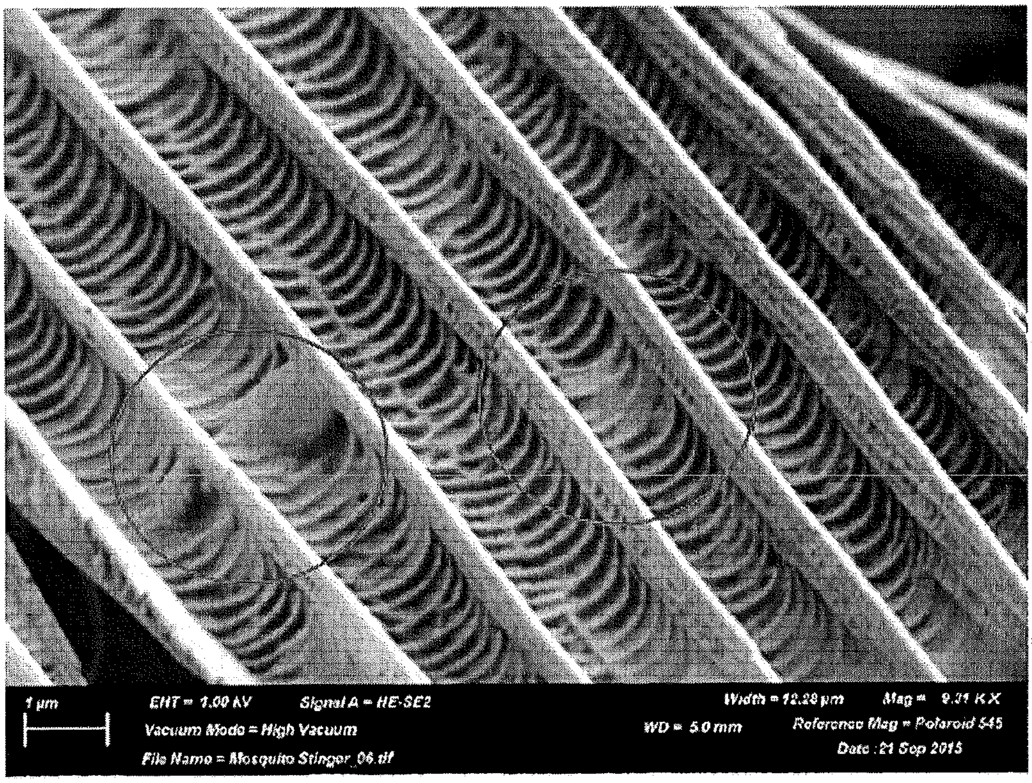
FIG. 12



7.5 kX image of particles on a scale a little away from the immediate mouth region.

The image was taken at 1 kV using the SESI Detector.

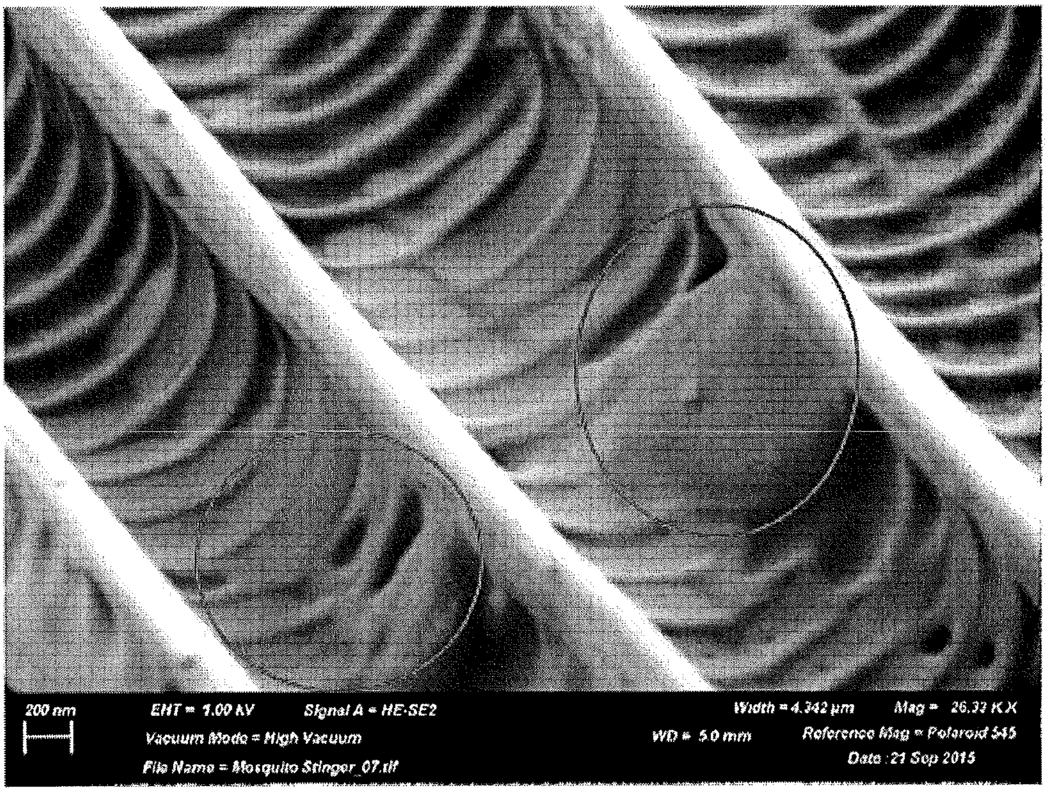
FIG. 13



9.3 kX image of particles on a scale a little away from the immediate mouth region.

The image was taken at 1 kV using the SESI Detector.

FIG. 14



26 kX image of particles on a scale a little away from the immediate mouth region.

The image was taken at 1 kV using the SESI Detector.

FIG. 15

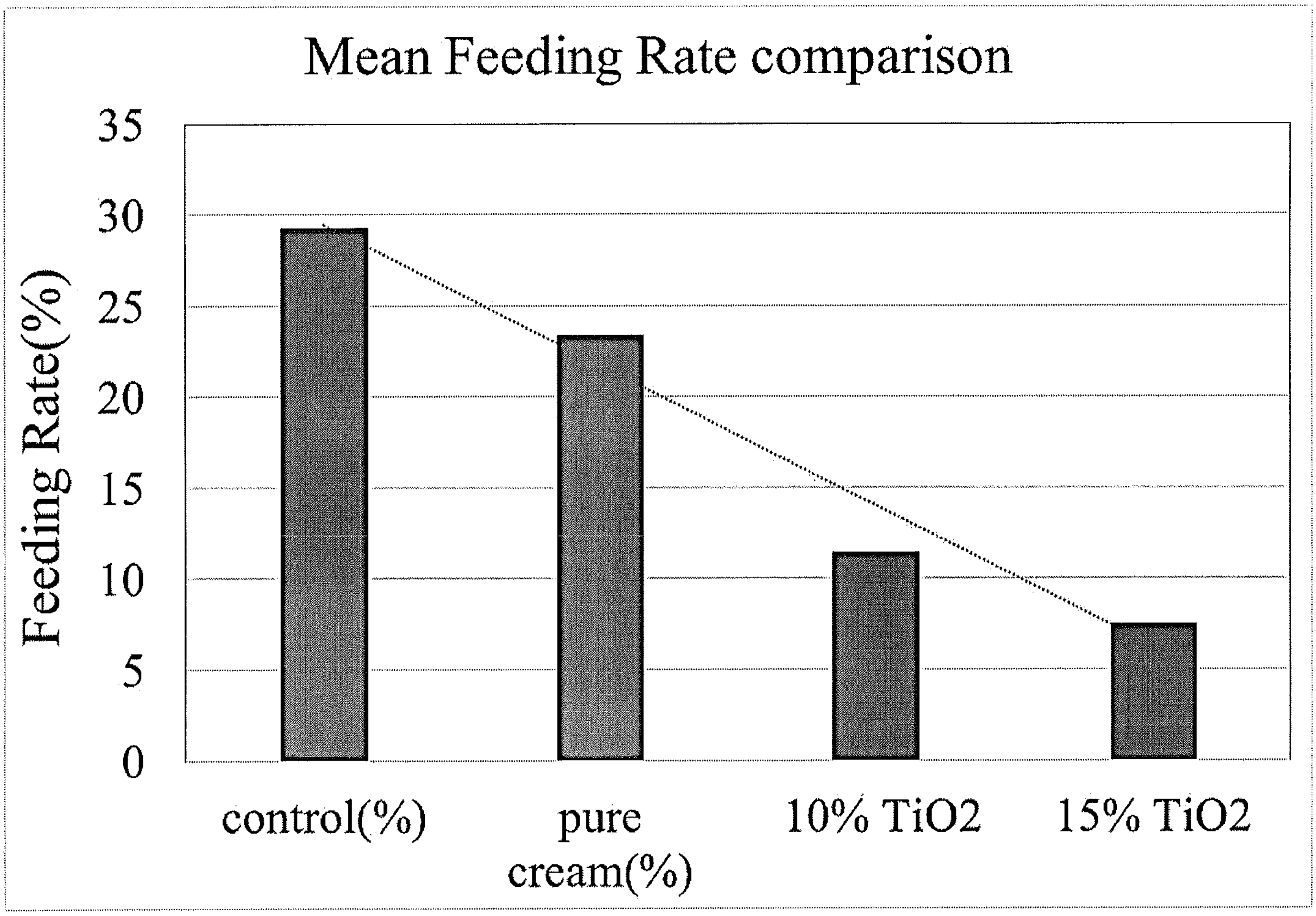

Mean Feeding Rate comparison
Feeding Rate(%)
35
30
25
20
15
10
5
0
control(%)
pure cream(%)
10% TiO2
15% TiO2

FIG. 16

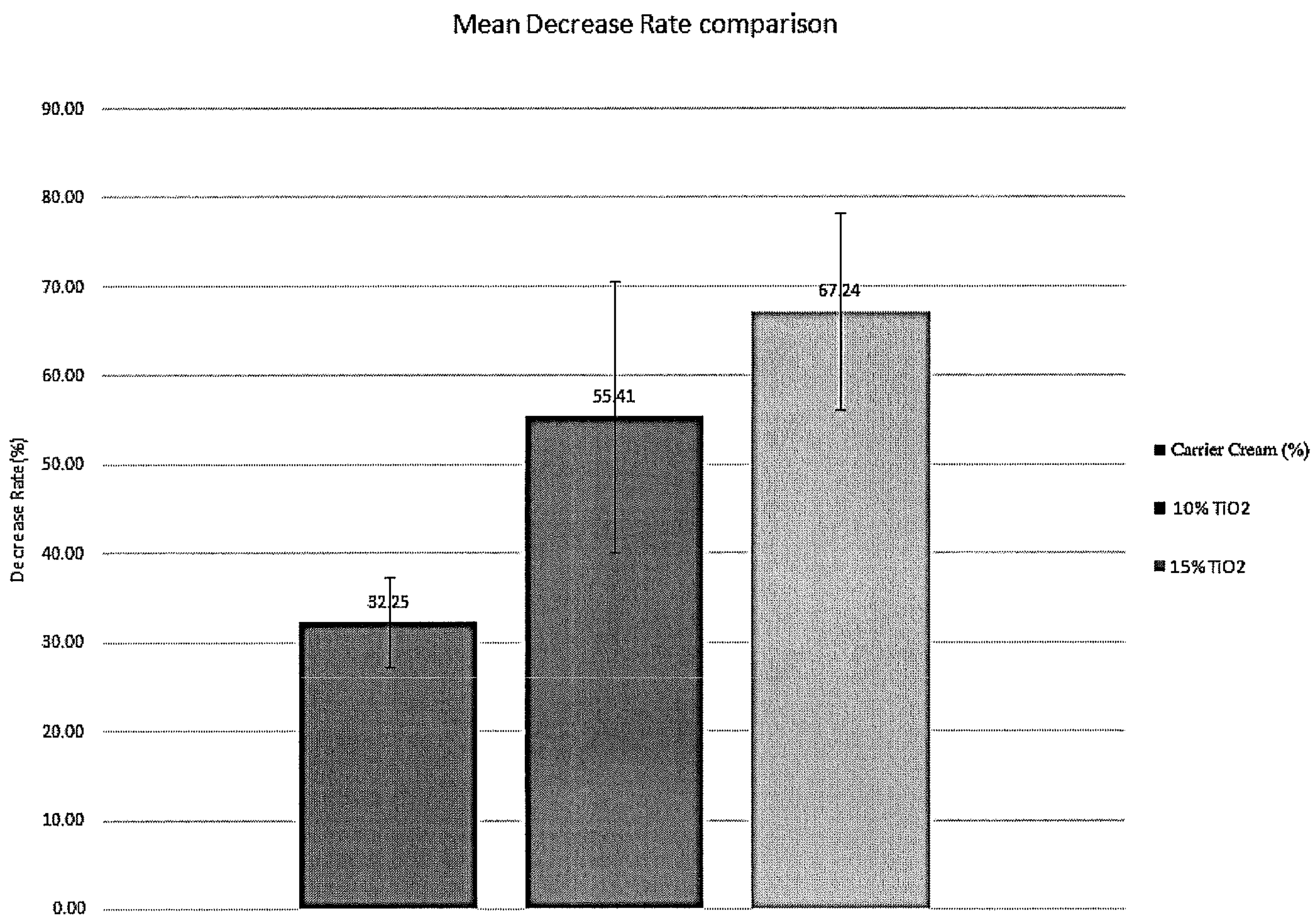

Mean Decrease Rate comparison
90.00
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
Decrease Rate (%)
32.25
55.41
67.24
Carrier Cream (%)
10% TiO2
15% TiO2

FIG. 17

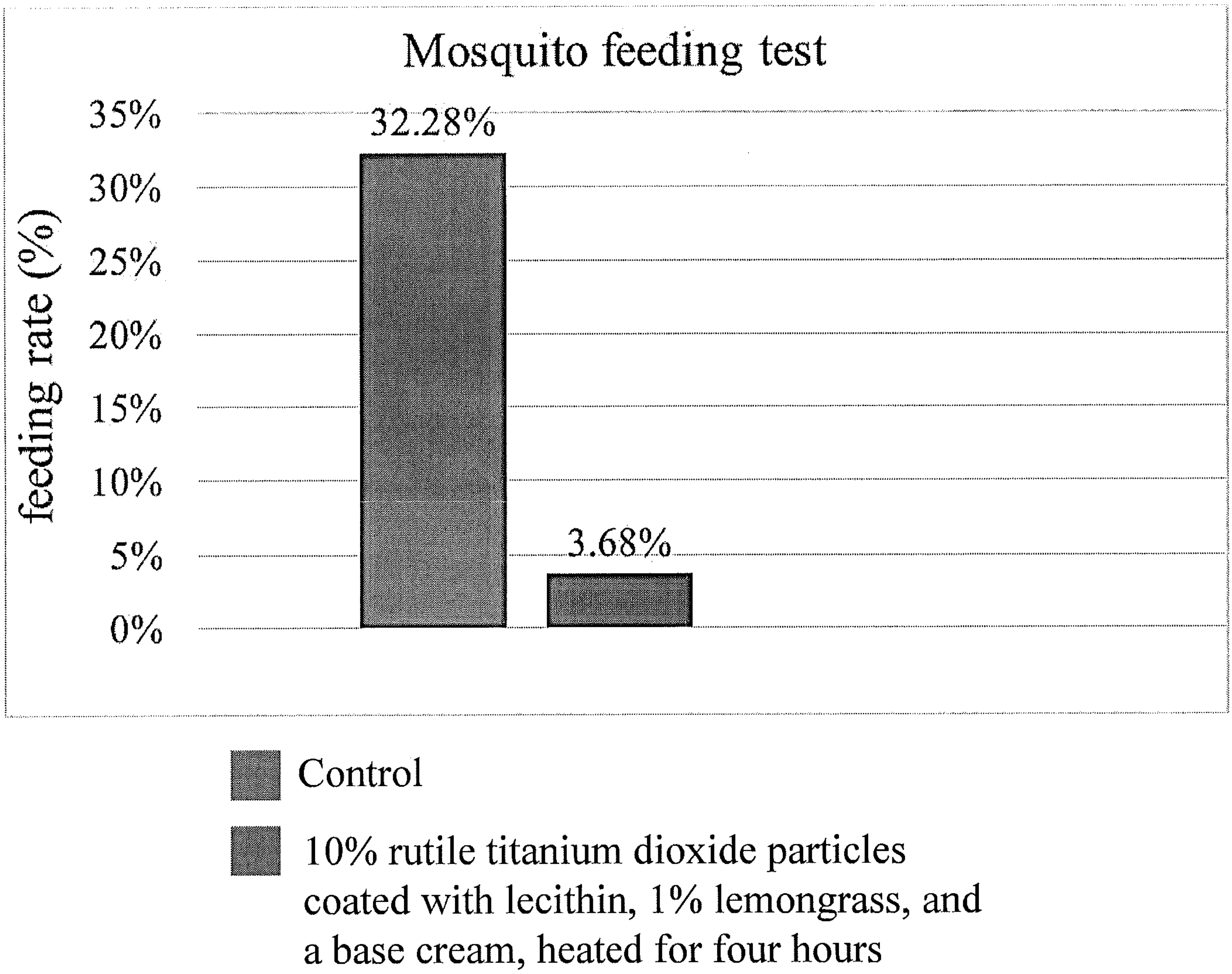

Mosquito feeding test
feeding rate (%)
35%
30%
25%
20%
15%
10%
5%
0%
32.28%
3.68%
Control
10% rutile titanium dioxide particles coated with lecithin, 1% lemongrass, and a base cream, heated for four hours

FIG. 18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/62501

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A01N 25/02, 25/08, 25/26, 59/16; A61K 8/29, 33/24, 47/06 (2017.01)
CPC - A01N 25/02, 25/08, 25/26, 59/16; A61K 8/29, 33/24, 47/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 5,575,988 A (KNOWLES. Jr, JH et al.) 19 November 1996; abstract; column 1, lines 59-62; column 2, lines 62-65; column 3, lines 11-29; column 4, lines 54-57; column 10, lines 1-12, 25-41; table 3; claims 7, 11, 14	1-3, 5, 9, 11, 15-20 -------------------- 4, 6-8, 10, 12-14
Y	US 2014/0271920 A1 (STROEBE, DS) 18 September 2014; paragraph [0006]; claims 1-3	4
Y	US 5,817,298 A (GALLEY, E et al.) 06 October 1998; abstract; column 2, lines 15-17, 40-57; table 1	6-8
Y	US 5,310,578 A (THURN-MULLER, A et al.) 10 May 1994; abstract; example 5; claim 4	10, 12-14
A	(SUMAN, TY et al.) "Larvicidal activity of titanium dioxide nanoparticles synthesized using Morinda citrifolia root extract against Anopheles stephensi, Aedes aegypti and Culex quinquefasciatus and its other effect on non-target fish." Asian Pacific Journal of Tropical Disease. July 2014, Vol. 5, No. 3, pages 224-230.	1-20
A	CN 104224614 A (Nantong Gongcheng Fine Chem Eng LTD) 24 December 2014; see English translation; entire document	1-20
A	US 7,790,202 B1 (MARTELL, HD) 07 September 2010; entire document	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 January 2017 (04.01.2017)	01 FEB 2017

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