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(54) Titre : TRAITEMENT DE LESIONS CUTANEES
(54) Title: SENSITIZING AGENTS FOR THE TREATMENT OF SKIN LESIONS

(57) Abrégé/Abstract:
The present invention provides compositions and methods for treating skin lesions by contacting the lesion with a sensitizing agent capable of eliciting a local immune response in the individual suffering from the lesion. The inventive compositions and methods may be applied in pharmaceutical and/or veterinary contexts.

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(54) Title: SENSITIZING AGENTS FOR THE TREATMENT OF SKIN LESIONS

(57) Abstract: The present invention provides compositions and methods for treating skin lesions by contacting the lesion with a sensitizing agent capable of eliciting a local immune response in the individual suffering from the lesion. The inventive compositions and methods may be applied in pharmaceutical and/or veterinary contexts.

TREATMENT OF SKIN LESIONS

Cross Reference to Related Application

This application claims priority to United States Patent Application Ser. No. 09/218,345 filed December 22, 1998.

Background of the Invention

Disorders of the skin can cause wide ranging effects. Some skin lesions are modestly annoying; others are devastating. Many skin lesions resist treatment with currently-available therapeutics and technologies. Skin lesions caused by viral infections tend to be particularly recalcitrant to treatment. Warts are but one example of a common, persistent viral skin lesion for which no reliable treatment is currently available.

Almost every individual will be afflicted with one or more warts at some point in his or her life. A variety of wart therapies is available, most of which focus on destruction of the wart and surrounding tissue. For example, warts are often removed by cryotherapy or by surgery. In other cases, warts are treated with locally destructive agents such as salicylic acid, lactic acid, or trichloroacetic acid. Each of these approaches has the disadvantage that significant damage can be caused to neighboring tissue. Moreover, these treatments are frequently not effective, and recurrence rates can be high. Additional approaches to treating warts range from attempting to alter the cutaneous environment to discourage wart growth (e.g., by applying retinoids, formalin, glutaraldehyde, or aluminum chloride), to discouraging wart proliferation through hypnotherapy.

There remains a need for an improved system for treatment of skin lesions, and particularly for wart treatment.

Summary of the Invention

The present invention provides a new approach to the treatment of skin disorders. The invention is particularly useful for the treatment of viral skin lesions, most particularly for the treatment of warts.

In general, the invention provides a system for stimulating a localized immune response in the area of the skin lesion, thereby inducing the immune system to attack. A preferred method of stimulating such a localized immune response is to apply a sensitizing agent to the skin in the area of the infection. Preferably, the agent is delivered so that its distribution to other areas of the body is inhibited or blocked. For example, the agent may be applied for only a short period of time. Alternatively or additionally, the agent is delivered by means of an applicator, such as a pen or a patch, that provides some physical containment of the agent. The agent may also be delivered to a physically confined location.

In certain preferred embodiments of the present invention, the sensitizing agent is provided in combination with a neutralizer, that can be applied an appropriate amount of time after application of the agent, to terminate the agent's effects. The selection of neutralizer, as well as its preferred mode of application, may depend on the choice of sensitizing agent utilized in a particular inventive embodiment.

In particularly preferred embodiments of the present invention, the sensitizing agent comprises a compound that is naturally found in the sap of poison ivy, poison oak or poison sumac. The agent may be provided as a poison ivy, poison oak, or poison sumac extract, or may alternatively be prepared from non-natural sources (e.g., by chemical synthesis or biological synthesis other than in natural context). Preferably, the agent comprises urushiol and/or includes at least one catechol. In other preferred embodiments, the sensitizing agent is a polynucleotide containing an unmethylated CpG.

The inventive methods and compositions are particularly applicable for the treatment of warts (e.g. common warts [verruca vulgaris], plantar warts, palmar warts, planar warts [verruca plana], mosaic warts [condyloma accuminatum; including venereal warts]) but may also useful for treatment of other skin lesions (e.g., nasal polyps, melanoma, herpes sores, basal cell carcinoma), including, in particular, other viral infections of the skin.

In particular embodiments, the present invention provides a composition for treating dermal disorders, comprising (i) a sensitizing agent characterized by an ability to induce a local immune response when applied to a skin lesion; and (ii) a delivery means for applying the sensitizing agent to skin. Preferably, the skin lesion is selected from the group consisting of nasal polyps, melanomas, herpes sores, basal cell carcinomas, and warts.

Certain inventive compositions further include a neutralizer that substantially blocks further action by the sensitizing agent, which neutralizer is provided separate from the sensitizing agent for application to the skin lesion subsequent to application of the sensitizing agent. Preferably, the neutralizer is a specific inhibitor of the particular sensitizing agent.

Particularly preferred inventive compositions include a sensitizing agent that is a compound naturally produced by a plant selected from the group consisting of poison ivy, poison oak, and poison sumac; preferably, the compound comprises one or more components of plant sap, for example an urushiol.

Alternative preferred inventive compositions include a sensitizing agent comprising a polynucleotide containing an unmethylated CpG motif, lipopolysaccharide, lipid A, heat-killed bacteria, pertussis virus epitopes, cytokines, cholera toxin, proholeragenoid, cholera toxin B subunit, and fungal polysaccharides.

Inventive compositions may be provided in combination with and/or in the context of a delivery means, for example comprising a first end including a reservoir in which the sensitizing agent is located, and a handle constructed and arranged for ease of grasping and manipulating. The delivery means may be constructed, for example, as a pen applicator, a cotton-tipped swab, a bulb-type applicator, or a patch.

The present invention also provides methods of treating skin lesions with the inventive compositions. Particularly preferred methods include methods of treating warts by applying one or more components of the sap of a poisonous plant.

Definitions

"Extract"-- the term "extract", as used herein, means a substance or collection of substances prepared from a natural source by removing one or more natural elements of the source. An extract may be a crude preparation in that only a small number of natural elements have been removed, or alternatively may be a substantially pure preparation in that all natural elements other than a selected natural element or collection thereof have been substantially removed.

"Individual"-- the term "individual", as used herein, means the person or animal on whom inventive compositions are applied or with respect to whom inventive methods are practiced. The individual is preferably a mammal, more preferably a human or a domestic animal (e.g., a dog, a cat, a bird, a horse, a cow, a sheep, a goat, etc.) Most preferably, the individual is a human.

"Lesion"-- a "lesion", as that term is used herein, is any disturbance of the skin. Preferred lesions according to the present invention are caused by viral infection. For example, warts, nasal polyps, melanomas, herpes sores, and basal cell carcinomas are all lesions according to the present invention. In certain preferred embodiments of the invention, the lesion is a wart such as a common wart (verruca vulgaris), a plantar wart, a palmar wart, a planar wart [verruca plana], or a mosaic warts [condyloma accuminatum; including venereal warts].

"Neutralizing agent"-- A "neutralizing agent" or "neutralizer", as those terms are used herein, is a compound, composition, or treatment, that substantially terminates the effects of a sensitizing agent. A neutralizing agent may act by substantially removing the sensitizing agent from the skin. For example, a detergent or soap can be an effective neutralizing agent. Alternatively or additionally, a neutralizing agent may block the biological action of a sensitizing agent. The choice of neutralizing agent may vary depending on the particular sensitizing agent being employed. Particularly preferred neutralizing agents are specific inhibitors of a chosen sensitizing agent).

"Patch"-- a "patch", as that term is used herein, is any entity capable of delivering a sensitizing agent to the skin. A patch may be a matrix or a container, may be a simple gauze pad or a complex multilayer device. Adhesive bandages are included within the term "patch" as that term is used herein.

"Pen"-- a "pen", as that term is used herein, is a sensitizing agent delivery device comprising at least one substantially elongated member. The chamber preferably terminates in a first end and a second end, at least one of which includes a sensitizing agent reservoir. In some preferred embodiments, the elongated member is substantially hollow and sensitizing agent can be loaded within it; in other preferred embodiments, the elongated member includes a sensitizing agent reservoir at its first end and a neutralizing agent reservoir at its second end.

"Reservoir"-- a "reservoir", as that term is used herein, is an area in which an active agent (i.e., a sensitizing agent or a neutralizing agent) is located for application onto an individual. It is not necessary that the reservoir have any significant depth; a flat surface will constitute a reservoir if an agent is localized on it. The reservoir may include a means for retaining the agent, which means may comprise, for example, an absorptive pad, a depression, a cavity, etc.

"Sensitizing agent"-- the term "sensitizing agent", as used herein, means any compound that, when applied to the skin of an individual, elicits a local immune response in that individual, in the area of application of the compound. Preferred sensitizing agents include compounds that are naturally produced by poison ivy, poison oak, or poison sumac. Such compounds include urushiols.

Alternative preferred sensitizing agents include, for example, polynucleotides containing unmethylated CpG motifs (see, for example, U.S. Patent No. 5,830,877 to Carson et al. and published PCT applications WO 96/02555, WO 98/18810, WO 98/16247, and WO 98/40100, each of which is incorporated herein by reference. Preferably, the polynucleotide is between 2 and 100 nucleotides (nt) or basepairs (bp) long and contains a consensus motif represented by the formula 5'-$X_1X_2CGX_3X_4$-3',

where (i) C and G are unmethylated; (ii) X_1, X_2, X_3, and X_4 are nucleotides; and (iii) a GCG trinucleotide is not present at or near the 5' or 3' terminus. Preferably, X_2 is adenine, guanine, or thymine; X_3 is cytosine or thymine; and $X_1 + X_4$ together comprise between about 0 and 26. One or more nucleotide residue within the polynucleotide may be a stabilized residue such as, for example, a phosphorothioate residue. Particularly preferred polynucleotides are within the range of 8-40 nt or bp long.

Still other preferred sensitizing agents include any of a variety of different compounds that can stimulate a local immune response when applied topically. A wide variety of immunostimulatory agents are known, some of which for example act by raising lymphokine levels in the area of their administration, and could be tested to determine their ability to initiate a topical immune response according to the present invention. Such compounds include, for example, lipopolysaccharide (LPS) (see, for example, Johnson et al., 1956), lipid A, and heat-killed bacteria (see, for example, Dienes, 1936), pertussis virus epitopes, cytokines (e.g., IL-12, IL-18, IFN-α, IFN-β, IFN-γ, TGF-α, etc.), cholera toxin, proholeragenoid, cholera toxin B subunit, fungal polysaccharides (e.g., schizophyllan, muramyl dipeptide, muramyl dipeptide derivatives, phorbol esters, microspheres, non-*Helicobacter pylori* bacterial lysates, labile toxin of *Escherichia coli*, block polymers, saponins, and ISCOMs).

Additional agents that could be tested to evaluate their suitability for use as sensitizing agents according to the present invention can be found, for example, in Azuma, *Vaccine* 10:1000, 1992; Pockley et al., *Immunol.* 73:19, 1991; Adam et al., *ISI Atlas of Science* 205, 1988; Clements et al., *Vaccine* 6:269, 1988; Ben Ahmeida et al., *Vaccine* 11:1302, 1993, Gupta et al., *Vaccine* 11:290, 1993; etc., each of which is incorporated herein by reference.

Description of the Drawing

Figure 1 depicts the chemical structure of poison oak urushiol, which is a mixture of four pentadecylcatechols and four heptadecylcatechols. This Figure is reproduced from Armstrong et al., *HerbalGram* 34:36, 1995.

Figures 2-4 show various embodiments of applicators for use in accordance with the present invention.

Figure 5 shows an exemplary protective disk that may be used to localize administered sensitizing agent according to the present invention.

Figure 6 shows an infrared (IR) profile of a concentrated extract of poison ivy.

Figure 7 shows an ultraviolet (UV) profile of a concentrated extract of poison ivy.

Figure 8 shows a thin layer chromatography (TLC) profile of a concentrated extract of poison ivy.

Figure 9 shows a UV spectrum of the urushiol fraction isolated from an extract of poison ivy by column chromatography using an LH-sephadex resin.

Figure 10 shows a TLC profile of the urushiol fraction isolated from an extract of poison ivy by column chromatography using an LH-sephadex resin.

Description of Certain Preferred Embodiments

In one aspect, the present invention provides compositions for treating skin lesions including warts or other viral infections of the skin. The inventive compositions include a sensitizing agent in a sufficient quantity to stimulate an immune reaction at the site of its application. Generally, the agent should be of

appropriate character, or administered in appropriately small quantity or for an appropriately short time, that no substantial systemic immune reaction is initiated. In certain cases, however, it may be desirable to employ a sensitizing agent in a manner that allows sufficient systemic immune reaction to result in reduction or cure of multiple lesions on the same individual. For example, it is possible that extended exposure to a particular sensitizing agent, originally applied to a single lesion site, will result in resolution of other similar but remote lesions as a result of an induction of systemic immune reactivity against lesion-causing agent(s).

Preferred sensitizing agents for use in the practice of the present invention include compounds that are naturally produced by poison ivy, poison oak, and/or poison sumac. In particular, preferred sensitizing agents include compounds that are naturally found in the sap of these plants. One known component of poison ivy, poison oak, and poison sap is urushiol, a mixture of phenolic compounds with long (15-17 carbons) hydrocarbon side chains (see, for example, Figure 1). The side chain may be saturated or unsaturated with 1-3 double bonds (Dawson, *Recent Chemical Progress* 15:39, 1954; Dawson, *Transac. NY Acad. Sci.* 18:427, 1956). Urushiol produced by poison oak plants is comprised primarily of compounds with 17-carbon side chains; that produced by poison ivy and poison sumac plants is comprised primarily of compounds with 15-carbon side chains.

As is known, the urushiol-containing sap of each of these poison plants elicits a dramatic local immune response when contacted with skin, typically resulting in a characteristic rash. The present invention demonstrates that this sap is also capable of stimulating a response in a host that results in the disappearance of skin lesions (e.g., warts) to which the sap is applied. Preferred sensitizing agents for use in accordance with the present invention, therefore, contain a sufficient collection of sap components to produce a substantial reduction in a skin lesion when applied to that lesion in a subject's skin.

Poison oak, poison ivy, and poison sumac are classified into either the *Rhus* or the *Toxicodendron* genus within the family *Anacardiaceae.* Urushiols are found in a

number of plants in addition to poison ivy, poison oak, and poison sumac. Among these are other members of the family *Anacardiaceae* including the cashew genus (*Anacardium*) and the mango genus (*Mangifera*). Contact with these plants elicits a dermatitis similar to that occurring after exposure to poison ivy, oak, or sumac in sensitive individuals. Cross sensitivity to plants of these various families is well known. Those skilled in the art will know or be able to determine whether a given plant falls within the family *Anacardiaceae*. References such as Cronquist, A.J. *An integrated system of classification of flowering plants*. Columbia University Press, New York, 1981; Reveal, J.L. *Indices nominum supragenericorum plantarum vascularium* (http://matrix.nal.usda.gov:8080/star/supragenericname.html),1995 and onward and Takhtajan, A.L., *Diversity and classification of flowering plants*. Columbia University Press, New York, 1997 contain information relevant in this regard.

Without wishing to be bound by any particular theory, we propose that the agent responsible for inducing the poison plant immune response (i.e., the urushiol) is also likely to be the agent responsible for inducing the reaction that results in skin lesion cure. Accordingly, certain preferred embodiments of the invention include compositions comprising one or more urushiols. Given the potency of most urushiols, large amounts are not required to induce the rash response. For example, some individuals respond to molecular traces of urushiol (≤2 μg), and 80-90% of adult Americans respond to ≤50 μg of purified material (Epstein et al., *Arch. Dermatol.* 109:356, 1974). It is likely that similar levels will be sufficient to induce the inventive response as well.

Again, not being bound by theory, it is believed that upon penetrating the epidermal layer of the skin urushiols are oxidized to more reactive species, namely quinones (Armstrong, et al., op cit.). The change is conversion of the two -OH groups to =O groups. The quinone form is able to bind to proteins and thus may be the form that actually elicits the immune response. Therefore biologically active derivatives and analogs of urushiols are within the scope of the invention. As used herein the terms "urushiol" and "urushiols" are intended to encompass biologically active

analogs and derivatives of urushiol. As discussed herein, one property of such biologically active compounds is the ability to elicit a contact dermatitis in sensitive individuals.

In particularly preferred embodiments of the present invention, the sensitizing agent comprises a compound that is naturally found in the sap of poison ivy, poison oak or poison sumac. In certain embodiments the compound is provided as an extract of poison ivy, poison oak, or poison sumac. In general, extraction, as the term is used pharmaceutically, entails separation of the medicinally active components of plant or animal tissue from the inactive components using selective solvents in standard extraction procedures. Such procedures are described, for example, in Nairn, J.G. in *Remington's Pharmaceutical Sciences*, 18th ed., 1990 and in the United States Pharmacopeia - National Formulary, (e.g., U.S.P. XXII/NF XVII, U.S. Pharmacopeial Convention, Inc., 1990) which also provides standards for extracts. The contents of these two works are incorporated herein by reference. Preparation of extracts typically involves placing the solid ingredients, e.g., plant tissues, in a closed container with a solvent and allowing the mixture to stand for a variable period of time to allow soluble matter to dissolve. The mixture may be mixed or agitated while standing. Alternatively, or in addition to the process described above, a solvent can be allowed to percolate through a compacted mass of raw material and the percolate collected. The solid material can be compressed and the expressed fluid added to the percolate. Following collection of the liquid, the active constituents may be concentrated by evaporation of much of the solvent. In some instances heat is used in the preparation of extracts although this is generally to be avoided. Typical solvents include water and alcohol, e.g., ethanol.

In developing an appropriate protocol for the preparation of an extract it is frequently important to provide a means of testing the extract to determine whether preparation procedures have retained any known or suspected active ingredient(s) and/or whether the activity of those ingredients has been altered. Tests are useful, in addition, to standardize extract preparation so that uniform batches of extract can be

produced from raw materials that may vary in terms of their concentration of active ingredient(s) or the ease with which they may be extracted.

In general the selection of an appropriate test will depend upon the nature of the presumed active ingredient(s). In some instances a biological assay of activity may be used. In other instances, or in combination with a biological assay, spectra of various types may be obtained, e.g., infrared (IR) or ultraviolet (UV) spectra. Spectroscopic methods suitable for analysis of extracts are described, for example, in Jerry Workman (Editor), Art W. Springsteen, *Applied Spectroscopy : A Compact Reference for Practitioners*, Academic Press, New York, 1998, which is herein incorporated by reference. Other techniques suitable for the analysis of crude and purified extracts at various stages of preparation include thin layer chromatography, gas chromatography and/or mass spectrometry. These techniques are described in *Practical Thin-Layer Chromatography : A Multidisciplinary Approach*, Bernard Fried and Joseph Sherma (Editors), CRC Press, Boca Ratan, 1996 *GC/MS : A Practical User's Guide*, Marvin C. McMaster and Christopher McMaster, Wiley and Sons, New York, 1998. The contents of these works are incorporated herein by reference.

In some cases, it may be desirable to test the particular individual for sensitivity to poison plant sap, and/or to one or more isolated urushiols, prior to determining the amount of urushiol, or urushiol-containing composition (e.g., sap or other plant extract, synthetic composition, etc.) to be delivered to a skin lesion on the individual's body.

Alternative preferred sensitizing agents for use in the practice of the present invention include, for example, polynucleotides containing one or more unmethylated CpG motifs, as described above. Such polynucleotides have been demonstrated to induce Th1 type cellular immune responses (see, for example, published PCT applications WO 98/16247 and WO 98/18810, incorporated herein by reference) when injected into mice, and are likely to be useful in accordance with the present invention.

Sensitizing agents may be formulated in any fashion suitable to local administration to a skin lesion such as a wart. It is preferred that the agent be formulated in a way that minimizes the risk of its unintended distribution elsewhere in the body. For example, the sensitizing agent may be formulated for short-duration contact with the lesion and/or may be provided in combination with a neutralizing agent that substantially reduces the risk of undesirable spread of reaction. The particular neutralizing agent selected will depend on the character of the sensitizing agent being employed. In certain preferred embodiments of the invention, the neutralizing agent is a specific inhibitor of the sensitizing agent. In other preferred embodiments, the neutralizing agent is a general actor, for example that is capable of removing the sensitizing agent from its site of application (e.g., the neutralizing agent is a soap or a detergent).

To give but a few examples of neutralizing agents, where a urushiol is employed as the sensitizing agent, a detergent, or other agent capable of removing the urushiol, can be an effective neutralizing agent. It is important when utilizing a detergent to control application such that solubilized urushiol is not spread to other parts of the body. Preferred detergents for use as urushiol neutralizing agents include, for example, common soap.

Where an unmethylated-CpG-containing polynucleotide is employed as a sensitizing agent, preferred neutralizing agents include, for example, inhibitors of NFκB activation (e.g., PDTC, gliotoxin, etc.), which have been shown to block the immunostimulatory effects of such polynucleotides (see, for example, published PCT application WO 98/18810). A detergent or other agent capable of removing the polynucleotide from its site of application may alternatively or additionally be employed.

The sensitizing agent of the present invention may be formulated for delivery by any of a variety of applicators. Figures 2-4 present certain embodiments of appropriate applicators for use in accordance with the present invention. These depicted embodiments should be understood to be merely exemplary; those of

ordinary skill in the art can readily appreciate that any of a variety of different delivery means is suitable for the practice of the present invention, so long as the sensitizing agent becomes applied to the area of the skin lesion in sufficient amount and for a sufficient period of time that an appropriate local immune reaction is induced.

Figure 2 presents one possible "pen" applicator embodiment according to the present invention. As depicted, the applicator **100** includes a first end **110** comprising a pad reservoir **120** impregnated with a sensitizing agent, an elongated handle member **130**, and a second end **140**. The applicator also includes a removable cap **150** dimensioned to cover the first end of the applicator when the device is not in use.

In the particular embodiment depicted in Figure 2, the pad reservoir **120** protrudes from the first end **110** of the applicator **100** in a manner analogous to the point on a felt-tipped pen. Such a configuration can be convenient for the purposes of controlling administration of the sensitizing agent to a defined area of skin, but is not required. Those of ordinary skill in the art will readily appreciate that alternative configurations such as, for example, a rounded mound or even a substantially flat surface constituting substantially the entire surface of the first end **110**.

The elongated handle member **130** shown in Figure 2 is presented as a substantially straight, cylindrical member. Those of ordinary skill in the art will readily appreciate that alternative constructions are equally suitable and may be preferable in certain cases. For example, the member **130** may be angled with respect to the first end **110**. Alternatively or additionally, the member **130** may be formed for comfortable grasping by a hand. For example, the member **130** may have one or more areas adapted to accept one or more fingers wrapped around the member **130**.

The type of applicator depicted in Figure 2 may include a second pad reservoir at its second end, impregnated with a neutralizing agent. Such an applicator would be used by first applying the sensitizing agent with the first end of the applicator, then waiting an appropriate period of time and reversing the applicator so that the

neutralizing agent may be applied from the second end. In an alternative embodiment of an inventive pen applicator, individual sensitizing agent and neutralizing agent applicators are provided separately. Such applicators may be provided together, for example in a kit, but would be used individually, in series.

Figure 3 presents an alternative embodiment of an applicator of the present invention. The applicator **100** shown in this Figure is a "bulb-type" applicator comprising a first end **110** from which sensitizing agent is delivered, an elongated reservoir chamber **160** in which sensitizing agent is disposed, and a compression bulb **170** or other means for exerting expulsive force through the chamber **160** so that sensitizing agent is delivered from the first end **110**.

In some embodiments of the invention, the bulb-type applicator is provided already loaded with sensitizing agent. In such embodiments, the first end **110** of the applicator is preferably capped or plugged so as to prevent leakage of the sensitizing agent prior to delivery. For example, a cap may be provided that fits securely over the first end **110**. Such a cap could be a single-use (i.e., designed so as not to be replaceable), or could be replaceable (for example, a screw-on). Those of ordinary skill in the art will appreciate that any of a variety of different closure means could be employed using readily-available technologies.

In one particular single-use embodiment of a bulb-type applicator as depicted in Figure 3, after the applicator is loaded with sensitizing agent, the first end **110** of the applicator is placed in softened wax so that an airtight wax cap **180** is formed that prevents leakage of the sensitizing agent from the applicator. When the sensitizing agent is to be applied to a skin lesion, the plugged first end **110** is simply removed from the applicator (e.g., by cutting) so that a new, open first end is created. Depression of the bulb **170** then ejects the sensitizing agent through the new opening.

Figure 4 presents yet another applicator embodiment for use in accordance with the present invention. The applicator depicted in Figure 4 is of the "dermal patch" type. Dermal patches are well known in art (to give but a few examples, see

U.S. Patent No. 5,147,339; U.S. Patent No. 4,666,441; each of which is incorporated herein by reference). Any available patch is suitable for the practice of the present invention. Generally, a patch should include a reservoir **190** in which the sensitizing agent is loaded, and a means of affixing the patch to the skin in the area of the lesion, so that the reservoir is sufficiently well positioned over the lesion that the sensitizing agent contacts the wart and/or neighboring tissue. Any available affixing means may be employed; preferred affixing means include adhesive bandages. As depicted in Figure 4, the affixing means **200** comprises adhesive tabs extending from the reservoir **190** so that the patch, once applied, is secured to the skin.

Preferred patches may include means of enhancing transdermal delivery of the sensitizing agent. A variety of such means is known in the art. To give but a few examples, known transdermal delivery patches often include an added substance that assists the penetration of the active ingredient (i.e., the sensitizing agent in the present invention) through the skin. Often, this substance is termed an "enhancer". Many such enhancers are known in the art (to give but one example, see U.S. Patent No. 5,023,252, incorporated herein by reference), some of which are water soluble, and some of which are water insoluble. In some cases, the enhancer also acts as an encapsulating means, that assists the transport of the active ingredient into the skin (e.g., liposome enhancers-- see, for example, U.S. Patent No. 5.718,914, incorporated herein by reference). Any known enhancer that is compatible with the selected sensitizing agent is useful in accordance with the present invention.

Other known techniques for enhancing delivery by transdermal delivery from patches include, for example, providing a heat generating means (see, for example, U.S. Patent No. 5,465,713; U.S. Patent No. 5,718,914, each of which is incorporated herein by reference).

One advantage of applying the sensitizing agent of the present invention by means of a dermal patch is that the occlusion caused by covering the lesion with the patch may itself enhance the resolution of the lesion (see, for example, U.S. Patent No. 5,476,664). An additional advantage is that the patch covers the lesion during the period of time that it is contacted with the sensitizing agent, and therefore reduces the

likelihood that sensitizing agent will inadvertently be contacted with other areas of the individual's body. Yet another advantage is that a neutralizing patch (i.e., a patch containing neutralizing agent) can readily be applied to replace the original patch when it is desired that the immune stimulation provided by contact with the original patch be terminated.

As mentioned above, Figures 2-4 represent only a few of the possible preferred applicators for use in accordance with the present invention. Sensitizing agents may be applied by any available means including, for example, by stick-type applicators (e.g., cotton-tipped swabs), by direct contact with a source of sensitizing agent (e.g., with the broken stem of a poison ivy, poison oak, or poison sumac plant), by hand (preferably a protected hand, e.g., covered with a glove), etc. Bottles, tubes, boxes, or other containers of sensitizing (and/or neutralizing agent) may be provided to the individual performing the application, and that individual may select the particular mode by which agent will be applied to lesion. Those of ordinary skill in the art will readily appreciate the wide range of applicating means that can be employed in the practice of the present invention.

In general, applicators for use in accordance with the present invention may be designed for single-use or multiple-use applications. Dermal patch-type applicators will typically be single-use; pen or bulb applicators may be either single-use or multiple-use. Where a multiple-use applicator is desired, it may be useful to utilize materials and arrangements that allow for sterilization (e.g., by autoclaving, contacting with alcohol, or other means) between applications of surfaces that contact skin. Alternatively, the applicator may be designed to release or apply sensitizing agent on a designated surface (e.g., a pad to subsequently be applied to the lesion, or directly to the lesion), so that the applicator itself does not actually contact skin.

It may also generally be desirable to use applicators in combination with one or more barrier means that limit the spread of the sensitizing agent (and/or neutralizing agent) from the immediate area to which it is applied. For example, where a pen-type or bulb-type applicator is utilized, it may be desirable to first apply

a protective barrier (e.g., an adhesive disc whose opening is positioned over the lesion) so that the applied sensitizing agent (and/or neutralizing agent) is restricted to the immediate vicinity of the lesion.

Alternatively or additionally, the ability of the sensitizing agent (and/or neutralizing agent) to spread from its site of application to other areas of the body can be limited by adjusting parameters of the formulation itself, such as viscosity and volatility. In general, spreading is more controllable with more viscous preparations. Also, the more rapidly a preparation volatilizes, the less likely it is to spread while in liquid form. Of course, if the sensitizing agent (and/or neutralizing agent) can still be transferred by contact even after volatilization of other components of the formulation, other precautionary measures may desirably be taken as well.

Examples

Example 1

Treating Warts with Poison Ivy Sap

Four patients, ranging in age from 4 to 47 years and suffering from between 1 and 4 warts, were enrolled in the present study. Each wart had been present for between 1 and 12 years, and three of the four patients had been treated unsuccessfully on 1-4 occasions. In total, 13 warts were treated.

A small amount of white sap from a poison ivy stem was placed on each wart and covered for 2-6 hours with a gauze pad. Subsequently, the sap was carefully washed away. Each wart turned black within 20-30 minutes after the treatment, presumably due to oxidation of the sap. As shown below in Table 1, 11 of the 13 warts became necrotic over the subsequent 3-6 weeks. Eventually, newly-formed, non-infected skin replaced the wart in all of these cases. None of these warts relapsed in the following 6-8 months.

Two of the treated warts did not become necrotic and persisted in the patients' skin, but have been shown to decrease in size. Each of these warts was significantly

larger than the warts that were resolved fully; it was not determined whether continued administration of plant sap would result in wart cure.

Table 1

PATIENT NUMBER	AGE	NO. OF WARTS	LOCATION OF WARTS (TYPE)	APPROX. SIZE OF WARTS	PRIOR TREATMENT	TOTAL/PARTIAL CURE
1	11 years	1	foot (plantar)	1 cm	multiple	0/1
2	8 years	5	hands (both) (common)	3 - 4 mm	multiple	5/0
3	12 years	2	hands + arms (common)	3 - 4 mm	none	4/0
4	47 years	4	hands (common)	3 mm - 0.5 cm	multiple	2/1

The only side effect observed was distant location contact dermatitis secondary to poison ivy suffered by two of the patients, probably due to a failure to completely wash away poison ivy sap from the treatment sites and/or due to contact of the treated area with other body parts. Such contact transmission might have been avoided or minimized had the treatment area been covered, e.g. with an adhesive bandage, for a longer period of time during treatment.

Example 2

Failure to Treat Warts with Poison Ivy Oil

Prior to the work described in Example 1, we attempted to treat warts by contacting them with the oil present on poison ivy leaves. In particular, we plucked four leaves from a wild poison ivy plant, ground the leaves in a mortar and pestle, and rubbed the ground leaves on the surface of a wart. Excess leaf material was wiped from the site of application, and an adhesive bandage was applied. After 6 hours, the

site was washed thoroughly with ordinary soap and warm water. No wart remission was observed. Of course, it is possible that the explanation for the lack of effectiveness of poison ivy oil as compared with poison ivy sap is that an insufficient amount of oil was employed in the present study. Under somewhat different circumstances, oil may act effectively as a sensitizing agent. Nonetheless, sap, or sap components is presently preferred for use in accordance with the invention.

Example 3

Preparation and Analysis of an Ethanolic Extract of Poison Ivy Leaves

Introduction

This Example summarizes a procedure that has been developed to extract poison ivy leaves and the analytical methods that have been developed to examine the resultant extracts. The focus of the analytical method development program has been to first identify and then quantify the level of urushiol, as well as other components that have not been identified, in the extract, and to follow those levels during storage of the extract as a measure of chemical stability. In this Example, the terms urushiol and urushiols may be used interchangeably, recognizing that, as discussed above, they are a family of related compounds comprised of catechols derivatized with long-chain polyunsaturated alkyl groups.

Extraction Method

Briefly, poison ivy leaves, stored frozen since the time of fresh harvest, are suspended in 95% denatured ethanol under refrigerated conditions (approximately 4°C) in a tightly closed jar flushed with nitrogen to avoid introduction of oxygen. The ratio used is 250 grams of leaves in 2 L of ethanol. The suspension is left under refrigerated conditions without agitation for four days, following which the extract is filtered through a nylon cloth into a 3L flask in order to remove solids. The extract is concentrated under reduced pressure by rotary evaporation to approximately 250 mL. The final concentrate is stored in sealed bottles, under nitrogen, in aliquots of approximately 50 mL. The storage temperature is maintained at no higher than –20°C.

Analytical Methods

The extract has been characterized by several analytical methods well known in the art of analytical chemistry, including infrared spectroscopy (IR), ultraviolet spectroscopy (UV), thin-layer chromatography (TLC), and column chromatography using an LH- sephadex resin. Data obtained by these analytical methods are utilized to compare extraction consistency as well as chemical stability of extracts during storage. Data obtained using these methods are both qualitative and quantitative in nature. The urushiol fraction has been positively identified and quantified. The relative levels of other, unidentified, components are followed by their chromatographic and spectroscopic behavior.

IR and UV spectra of the concentrated extract prepared as described above were obtained using standard techniques. In the concentrated extract, it appears that components other than urushiol dominate the spectroscopic profile in both the IR and UV spectra, as may be expected. IR and UV spectra obtained by analysis of the unfractionated, concentrated extract are shown in Figures 6 and 7 respectively. Figure 9 shows the UV spectrum of the urushiol-containing fraction obtained by purification of unfractionated, concentrated extract using LH-sephadex. It is not possible at this time to unambiguously assign any IR or UV peak maxima to the presence of urushiol itself. For example, by comparison of Figures 7 and 9, the UV maxima observed for purified urushiol (Figure 9) are not distinguished in the UV spectrum of the un-fractionated extract (Figure 7). These methods have, however, also been utilized to analyze extract components purified by column chromatography, as described below.

Thin-layer chromatography provided definite evidence of the presence of urushiol in the extract. In this method, silica gel 60 plates, to which the concentrated extract had been applied, were developed with methylene chloride. Several components (yellow to green in color) were visible on the developed plate. The developed plate was sprayed with a 1% solution of ferric chloride in methanol, resulting in the reduction of ferric ion to metallic iron by the phenolic urushiols, giving rise to a dark spot on the plate where urushiol is present (Figure 8). This method may also be utilized to provide semi-quantitative evidence for the amount of urushiol in the extract.

Analysis of the extract by column chromatography using an LH-sephadex resin has also been performed. In this method, a sample of extract was dried to an oil, dissolved in methylene chloride, and applied to a column containing approximately 5 g of LH-sephadex. The column effluent was monitored by UV at 274 nm (corresponding roughly to the λ_{max} for urushiol). The column was then eluted with stepwise gradients of methylene chloride, 2% methanol in methylene chloride, and then 16% methanol in methylene chloride. Components corresponding to urushiols eluted primarily in the 2% methanol gradient. UV-absorbing material in the 2% methanol gradient was recovered and analyzed by UV and TLC to confirm the identification of the urushiols (Figures 9 and 10). In Figure 10 (thin-layer chromatogram after ferric chloride staining), lanes 1 and 8 are controls consisting of unfractionated extract. Each pair of lanes 2 - 7 represents samples from fractions of the 2% and 16% methanol gradients from three different chromatographic runs. Thus lanes 2, 4, and 6 represent fractions from the 2% methanol gradient from three separate runs while lanes 3, 5, and 7 represent fractions from the 16% methanol gradient from the same runs, i.e., lanes 2 and 3, 4 and 5, and 6 and 7 represent samples obtained from the same three runs. The only components evident in lanes 2, 4, and 6 clearly correspond to urushiol, by comparison with Figure 8. Lastly, determination of the urushiol content in this fraction, by UV spectroscopy, permits the calculation of the urushiol content of the extract by factoring in sample volume. The catechol *m*-hydroxy phenol was utilized to calibrate the UV spectra for urushiol, based on the assumption that their molar-extinction coefficients are comparable.

Conclusions

The extraction procedure that has been developed is simple, convenient, and reproducible. The analytical methods which have been developed to analyze these extracts provide both qualitative and quantitative data for components of the extracts. Further, the presence of the known urushiol fraction has been demonstrated and quantified by a combination of column chromatography and ultraviolet spectroscopy. Lastly, the methods described above will also permit the analysis of the stability of the extracts during storage.

Example 4

Delivery of a Sensitizing Agent from a Bulb-type Applicator

The bulb **170** of a bulb type applicator substantially as depicted in Figure 3 is depressed slightly prior to insertion of the applicator first end **110** into a composition comprising an extract of poison ivy. The bulb **170** is released so that a pre-determined amount of extract is loaded into the chamber **160**. The first end **110** is subsequently placed in softened, high-melting-point wax so that an airtight seal is formed. Optionally, the applicator is then packaged for shipment to the site of application.

The poison ivy extract is subsequently delivered from the applicator to a subject suffering from a skin lesion such as a wart. First, an adhesive protective disk, such as that depicted in Figure 5, is applied to the subject, so that the open center of the disc is positioned over the lesion and the lesion is otherwise surrounded by disk. A variety of protective disks are commercially available. The size of the disk is selected to be appropriate to the size of the lesion being treated.

Next, the plugged first end **110** of the applicator is removed with scissors, so that a new first end is created through which ivy extract can be delivered. The new first end is then positioned over the exposed lesion in the center of the disk, and the bulb **170** is depressed so that ivy extract is expelled through the new first end of the applicator and onto the lesion. Optionally, the lesion is subsequently covered with an adhesive bandage.

After a pre-determined period of time has passed, any adhesive bandage is removed and the lesion is washed carefully to remove ivy extract. The protective disk is then also removed, and the lesion is washed again.

Other Embodiments

Those of ordinary skill in the art will appreciate that the foregoing has been a description of certain preferred embodiments of the present invention. Various changes, substitutions, and modifications, in the described embodiments can be made

without departing from the spirit or scope of the present invention, as encompassed within the following claims.

We claim:

Claims

1. A composition for treating dermal disorders, the composition comprising:

a sensitizing agent characterized by an ability to induce a local immune response when applied to a skin lesion; and

a delivery means for applying the sensitizing agent to skin.

2. The composition of claim 1 wherein the skin lesion is selected from the group consisting of nasal polyps, melanomas, herpes sores, basal cell carcinomas, and warts.

3. The composition of claim 1 wherein the skin lesion comprises a viral infection of the skin.

4. The composition of claim 1 wherein the skin lesion comprises at least one wart.

5. The composition of claim 4 wherein the at least one wart is selected from the group consisting of at least one common wart (verruca vulgaris), at least one plantar wart, at least one palmar wart, at least one planar wart (verruca plana), at least one mosaic wart (condyloma accuminatum), at least one venereal wart, and combinations thereof.

6. The composition of claim 5 wherein the at least one wart is at least one plantar wart.

7. The composition of claim 5 wherein the at least one wart is at least one common wart.

8. The composition of claim 1 further comprising a neutralizer that substantially blocks further action by the sensitizing agent, the neutralizer being provided separate

from the sensitizing agent for application to the skin lesion subsequent to application of the sensitizing agent.

9. The composition of claim 1 wherein the sensitizing agent comprises a compound that is naturally produced by a plant selected from the group consisting of poison ivy, poison oak, and poison sumac.

10. The composition of claim 1 wherein the sensitizing agent comprises a compound that is naturally produced by a plant selected from the group consisting of members of the family *Anacardiaceae*.

11. The composition of claim 9 or claim 10 wherein the sensitizing agent comprises one or more components of plant sap.

12. The composition of claim 9 or claim 10 wherein the sensitizing agent comprises an urushiol.

13. The composition of claim 12 wherein the urushiol is selected from the group consisting of poison oak urushiol, poison ivy urushiol, and poison sumac urushiol.

14. The composition of claim 1 wherein the sensitizing agent comprises an extract derived from a plant selected from the group consisting of poison oak, poison ivy, poison sumac.

15. The composition of claim 1 wherein the sensitizing agent comprises an extract derived from a plant selected from the group consisting of members of the family *Anacardiaceae*.

16. The composition of claim 1 wherein the sensitizing agent comprises a polynucleotide containing an unmethylated CpG motif.

17. The composition of claim 16 wherein the polynucleotide contains a consensus motif represented by the formula 5'-$X_1X_2CGX_3X_4$-3' and:

(i) C and G are unmethylated

(ii) X_1, X_2, X_3, and X_4 are nucleotides;

(iii) a GCG trinucleotide is not present at or near the 5' or 3' terminus of the polynucleotide; and

(iv) The polynucleotide has a length between 2 and 100 nt or bp.

18. The composition of claim 16 wherein the polynucleotide contains a consensus motif represented by the formula 5'-$X_1X_2CGX_3X_4$-3' and:

(i) X_2 is adenine, guanine, or thymine;

(ii) X_3 is cytosine or thymine; and

(iii) $X_1 + X_4$ together comprise between about 0 and 26 nt or bp.

19. The composition of any one of claims 16-18 wherein one or more nucleotide residue within the polynucleotide is a stabilized residue.

20. The composition of claim 19 wherein the stabilized residue comprises a phosphorothioate residue.

21. The composition of any one of claims 16-18 wherein the polynucleotide has a length within the range of 8-40 nt or bp.

22. The composition of claim 1 wherein the sensitizing agent is selected from the group consisting of lipopolysaccharide, lipid A, heat-killed bacteria, pertussis virus epitopes, cytokines, cholera toxin, proholeragenoid, cholera toxin B subunit, and fungal polysaccharides.

23. A composition comprising:

a sensitizing agent selected from the group consisting of poison oak, poison ivy, poison sumac, and extracts thereof; and

a delivery means associated with the agent for contacting the agent with a skin lesion.

24. A composition comprising:

a sensitizing agent selected from the group consisting of plants that are members of the family *Anacardiaceae*, and extracts thereof; and

a delivery means associated with the agent for contacting the agent with a skin lesion.

25. The composition of claim 23 wherein the delivery means is arranged and constructed for application of the agent to skin surface.

26. The composition of claim 24 wherein the delivery means is arranged and constructed for application of the agent to skin surface.

27. The composition of any of claims 1, 25, or 26 wherein the delivery means comprises an applicator having a first end including a reservoir in which the sensitizing agent is located, and a handle constructed and arranged for ease of grasping and manipulating.

28. The composition of claim 27 wherein the delivery means is constructed substantially as a pen applicator.

29. The composition of claim 27 wherein the reservoir comprises an impregnated pad.

30. The composition of claim 29 wherein the pad protrudes from the surface of the first end of the handle.

31. The composition of claim 29 wherein the pad substantially covers the first end of the handle.

32. The composition of claim 28, further comprising a cap adapted to fit securely over the first end so as to prevent loss of the sensitizing agent from the delivery means.

33. The composition of claim 27 wherein the delivery means comprises a cotton-tipped swab impregnated with sensitizing agent.

34. The composition of any of claims 1, 25, or 26 wherein the delivery means comprises:

a hollow elongated member in which the sensitizing agent is disposed; and

a means of exerting pressure through the hollow elongated member so as to expel the sensitizing agent therefrom.

35. The composition of claim 34 wherein the means of exerting pressure comprises a compressible bulb.

36. The composition of any of claims 1, 25, or 26 wherein the delivery means comprises a dermal patch and the mode of delivery involves contact with skin.

37. The composition of claim 27, further comprising a neutralizer.

38. The composition of claim 37, wherein the neutralizer is provided in a manner physically separate from the sensitizing agent.

39. The composition of claim 27, further comprising:

a second end including a second reservoir in which a neutralizer is located that, when applied to a skin lesion to which a sensitizing agent has previously been applied, substantially blocks further immune stimulation as a result of contact with the sensitizing agent.

40. A method for treating a skin lesion, the method comprising steps of:

identifying an individual suffering from one or more skin lesions;

providing a sensitizing agent capable of eliciting a local immune response in skin of the individual; and

contacting the one or more skin lesions with the sensitizing agent.

41. The method of claim 40 wherein the step of contacting comprises contacting a surface of the one or more skin lesions with the sensitizing agent.

42. The method of claim 40 wherein the step of identifying comprises identifying an individual suffering from one or more viral skin lesions.

43. The method of claim 40 wherein the step of identifying comprises identifying an individual suffering from one or more warts.

44. The method of claim 43 wherein the one or more warts are selected from the group consisting of common warts, plantar warts, palmar warts, planar warts, mosaic warts, venereal warts, and combinations thereof.

45. The method of claim 40 wherein the step of contacting comprises applying the sensitizing agent onto the surface of the skin containing the lesion.

46. The method of claim 45 wherein the sensitizing agent comprises one or more compounds naturally occurring in sap of a plant selected from the group consisting of poison ivy, poison oak, and poison sumac.

47. The method of claim 45 wherein the sensitizing agent comprises an extract derived from a plant selected from the group consisting of poison ivy, poison oak, and poison sumac.

48. The method of claim 45 wherein the sensitizing agent comprises one or more compounds naturally occurring in a plant selected from the group consisting of members of the family *Anacardiaceae*.

49. The method of claim 46 or claim 48 wherein the sensitizing agent comprises an urushiol.

50. The method of claim 45 wherein the sensitizing agent comprises a polynucleotide containing an unmethylated CpG motif.

51. The method of claim 50 wherein the polynucleotide contains a consensus motif represented by the formula 5'-$X_1X_2CGX_3X_4$-3' and:

(i) C and G are unmethylated

(ii) X_1, X_2, X_3, and X_4 are nucleotides;

(iii) a GCG trinucleotide is not present at or near the 5' or 3' terminus of the polynucleotide; and

(iv) The polynucleotide has a length between 2 and 100 nt or bp.

52. The method of claim 50 wherein the polynucleotide contains a consensus motif represented by the formula 5'-$X_1X_2CGX_3X_4$-3' and:

(i) X_2 is adenine, guanine, or thymine;

(ii) X_3 is cytosine or thymine; and

(iii) $X_1 + X_4$ together comprise between about 0 and 26 nt or bp.

53. The composition of any one of claims 50-52 wherein one or more nucleotide residue within the polynucleotide is a stabilized residue.

54. The method of claim 53 wherein the stabilized residue comprises a phosphorothioate residue.

55. The method of any one of claims 50-52 wherein the polynucleotide has a length within the range of 8-40 nt or bp.

56. The method of claim 45 wherein the sensitizing agent is selected from the group consisting of lipopolysaccharide, lipid A, heat-killed bacteria, pertussis virus

epitopes, cytokines, cholera toxin, proholeragenoid, cholera toxin B subunit, and fungal polysaccharides.

57. The method of claim 40 wherein the step of contacting comprises delivering the sensitizing agent via a delivery means.

58. The method of claim 57 wherein the delivery means is selected from the group consisting of a pen applicator, a bulb applicator, and a dermal patch.

59. The method of claim 57 wherein the delivery means comprises an applicator having a first end including a reservoir in which the sensitizing agent is located, and a handle constructed and arranged for ease of grasping and manipulating.

60. The method of claim 59 wherein the delivery means is constructed substantially as a pen applicator.

61. The method of claim 59 wherein the reservoir comprises an impregnated pad.

62. The method of claim 61 wherein the pad protrudes from the surface of the first end of the handle.

63. The method of claim 61 wherein the pad substantially covers the first end of the handle.

64. The method of claim 59, further comprising a cap adapted to fit securely over the first end so as to prevent loss of the sensitizing agent from the delivery means.

65. The method of claim 60 wherein the delivery means comprises a cotton-tipped swab impregnated with sensitizing agent.

66. The method of claim 59 wherein the delivery means comprises:

a hollow elongated member in which the sensitizing agent is disposed; and

a means of exerting pressure through the hollow elongated member so as to expel the sensitizing agent therefrom.

67. The method of claim 66 wherein the means of exerting pressure comprises a compressible bulb.

68. The method of claim 57 wherein the delivery means comprises a dermal patch including a reservoir and an affixing means.

69. The method of claim 68 wherein the reservoir comprises a matrix impregnated with sensitizing agent.

70. The method of claim 69 wherein the matrix comprises a gauze pad.

71. The method of claim 68 wherein the affixing means comprises an adhesive.

72. The method of any one of claims 68-71, wherein the sensitizing agent comprises an urushiol.

73. The method of claim 72 wherein the urushiol is selected from the group consisting of poison oak urushiol, poison ivy urushiol, and poison sumac urushiol.

74. The method of claim 40 wherein the skin lesion is selected from the group consisting of: melanomas, nasal polyps, herpes sores, and basal cell carcinomas.

75. The method of claim 40, further comprising a step, performed subsequent to the step of contacting the one or more skin lesions with a sensitizing agent, of substantially terminating induction of a local immune response by the sensitizing agent.

76. A kit comprising:

a first applicator containing a sensitizing agent characterized by an ability to induce a local immune response sufficient to reduce a skin lesion if applied to the lesion; and

a second applicator containing a neutralizing agent characterizes by an ability to substantially terminate an immune response induction when applied to a skin lesion to which a sensitizing agent has previously been applied.

77. A composition comprising:

a sensitizing agent comprising one or more components of sap of a plant selected from the group consisting of poison ivy, poison oak, and poison sumac, the one or more components being characterized by their ability, when contacted with a wart surface, to induce a host response that results in diminution of the wart; and

a delivery means for applying the agent to the wart.

78. A composition comprising:

a sensitizing agent comprising an extract derived from a plant selected from the group consisting of poison ivy, poison oak, and poison sumac, the extract being characterized by its ability, when contacted with a wart surface, to induce a host response that results in diminution of the wart; and

a delivery means for applying the agent to the wart.

79. A method of treating warts comprising:

identifying an individual suffering from one or more warts; and

applying to the surface of at least one of the warts a sensitizing agent comprising one or more components of sap of a plant selected from the group consisting of poison ivy, poison oak, and poison sumac, the one or more components being characterized by their ability, when contacted with a wart surface, to induce a host response that results in diminution of the wart.

80. A method of treating warts comprising:

identifying an individual suffering from one or more warts; and

applying to the surface of at least one of the warts a sensitizing agent comprising an extract derived from a plant selected from the group consisting of poison ivy, poison oak, and poison sumac, the extract being characterized by its ability, when contacted with a wart surface, to induce a host response that results in diminution of the wart.

81. A composition comprising:

a sensitizing agent comprising an extract derived from a plant selected from the group consisting of plants that are members of the family *Anacardiaceae*, the extract being characterized by its ability, when contacted with a wart surface, to induce a host response that results in diminution of the wart; and

a delivery means for applying the agent to the wart.

82. A method of treating warts comprising:

identifying an individual suffering from one or more warts; and

applying to the surface of at least one of the warts a sensitizing agent comprising an extract derived from a plant selected from the group of plants that are members of the family *Anacardiaceae*, the extract being characterized by its ability, when contacted with a wart surface, to induce a host response that results in diminution of the wart.

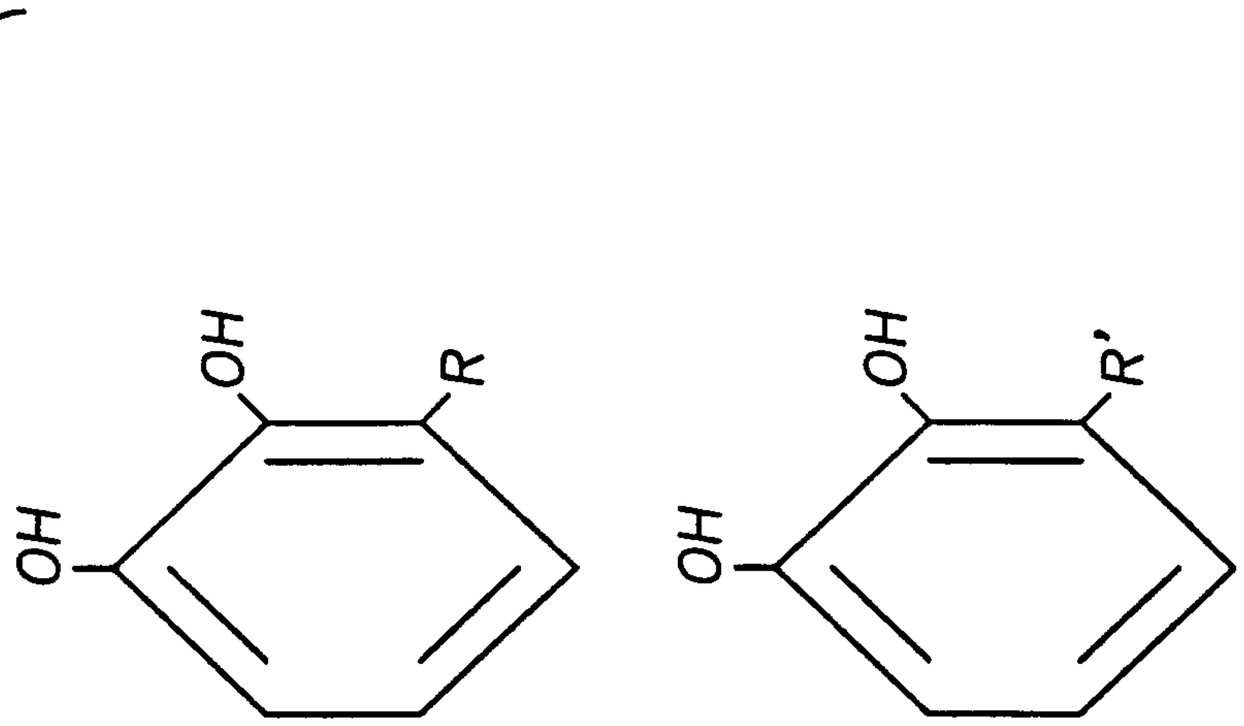


FIG. 1

PENTADECYLCATECHOL:

$R=C_{15}H_{31}, C_{15}H_{29}, C_{15}H_{27}, \& C_{15}H_{25}$

HEPTADECYLCATECHOL:

$R'=C_{17}H_{35}, C_{17}H_{33}, C_{17}H_{31}, \& C_{17}H_{29}$

FIG.2

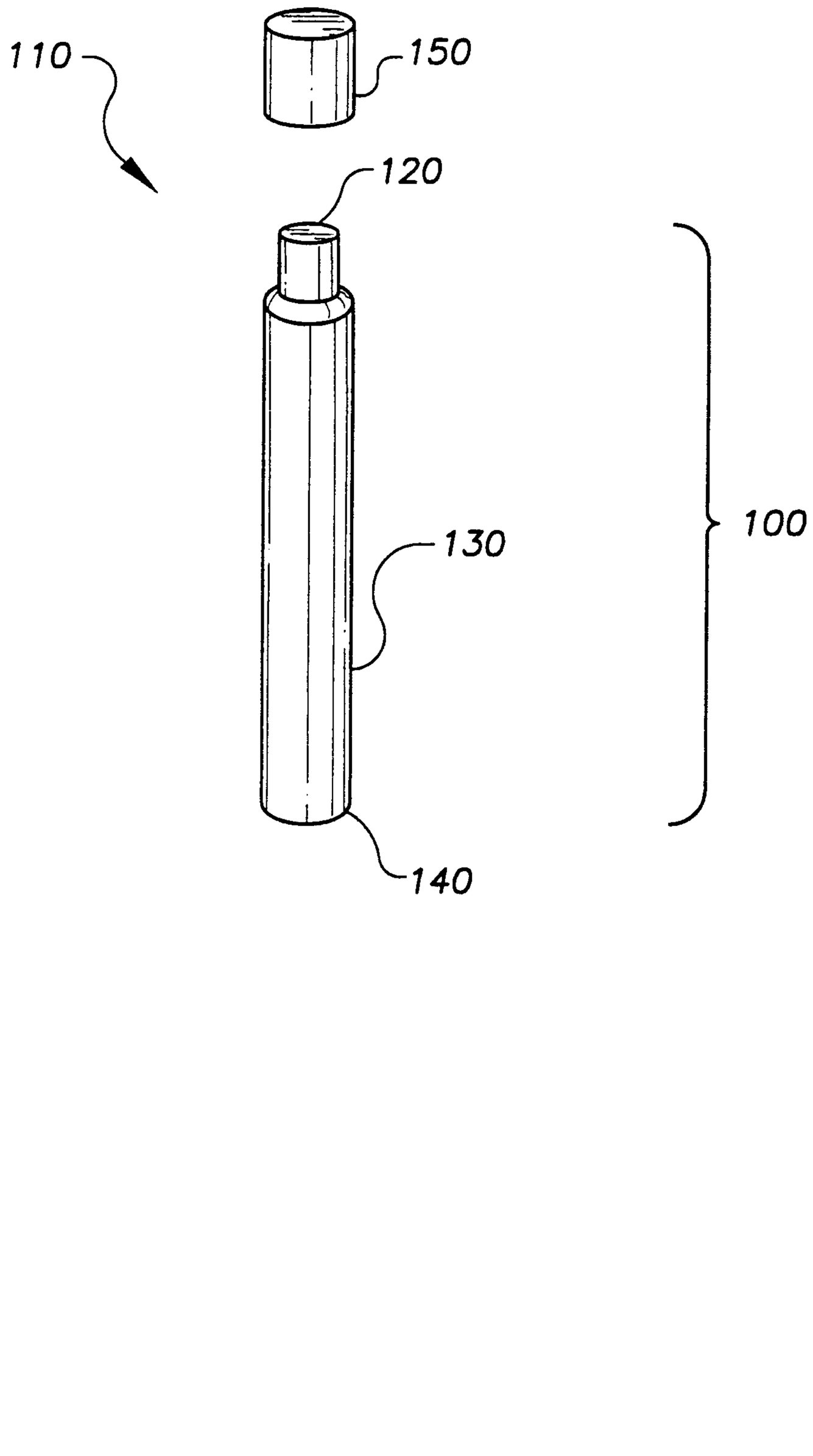


FIG.3

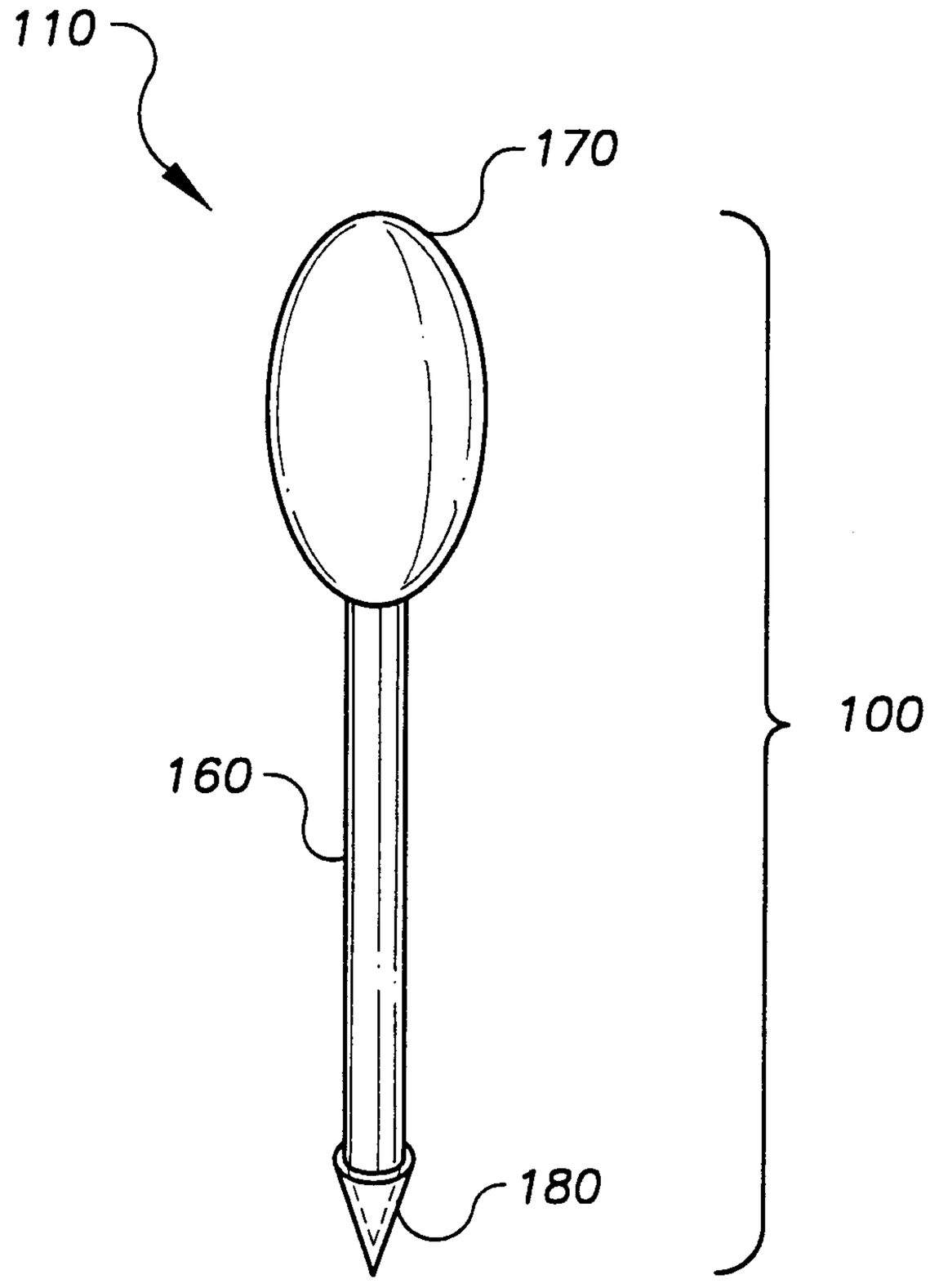


FIG.4

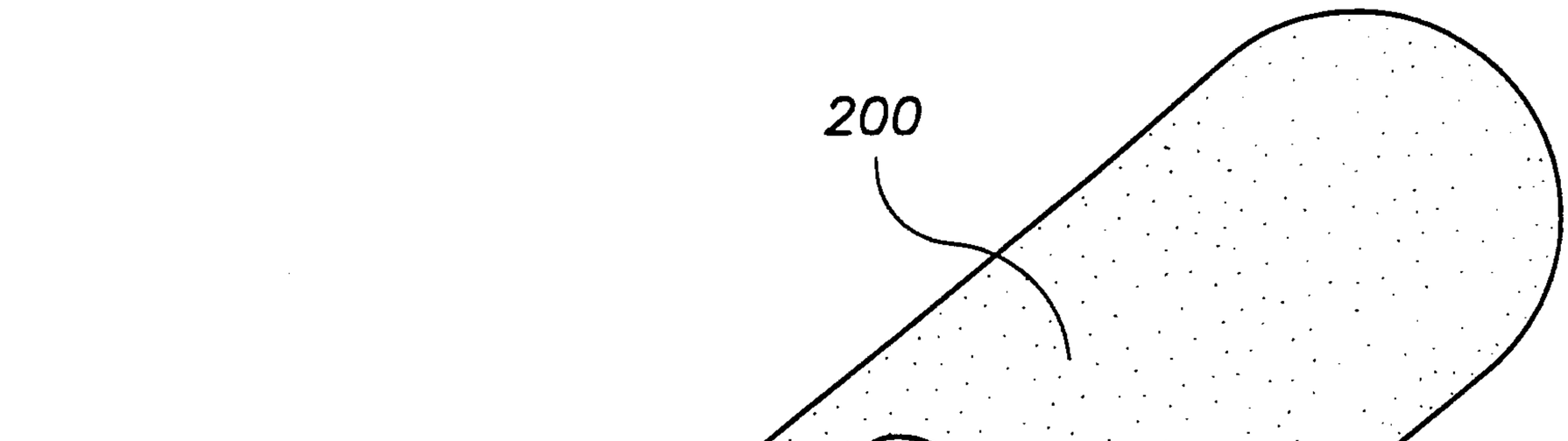
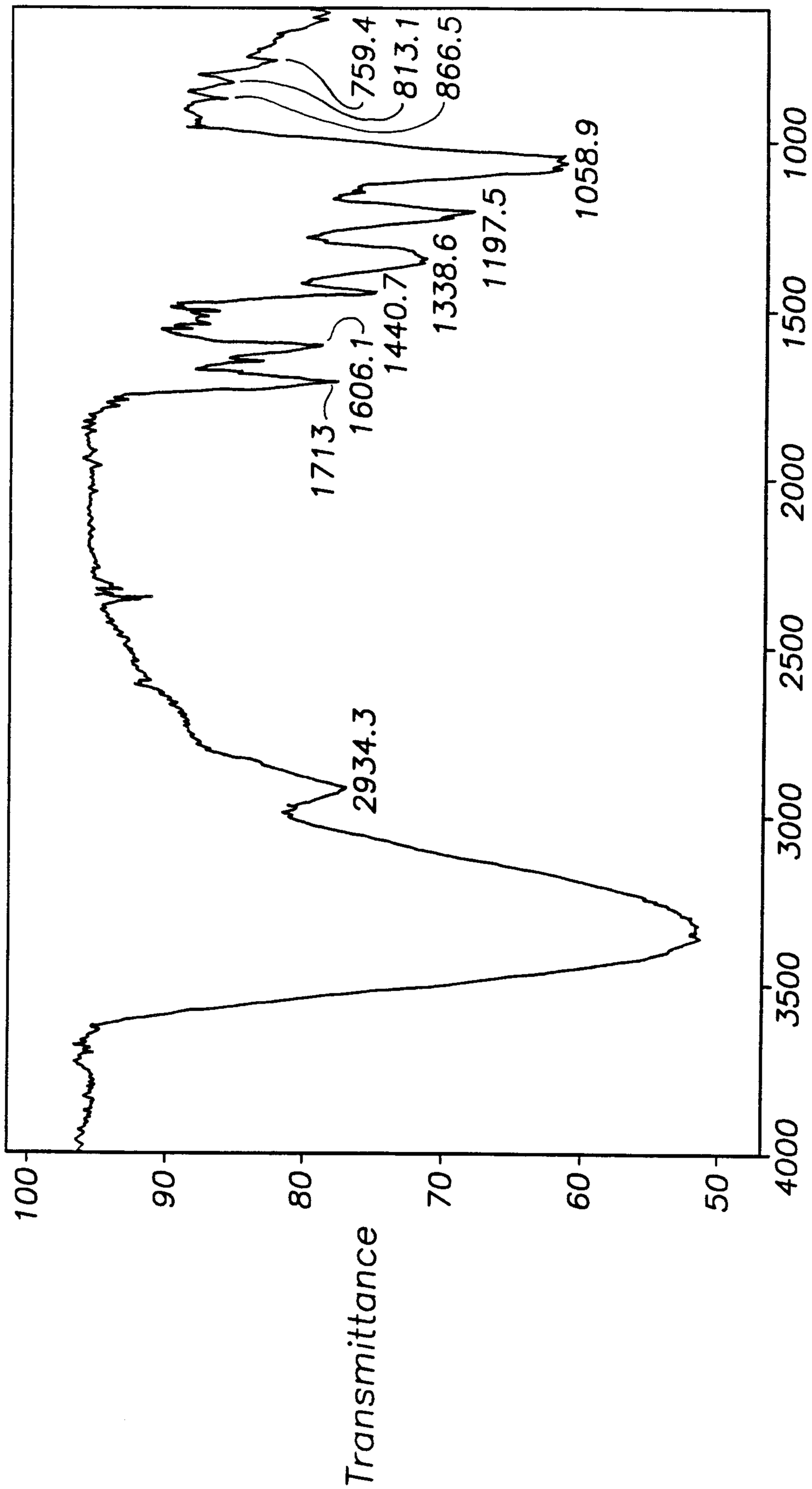


FIG.5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866.5
1058.9
1197.5
1338.6
1440.7
1606.1
1713
2934.3
1000
1500
2000
2500
3000
3500
4000
50
60
70
80
90
100
Wavenumber (cm−1)
Transmittance

FIG. 6

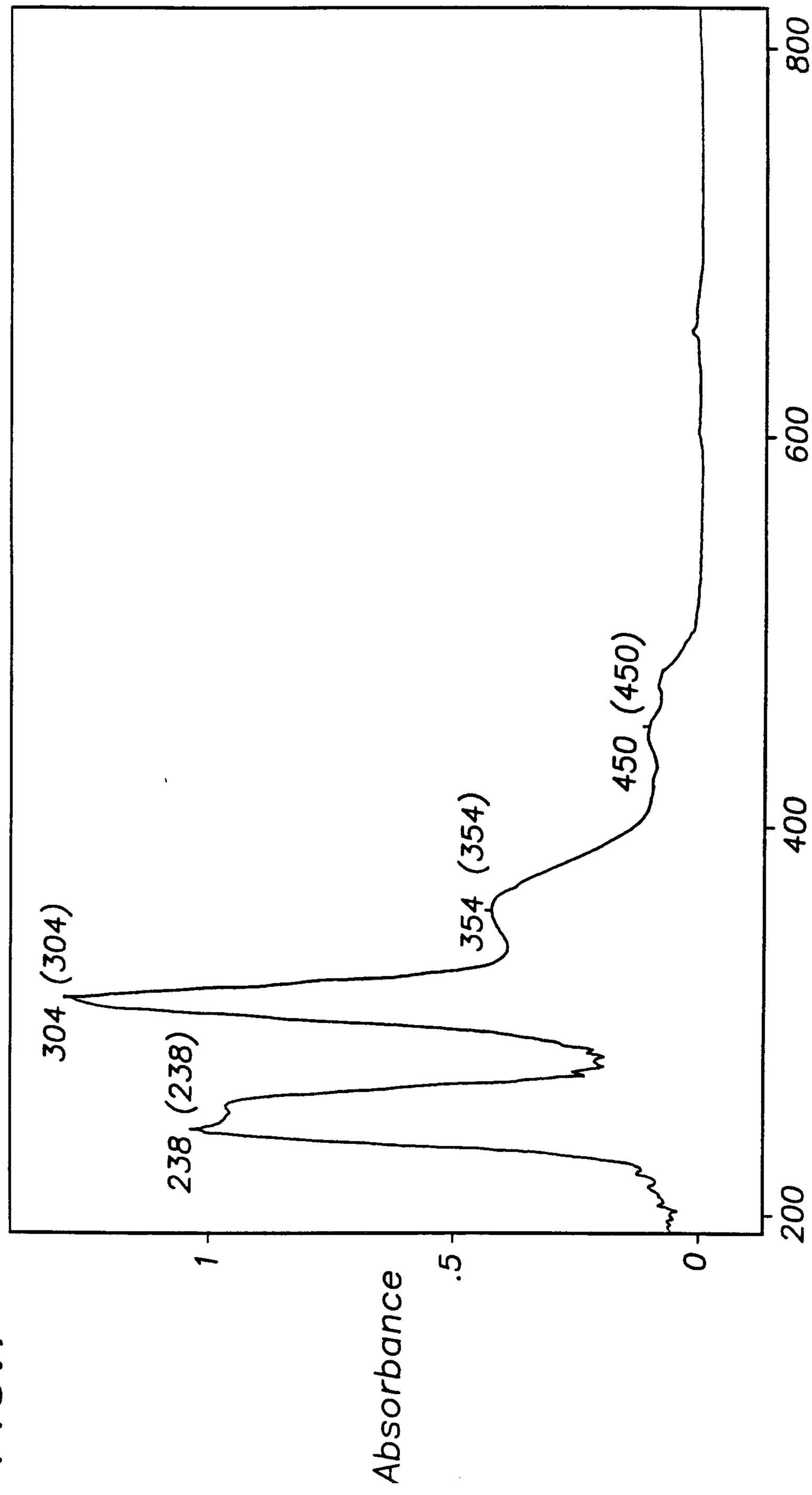
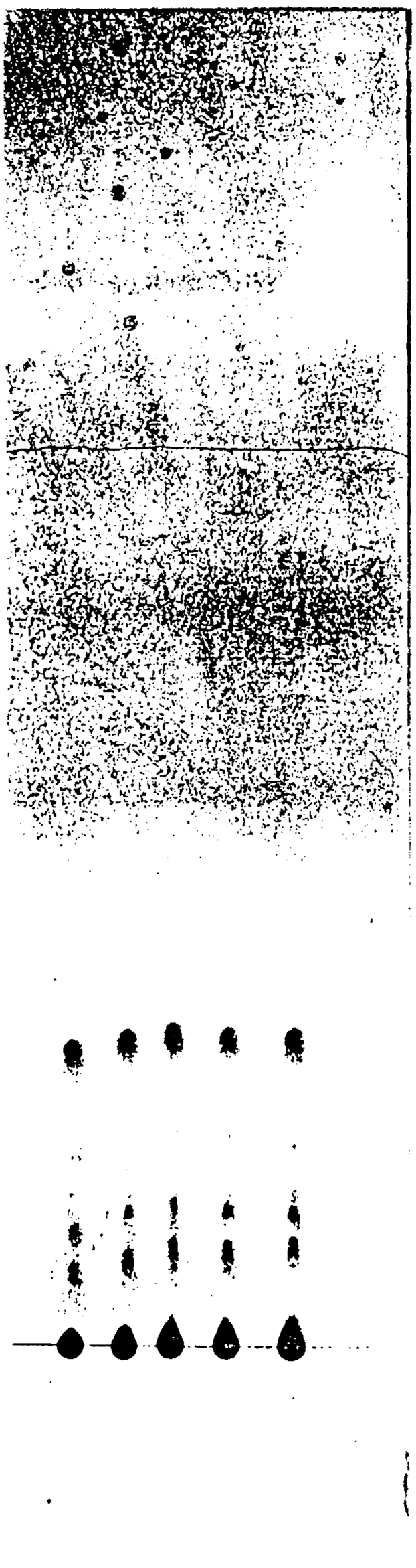

800
600
400
200
Nanometers
304 (304)
238 (238)
354 (354)
450 (450)
1
.5
0
Absorbance

FIG. 7

FIG. 8



TLC Profile of Concentrated
Ethanol Extract of Poison Ivy

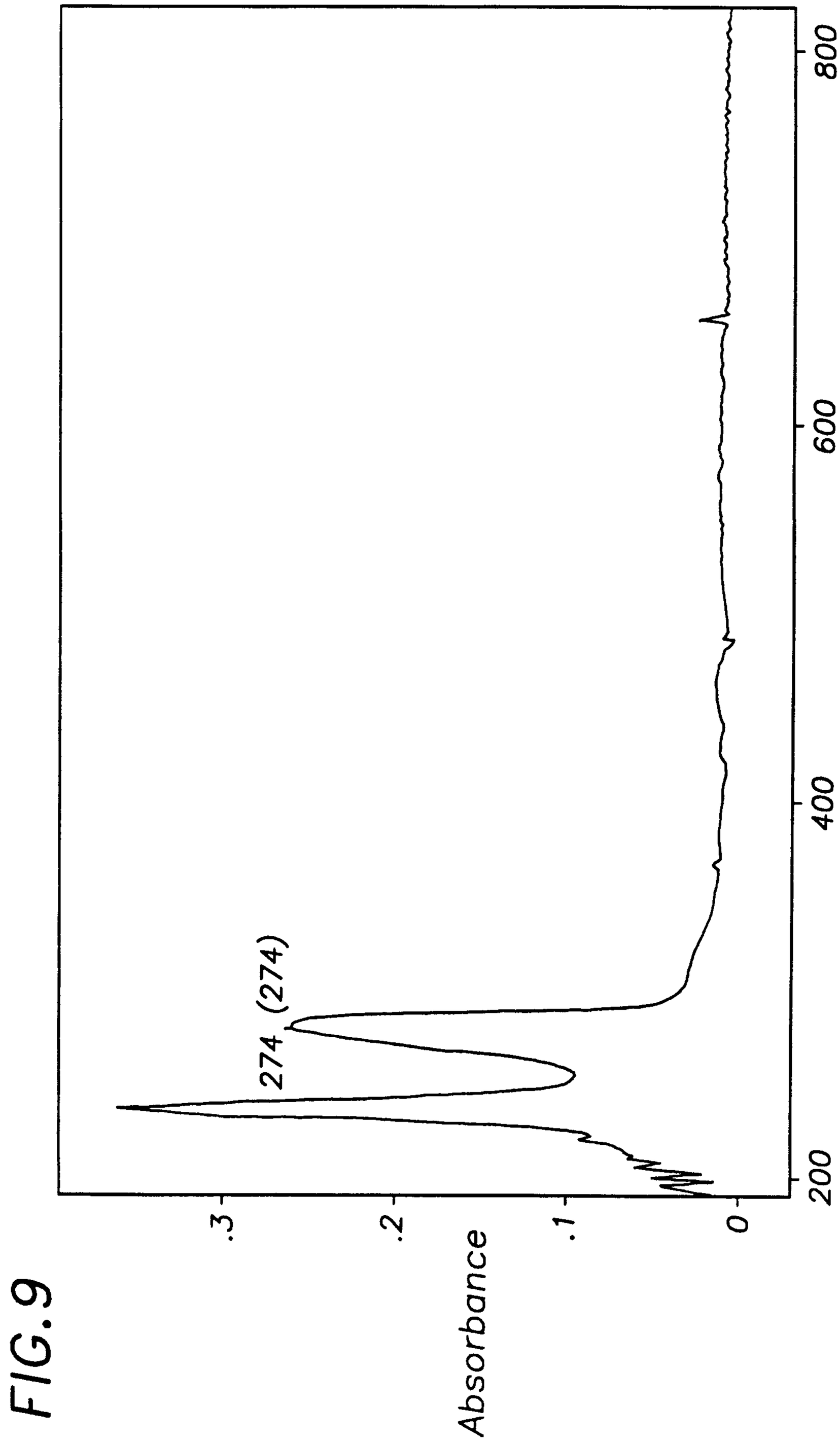
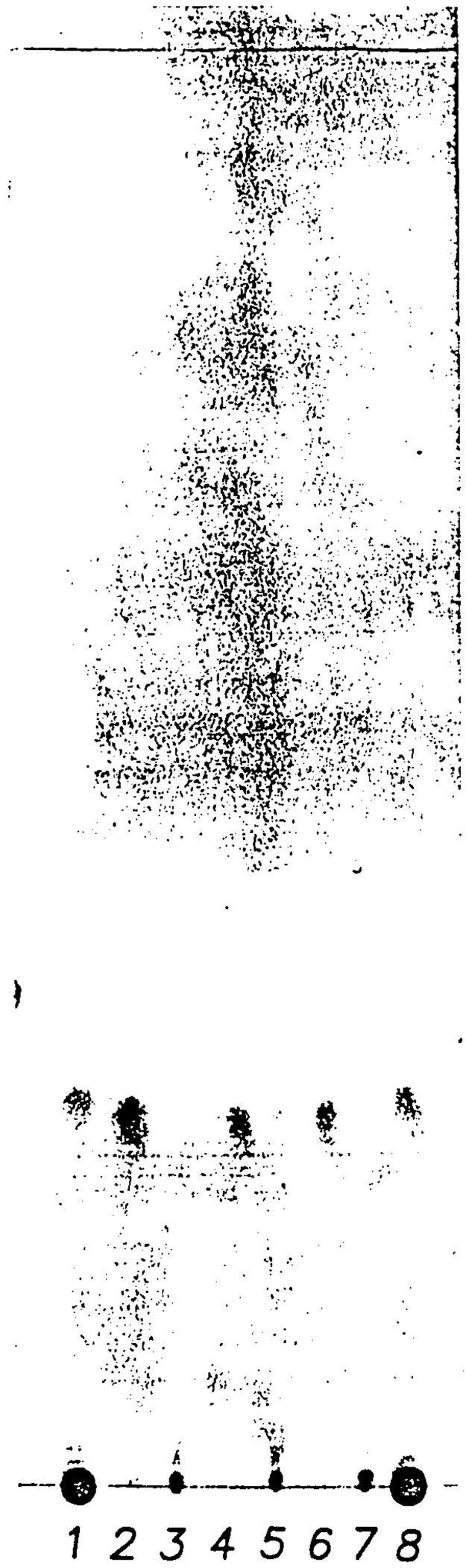


FIG.9

FIG. 10



TLC Profile of Urushiol–Containing Fraction
from LH–sephadex Column