



## Original article

## Bioactive epoxides and hydroperoxides derived from naturally monoterpene geranyl acetate

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## ABSTRACT

Geranyl acetate (**1**) was oxidized thermally and photochemically using (mcpba, H<sub>2</sub>O<sub>2</sub>) respectively to obtain (E)-5-(3, 3-dimethyloxiran-2-yl)-3-methylpent-2-enyl acetate (**2**) and 3-(2-(3, 3-dimethyloxiran-2-yl) ethyl)-3-methyloxiran-2-yl methyl acetate (**3**). On the other hand, photooxygenation of **1** with tetraphenyl porphyrin (TPP) as a photo sensitizer gave corresponding acitic acid 2,6-bis-hydroperoxy-7-methyl-3-methylene-oct-7-enyl-ester (**4**), acitic acid 7-hydroperoxy-3,7-dimethyl-octa-2,5-dienyl ester (**5**) and Acitic acid 3-hydroperoxy-7-methyl-3,7-dimethyl-octa-1,6-dienyl ester (**6**). Antifungal studies were carried out on geranyl acetate and its derivatives. Studies on the antifungal activity especially *Microsporum gypsum*, *Trichophyton vercossum* and *Candida tropicalis* showed that geranyl acetate, its epoxide and hydroperoxide derivatives have good antifungal action.

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## 1. Introduction

In the last years, there has been a rise in the usage of aromatic medicinal plants and their essential oils in technical research and industrial applications including nutritious therapeutic, and cosmetic uses (Kebede & Hayelom 2008; Kejlová et al., 2010; Nisae et al., 2011; Ekor 2013; Ramadan 2015; Emmanuel et al., 2016). The therapeutic properties of certain medicinal plants generally related to their content of secondary metabolites, such as polyphenols, terpenes, phytosteroids, and alkaloids, which produced in considerable amounts and variable proportions (Emam et al., 2009). The essential oils of the plants are the principle of their fragrance. They are called also ethereal oils, or volatile oils because they vaporize rapidly when exposed to the air at ordinary temperatures. In general, the essential oils consist of many mixtures including different sorts of molecules. These chemical constituents divided into two broad classes: terpenes and phenylpropanoids. Nevertheless, most essential oils consist mainly of monoterpenes,

which are the main chemical constituents of the essential oils of these plants that found as mixtures of odoriferous components and can be obtained by steam distillation or solvent extraction from a large variety of aromatic plants. They are found in edible as well as in medicinal plants with a therapeutic properties (Dudai et al., 2005; Sousa et al., 2006; Quintans-Junior et al., 2008; Nerio et al., 2010; Reinaldo et al., 2011).

On the other hand, the chemistry of singlet molecular oxygen (<sup>1</sup>O<sub>2</sub>), (which prepared through photooxidation reaction) has amazing consideration by chemists because of its environmental and biomedical importance beside its interesting mechanistic and synthetic aspects (Stratakis and Orfanopoulos, 2000; Khayyat 2011). Moreover, unsaturated terpenes are adept of trapping activated oxygen species *in vivo* to give intermediate epoxides which can alkylate DNAs, proteins, and other biological species (Richter, 2003; Elgendy and Khayyat, 2008; Khayyat and Saddiq, 2015). Geranyl acetate (**1**) is a monoterpene extant in the volatile oils of many plant species, such as Cypress, Origanum, and Eucalyptus oils (Aligiannis et al., 2001; Delaquis et al., 2002) (see Fig. 1).

Taking into account significant therapeutic value of monoterpene especially geranyl acetate and the important applications of its epoxides and hydroperoxide derivatives, in this study, we investigated some oxidation reaction of geranyl acetate and the biological activities of its products

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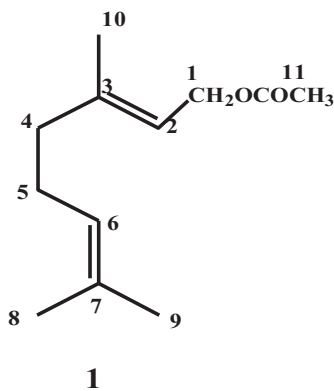


Fig. 1. Structure of geranyl acetate.

## 2. Materials and methods

### 2.1. Chemistry

<sup>1</sup>H-NMR spectra were obtained in CDCl<sub>3</sub> solution with a Bruker AVANCE D.P.X. 600 MHz apparatus. A sodium lamp (Phillips G/5812 SON) was used for photo-irradiation reactions. Thin layer chromatography (TLC) and preparative layer chromatography (PLC): Polygram SIL G/W 254, Mecherey-Nagel.

### 2.2. General epoxidation procedures of geranyl acetate (1)

#### 2.2.1. Method A: Photochemical epoxidation using hydrogen peroxide

A solutions of H<sub>2</sub>O<sub>2</sub> (2.5 mL, 50%) was added cautiously drop wise over 5 min to a stirred solution of **1** (5 mmol) in C<sub>2</sub>H<sub>5</sub>OH (25 mL) at 0 °C. The mixtures were irradiated using sodium lamp in an atmosphere of nitrogen. The reaction mixture evaporated and purified through column chromatography by petroleum ether 60–80 °C and ether (8:2) as elution (Elgendy and Khayyat, 2008) (Table 1).

#### 2.2.2. Method B: Thermal epoxidation using *m*-chloroperbenzoic acid

Solution of **1** (1.0 mmol) in CHCl<sub>3</sub> (25 mL) was cool at 0 °C. mcpba (5.0 mmol, 80%) was added portion wise to the reaction mixtures, then stirred at room temperature (TLC, peroxide test by KI, 10%). The reaction mixture was washed with a saturated aqueous solution of NaHCO<sub>3</sub> (3 × 10 mL), then with distilled water (3 × 10 mL). The organic layer was separated, dried, evaporated and purified by column chromatography using petroleum ether 60–80 °C and ether (8:2) gave the epoxide derivatives as viscous oils (Elgendy and Khayyat, 2008) (Table 1).

### 2.3. Photooxygenation reaction of geranyl acetate

One gram of **1** was take place in test tube, mixed with CHCl<sub>3</sub> and TPP as a sensitizer, then exposed to sodium lamp at –20 °C. stream of dry oxygen gas was passed into the mixture of reaction throughout the irradiation. The solvent was evaporated at 20 °C. Then the crude product was purified by column chromatography on silica gel as adsorbent and a mixture of petroleum ether and ethyl acetate as elution to give the hydroperoxides products **4**, **5** and **6**,

which were successfully separated in pure form in the yields (Elgendy and Khayyat, 2008) (Table 2).

### 2.4. Spectroscopic data

#### 2.4.1. Acetic acid 3,7-dimethyl-octa-2,6-dienyl ester (1)

Colorless oil, C<sub>12</sub>H<sub>20</sub>O<sub>2</sub> (M 196.29). IR (thin film): ν<sup>–</sup>: 1021, 1227, 1365, 1738.5 (COO), 2914.9 (CH str.) cm<sup>–1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ :1.72(s, 3H, <sup>10</sup>CH<sub>3</sub>), 1.8 (s, 6H, <sup>8,9</sup>CH<sub>3</sub>), 2.0 (s, 3H, CH<sub>3</sub>, H-11), 2.5 (Comp. pat., 4H, H-4, 5), 4.6 (d, 2H, J = 8 Hz, H-1), 5.06 (dd, 1H, J = 11 Hz, H-6), 5.33 (dd, 1H, J-11 Hz, H-2). <sup>13</sup>C NMR spectrum, δ ppm : 15.8 (<sup>10</sup>C), 17.4 (<sup>8,9</sup>C), 20.3 (OCH<sub>3</sub>), 25.4 (<sup>9</sup>C), 25.9 (<sup>5</sup>C), 39.1 (<sup>4</sup>C), 60.7 (<sup>1</sup>C), 118.0 (<sup>2</sup>C), 123.3 (<sup>6</sup>C), 131.1 (<sup>7</sup>C), 141.4 (<sup>3</sup>C), 170.3 (CO).

#### 2.4.2. (E)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-enyl acetate (2)

Colorless oil, C<sub>12</sub>H<sub>20</sub>O<sub>3</sub> (M 212.29). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ :1.27 (s, 3H, CH<sub>3</sub>, H-8), 1.30(s,3H, CH<sub>3</sub>, H-9), 1.73 (s, 3H, CH<sub>3</sub>, H-10), 2.2 (Comp. pat., 4 Hz, H-4,5), 2.61 (dd, 1H, J = 8 Hz, H-6), 4.5 (d, 2H, J = 8 Hz, H-1), 5.30 (dd, 1H, J-11 Hz, H-2). <sup>13</sup>C NMR spectrum, δ ppm: 16.1 (<sup>10</sup>C), 20.7 (COCH<sub>3</sub>), 24.2 (<sup>8,9</sup>C), 35.2 (<sup>4</sup>C), 26.1(<sup>5</sup>C), 42.2 (<sup>6</sup>C), 61.2 (<sup>7</sup>C), 118.6 (<sup>2</sup>C), 140.5 (<sup>3</sup>C), 170.2 (CO).

#### 2.4.3. 3-(2-(3,3-dimethyloxiran-2-yl)ethyl)-3-methyloxiran-2-yl methyl acetate (3)

Colorless liquid, C<sub>12</sub>H<sub>20</sub>O<sub>4</sub> (M 228.29). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ :1.22 (s, 3H, <sup>9</sup>CH<sub>3</sub>), 1.32 (s, 3H, <sup>8</sup>CH<sub>3</sub>), 1.34 (s, 3H, <sup>10</sup>CH<sub>3</sub>), 1.81 (Comp. pat. 4H, H-4,5), 2.10 (s, 3H, COCH<sub>3</sub>), 2.61 (dd, 1H, J = 8 Hz, H-6), 2.71 (Comp. pat. 1H, H-2), 4.08 (Comp. pat., 1H, H-1), 4.30 (Comp. pat., 1H, H-1). <sup>13</sup>C NMR spectrum, δ ppm: 16.56 (<sup>10</sup>C), 20.56 (CH<sub>3</sub>-CO), 24.1 (<sup>8,9</sup>C), 24.4 (<sup>5</sup>C), 35.1 (<sup>4</sup>C), 58.1 (<sup>6</sup>C), 58.9 (<sup>2</sup>C), 59.98 (<sup>1</sup>C), 63.01 (<sup>7</sup>C), 76.9 (<sup>3</sup>C), 170.5 (CO).

#### 2.4.4. Acetic acid 2,6-bis-hydroperoxy-7-methyl-3-methylene-oct-7-enyl-ester (4)

Colorless liquid, C<sub>12</sub>H<sub>20</sub>O<sub>6</sub> (M 260.28). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ :1.72 (bs, 2H, H-5), 2.06 (bs, 2H, H-4), 2.19 (s, 3H, COCH<sub>3</sub>), 4.26 (bs, 2H, H-1,6), 4.57 (bs, 2H, H-1,2), 4.97 (bs, 1H, H-8), 5.07 (bs, 1H, H-10), 5.33 (bs, 1H, H-8), 5.66 (bs, 1H, H-10), 8.95 (s, 1H, OOH), 9.46 (s, 1H, OOH). <sup>13</sup>C NMR spectrum, δ ppm : 17.4(<sup>9</sup>C), 20.7 (COCH<sub>3</sub>), 24.2 (<sup>4</sup>C), 26.6 (<sup>3</sup>C), 61.2 (<sup>1</sup>C), 81.5 (<sup>2</sup>C), 88.4 (<sup>6</sup>C), 114.0 (<sup>10</sup>C), 118.2 (<sup>8</sup>C), 142.0 (<sup>7</sup>C), 143.8 (<sup>3</sup>C), 172.4 (CO).

#### 2.4.5. Acetic acid 7-hydroperoxy-3,7-dimethyl-octa-2,5- dienyl ester (5)

Colorless liquid, C<sub>12</sub>H<sub>20</sub>O<sub>4</sub> (M 228.14). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ :1.3 (s, 6H, <sup>8,9</sup>CH<sub>3</sub>), 1.7 (s, 3H, <sup>10</sup>CH<sub>3</sub>), 2.1 (s, 3H, 11CH<sub>3</sub>), 2.86 (Comp. Pat., 2H, H-4), 4.5 (bs, 1H, H-1), 5.53 (dd, 1H, H-6), 6.1 (Comp. Pat., 1H, H-5), 7.3 (s, 1H, OOH). <sup>13</sup>C NMR spectrum, δ ppm : 17.3 (<sup>10</sup>C), 24.2 (<sup>8,9</sup>C), 45.0 (<sup>4</sup>C), 60.4 (<sup>1</sup>C), 82.0 (<sup>7</sup>C), 125.5 (<sup>2</sup>C), 128.5 (<sup>5</sup>C), 136.2 (<sup>6</sup>C), 142.5 (<sup>3</sup>C), 174.9 (CO).

#### 2.4.6. Acetic acid 3-hydroperoxy-7-methyl-3,7-dimethyl-octa-1,6-dienyl ester (6)

Colorless liquid, C<sub>12</sub>H<sub>20</sub>O<sub>4</sub> (M 228.14). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ :1.27 (s, 5H, H-4,10), 1.5–1.9 (Comp. pat., 8H, H-5,8,9), 2.21 (s, 3H,

Table 1  
Thermal and photo epoxidation of Geranyl acetate.

Comp. No.	Epoxidation	Solvent	Yield	Epoxid. Prod.
1	Thermally (mcpba)	CHCl <sub>3</sub>	0.80%	2: 60% 3: 20%
1	Photochemically (H <sub>2</sub> O <sub>2</sub> )	C <sub>2</sub> H <sub>5</sub> OH	0.55%	3: 55%

Table 2  
Photooxidation reaction of Geranyl acetate.

Comp No.	Start Wt. gm	Sensitizer	Solvent	Irradiation time	Yield	Photo products:
1	1	TPP	CHCl <sub>3</sub>	12	0.68%	4: 20% 5: 33% 6: 15%

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