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Ginger As The Natural Source Of α -Terpineol Which Can Scavenge The Free Radicals Through Thermal And Photo Reactions.

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ABSTRACT

Ginger *(Zingiber officinale*) is the oldest plant which has a high fame due to its therapeutic scope from centuries. α-Terpineol extracted from *Zingiber officinale* and has been subjected to extensive research. Otherwise, α-terpineol was examined for antioxidant activity through photo-epoxidation reaction with hydrogen peroxide under irradiation of a sodium lamp and thermal-epoxidation reaction with *m*-chloroperoxybenzoic acid to obtain 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-7-ol in different yield. Whereas, Photooxygenation reaction was carried out in the presence of tetraphenylporphyrin or chlorophyll to give a mixture of two isomeric hydroperoxides, 2-(3-hydroperoxy-4-methylene cyclohexyl)propan-2-ol &2-(4-hydroperoxy-4-methylcyclohex-2-enyl)propan-2-ol**.** This research deduced that ginger acts as natural antioxidant. It can be used to give α-Terpineol which can act as natural antioxidant and flavoring agent. It can be considered an active therapy for humans.

Keywords: α-Terpineol; photochemical epoxidation; photosensitization; hydroperoxides, scavenging agent.

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INTRODUCTION

Zingiberaceae is the family of ginger (*Zingiber officinale*) has green-purple flowers and an essential rhizome (subsurface stem). It can be used as a fresh or dried powder as medicinal plant since ancient times [1]. Much cardiovascular [2] and arthritis, rheumatic [3] diseases can be treated by ginger. Ginger is a natural antioxidants source in foods [4]. It can be used *in vitro* to inhibit growth of ovarian cancer cells [5] and to evaluate anti-cancer properties of its leaves [6].

The percentage of ginger volatile oil is around 2-3%, whose α-Terpineol as monoterpenoid fraction [7]. Ginger volatile oil has antibacterial effect [8].

Terpineol is a naturally occurring alcoholic monoterpene that has been isolated from essential oil of ginger. It has four isomers, *alpha*-, *beta*-, *gamma*-terpineol, and terpinen-4-ol. *α*-Terpineol is the major constituent of all isomers mixture [9]. It used in perfumes, cosmetics [9], pharmaceutical as an antifungal [10] and food industry as a preservative owing to its antioxidant and antibacterial activities [11-13].

Oxidation of phyto-monoterpene shows great part in the production of many significant compounds. Epoxides are excessively used for the synthesis of epoxy resins and diols, which act as intermediates in a huge number of organic compounds and as constituents of painting and dyes. In the meantime, using hydroperoxides instead of oxygen as oxidizing reagents seem more logic. Some hybrid organic–inorganic catalysts have been presented that are able to carry out the epoxidation of olefins in air with good selectivity [14-16].

Newly, oxidation is revitalized by irradiation [17]. Attacking singlet oxygen could be activated oxidation reaction, as in photooxidation in the presence of photosensitizers, light energy and oxygen, to design hydroperoxides through ene mechanism [18]. Hydroperoxides may give rise to secondary oxidation compounds as hydroxy, oxo and epoxy derivatives [19]. Moreover, reactive oxygen species can be absorbed by unsaturated terpenes in vivo to form epoxide and hydroperoxide, intermediates which can damage or alkylate DNA, proteins and other biomolecules [20-22].

It is renowned that some monoterpenes under thermal conditions subjected to oxidation in presence of hydrogen peroxide to give the epoxy derivatives [23], however, no attempts have been paid for preparation of epoxides through photo oxygenation reactions. Taking into consideration curative and protective valuable of monoterpene. So, oxidation reactions of α-Terpineol (**I**) has to be discussed.

MATERIALS AND METHODS

Materials and Measurements:

Volatile oil of Ginger rhizome, has α-Terpineol (**I**) which can be separated. On a thin film, IR spectra can be determined using Perkin–Elmer 16 FPC FT-IR spectrophotometer. To measure the NMR spectra from solutions in $CDCl_3$, Bruker Avance DPX 400 instrument (400 MHz for 1H) can be used.

Gas chromatography– mass spectrometry can be determined by Joel JMS 600H mass spectrometer. Sodium lamp was used as irradiation source. Preparative thin-layer and thin-layer chromatography (TLC) used silica gel (Mecherey-Nagel). To remove solvents from reaction mixtures, rotary evaporator were used. Chemical reagents and solvents are in fine category.

Methods

Photo-epoxidation of α-Terpineol (I) with H_2O_2:

To α-Terpineol, solution of 30% of H_2O_2 solution, (2.5 ml) was mingled drop wise **(**5 mmol)**,** over a period of five min. The solution was irradiated at 0°C using a sodium lamp for 66 h. At room temperature, it was evaporated under reduced pressure to form gummy residue [24]. Using the method of **(**Elgendy 2008). To detach 0.46 g. of **II**, yield 60% as a viscous oil in table (1).

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Table 1: Photo-epoxidation of α-Terpineol(I) with H_2O_2

Comp.	Start Wt Gm	Irrad. Time (h)	Yield %	product gm
α-Terpineol (I)	**0.77**	66	60 %	**II= 0.46 gm**

Oxidation of α-Terpineol (I) with m-chloroperoxybenzoic acid

To a solution of α-Terpineol (**I**) **(**5 mmol)**,** *m*-chloroperoxybenzoic acid [*m*cpba] 80% solution (10 mmol) was added carefully over a period of 15 min. in 25 ml of chloroform. At room temperature, under nitrogen, it was stirred. The advance of the reaction can be detected by TLC and with a 10% solution of KI, peroxide can be tested. With a saturated aqueous solution of $NaHCO_3$ (3 × 10 ml), the solution was carefully washed. At room temperature the organic coat was isolated, dried using anhydrous Na_2SO_4, under reduced pressure, it vaporized [25]. Using petroleum ether (bp 60–80°C)– ethyl acetate (9 : 1) as eluent , to isolate 0.50 g. of **II,** yield 65% as a viscous oil in table (2).

Table 2: Oxidation of α-Terpineol (I) with *m*-chloroperoxybenzoic acid

Comp.	Starting Wt. gm	Yield %	Epoxide Prod.
α-Terpineol (I)	**0.77**	**65**	**II: 0.50 gm**

Photooxygenation of α-Terpineol (I)

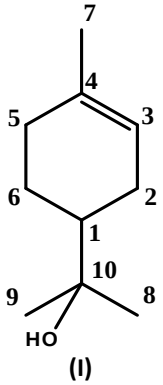
Singlet oxygen sensitizer can be added according to the suitable solvents (chloroform or ethanol), to a solution of 0.01 mol of **I**, during passing A dry oxygen. The mixture was irradiated at –5°C using a sodium lamp. The gummy material, which was formed after removing the solvent can be isolated using the method of **(**Elgendy and Semeih, 2019) [26]. The isomer mixture **IIIa/IIIa'**was isolated. The yields of the photoproducts and the reaction situations (sensitizer, solvent, reaction time) are declared in (table 3).

Table 3: Photosensitized oxygenation of α-Terpineol (I)

Comp.	Starting Wt. gm	Sens.	Reaction Time	Yield gm,%	Yield Prod.%
α-Terpineol	1.5 gm	TPP Cl	15 16	0.75, 50% 0.47, 31.5%	**IIIa: 47%, IIIb:53% IIIa: 47%, IIIb:53%**

Terpineol 2-(4-Methyl-cyclohex-3-enyl)-propan-2-ol (I) :

Colorless oil, $C_{10}H_{18}O$ (*M* 154). ^{1}H-NMR spectrum, δ, ppm: 1.17 s (3H, $^9CH_3$), 1.2 s (3H, $^8CH_3$), 1.49 Comp. pat. (2H, H-6), 1.62 Comp. pat. (1H, H-1), 1.64 s (3H, $^7CH_3$), 1.79 t (1H, H-5, J= 16 Hz), 1.89 d.t (1H, 4 Hz, H-5 J=16), 1.95 d.t (1H, H-2, J=16 , 4Hz), 2.05 d.t (1H, H-2, J=16, 10,4 Hz), 2.77 s (1H, OH), 5.38 br.s (1H, H-3). ^{13}C-NMR spectrum, δC, ppm: 23.2 (^{7}C), 23.7(^{6}C), 26.7 (^{2}C), 27.2 (^{9}C), 27.25 ($^8CH_3$), 30.8 (^{5}C), 44.7 (^{1}C), 72.5 (^{10}C), 120.4 (^{3}C), 133.7 (^{4}C). IR, Cm^{-1}, ν : 3417 (OH), 2963, 2922 (CH str.), 1159 (C-O). GC-MS: RT 7.25 min; m/z (*I*rel, %): 154 (2) (M^+), 153 (15) (M^+-1), 139 (2) (M^+- CH_3), 136 (45) (M^+ -H_2O), 95 (20) (C_7H_{11}), 59(100)(C_4H_9).



(I)

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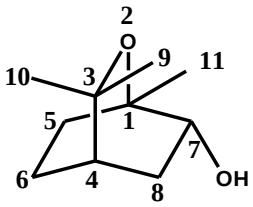
Thermal and Photoepoxidation of Terpineol

1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-7-ol.(II):

Colorless oil, $C_{10}H_{18}O_2$ (*M* 170). ^{1}H-NMR spectrum, δ, ppm: 1.25 s (6H, $^{9,10}CH_3$), 1.15-1.4 Comp. pat. (3H, H-5,6,8), 1.46 s (3H, $^{11}CH_3$), 1.42-1.69 comp.pat. (3H, H-5,6,8), 1.77 s (1H, OH) , 1.80 Comp. pat. (1H, H-4), 4.10 comp.pat. (1H, H-7). ^{13}C-NMR spectrum, δC, ppm: 22.7 (^{5}C), 23.2($^{11}CH_3$), 28.4 ($^{9,10}CH_3$), 29.2 (^{6}C), 30.6 (^{8}C), 31.7 (^{4}C) , 71.9 (^{7}C), 72.5 (^{1}C), 76.8 (^{3}C). GC-MS: RT 16.713 min; m/z (*I*rel, %): 170 (15)(M^+), 155 (7)(M^+ -CH_3), 153 (5) (M^+ - O H), 152(3) (M^+ -H_2O), 135(45) (M^+ -H_3O_2), 106 (2) (C_8H_{10}), 91(15) (C_7H_7), 77 (70) (C_6H_5), 43 (100) (C_3H_7).

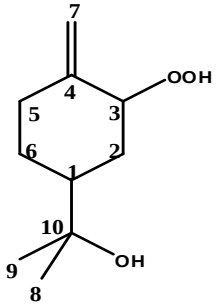


Terpineol Photooxygenation:

IIIa and IIIa as a mixture :

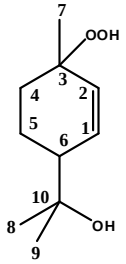
2-(3-hydroperoxy-4-methylenecyclohexyl)propan-2-ol (IIIa):

Colorless oil, $C_{10}H_{18}O_3$ (*M* 186). ^{1}H-NMR spectrum, δ, ppm: 1.22 s (6H, $^{8,9}CH_3$), 1.35 br.s (2H, H-2,6), 1.60 br.s (2H, H-2,6), 2-2.4 comp. pat. (3H, H-1,5), 3.21 d. (1H, H-7, J= 17Hz), 3.7 br.s (1H, OH), 4.3 comp. pat. (1H, H-3), 5.08 d. (1H, H-7, J=17 Hz), 7.9 s. (1H, OOH). ^{13}C-NMR spectrum, δC, ppm: 27.6 (^{8,9}C), 26.5 (^{2}C), 28.0 (^{6}C), 32.5(^{5}C), 43.0 (^{1}C), 73.5 (^{10}C), 77.8 (^{3}C), 120.0 (^{7}C), 145.0 (^{4}C). GC-MS: RT 19.98 min; m/z (*I*rel, %)**.**



2-(4-hydroperoxy-4-methylcyclohex-2-enyl)propan-2-ol (IIIa$^-$):

Colorless oil, $C_{10}H_{18}O_3$ (*M* 186). ^{1}H-NMR spectrum, δ, ppm: 1.30 s. (6H, $2^{8,9}CH_3$), 1.32 s. (3H, $^7CH_3$), 1.62 – 1.78 Comp. Pat. (4H, H-5,6),[AMX], 2.03 =X Comp.pat. (1H, H-1), 3.7 br.s (1H, OH), 5.89=M d.d. (1H, H-3, J=11, 2.4 Hz), 5.92=A d.d. (1H, H-2, J=17, 11Hz) , 8.3 s. (1H,OOH). ^{13}C-NMR spectrum, δC, ppm: 20.0 (^{6}C), 21.4(^{7}C), 25.8 (^{5}C), 27.7 (^{8,9}C), 45. 0 (^{1}C),73.5 (^{10}C), 82.0 (^{4}C), 132.0 (^{3}C), 135.0 (^{2}C). GC-MS: RT 20.08 min; m/z (*I*rel, %)**:** 186 (5) (M^+),170 (2) (M^+-O), 154 (50) (M^+-O_2), 139(40) (M^+- O_2CH_3), 136 (15)(M^+ - O_2CH_5), 121(25) (C_8H_9O), 95 (20)(C_7H_{11}), 43(100) (C_3H_7).



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RESULTS AND DISCUSSION

α-Terpineol [2-(4-Methyl-cyclohex-3-enyl)-propan-2-ol] (**I**) is an alcoholic cyclic monoterpene, which extracted from the volatile oil of Ginger rhizome. The ^{1}H NMR spectrum of (**I**) showed a broad singlet and singlet signals at δ 5.38 and 2.77 ppm to the olefinic proton 3 and hydroxyl proton respectively.

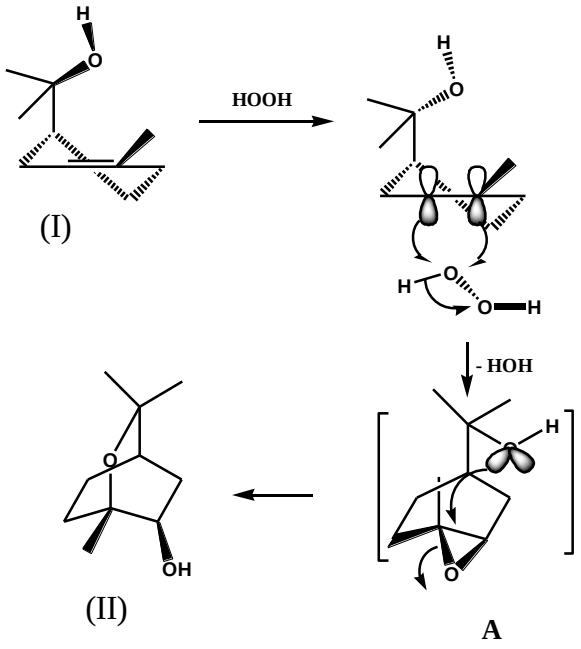
Thermal and Photochemical epoxidation of α-Terpineol

Epoxidation of α-Terpineol (**I**) was carried out photochemically using a sodium lamp in presence of H_2O_2 (30%) produced a 1,3,3-trimethyl-2- oxabicyclo [2.2.2]octan-7-ol **(II)** (Scheme 1). Whereas, oxidation of α-Terpineol (**I**) at room temperature with peracid (*m*cpba), it has been obtained as a sole product (Scheme 2).

The spectral measurements were used to locate the structure of compound **II**. The ^{1}H NMR spectrum of **II** showed one upfield complex pattern at δ **4.10** ppm due to proton in position 7 (methylene proton in position 3 for start **I).** Compound **II** was identified by, retention time (RT) = 16.45 min, and with molecular ion (M^+) (170) for the (GC–MS data).

Epoxy derivative **II** can be formed through the probable mechanism, which is shown in (Scheme 1and 2).

Double bond at position 3,4 attack by H_2O_2 or mcpba in **I** to form intermediate oxirane **A,** which undergo back attack to form compound **II**.



Scheme 1

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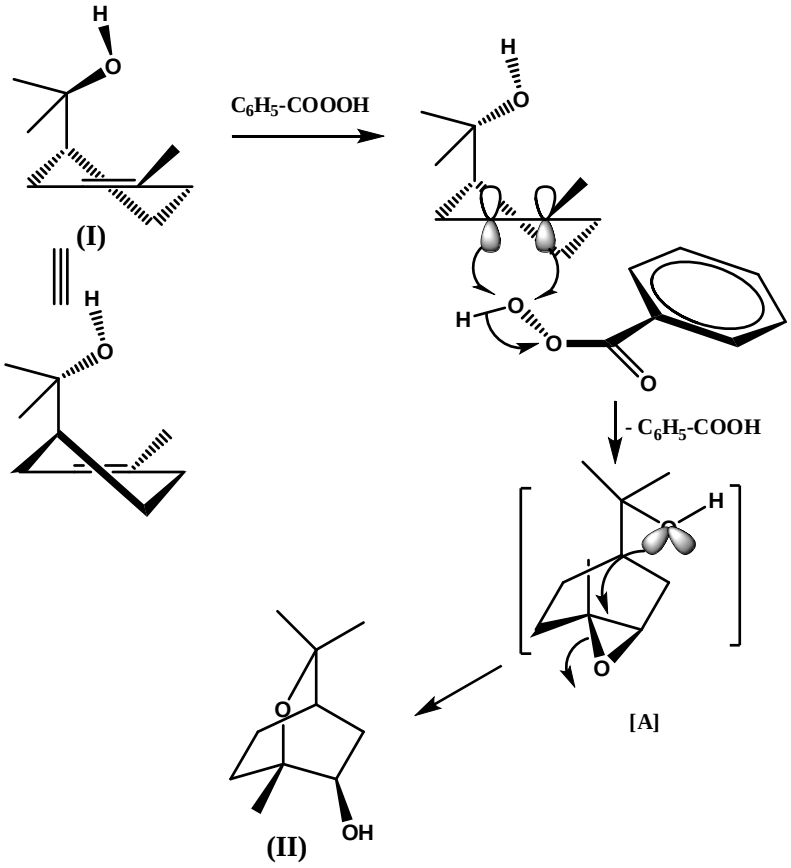

Scheme 2

It is believed that oxidation of α-Terpineol (**I**) was studied previously by Bueno, 2012, who reported that **I** was oxidized to monoterpenic allylic acetates in good yield, with Palladium/p-benzoquinone -catalyzed [27].

Whereas, Leviss *et.al*. , 2016[28] was studied the oxidation of α-terpineol by ozonolysis yielded trans- and cis-lactols and a lactone in 46%, 27%, and 20% respectively. A triol metabolite (1,2,8-trihydroxy-p-menthane) can be formed through epoxidation of α-terpineol , followed by hydrolysis [29].

Photooxygenation of α-Terpineol:

Importantly, in the existence of singlet oxygen sensitizer as (CP), or (TPP), the photooxygenation of α-Terpineol **(I)** carried out to give a mixture of 2-(3-hydroperoxy-4-methylene-cyclohexyl)propan-2-ol **(IIIa)**& 2-(4-hydroperoxy-4-methylcyclohex-2-enyl)propan-2-ol **(IIIa$^-$)** (Scheme 3), due to 1H NMR data, the rate IIIa : IIIa-is around 47 : 53 in two status. According to sensitizer activity, the yield decreased descending from TPP to CP (C.f. table 3). By spectral data, the frame work of **IIIa** and **IIIa$^-$** was proved. **IIIa** hydroperoxide confirmed in the 1H NMR spectrum, two upfield doublets at δ 5.08 &3.21 ppm (*J* = 17 Hz) from the two protons in position 7 and singlet at δ 7. 9 ppm from the OOH proton. The 1H NMR spectrum of **IIIa$^-$**contained downfield **[AMX] system**, two double doublet at δ **5.92** (A)**, 5.89(M)** ppm , complex pattern at δ **2.03 ppm**(**X)** and singlet signals at δ 8.3 ppm to protons 2,3,1 and OOH respectively. According to the GC–MS data, the molecular ions of **IIIa** and **IIIa$^-$** have an *m/z* value of 186, and their retention times are19.98 and 20.08 min, respectively (GC peak area ratio 47: 53).

The mixture of hydroperoxides **(IIIa)** and **(IIIa$^-$)** is formed in the photo oxygenation reaction of α-Terpineol (**I**), via intermediate peroxirane B through routes **a** and **b** (Scheme 3).

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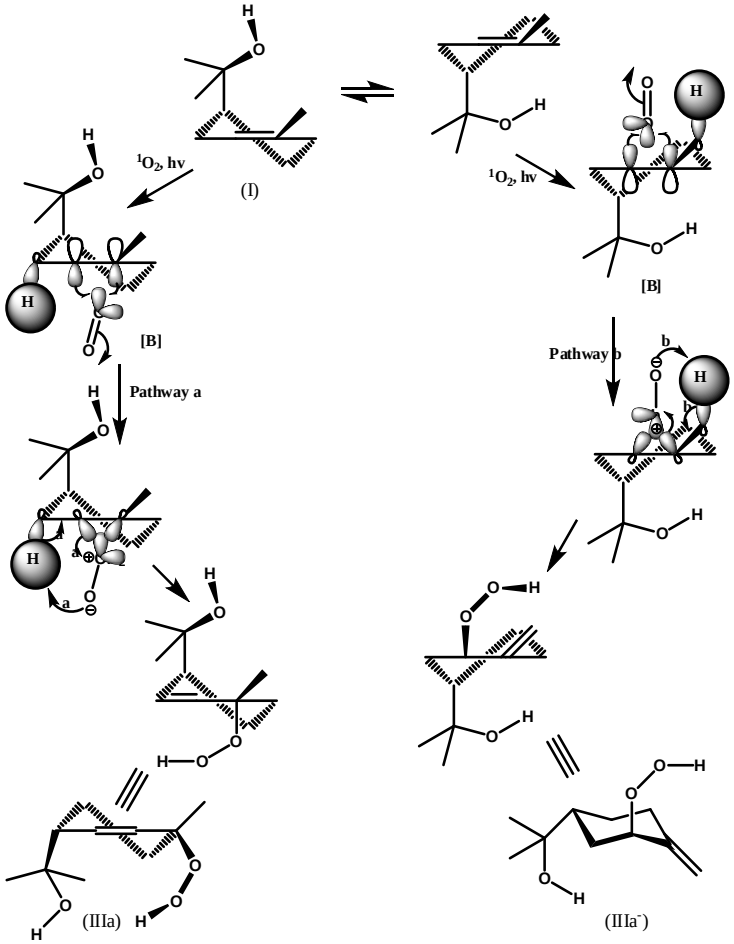

Scheme 3

CONCLUSION

It can be terminated that α-terpineol, which isolated from ginger has perfect antioxidant possibility through photo-epoxidation and photosensitization reactions. So, this spice considers as a natural antioxidant, flavoring agent and can be added to different food products. Through photooxygenation reaction, novel hydroperoxides can be obtained from α-terpineol. Perhaps, such hydroperoxides are generated *in situ* across α-terpineol irradiation in the existence of DNA. They can be given to cancer patients. Thence, it seemed to be pertinent to explain biological result of hydroperoxides with many cell ingredient and DNA.

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