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Safranal epoxide – A potential source for diverse therapeutic applications

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ABSTRACT

Safranal is an organic compound isolated from saffron oil. Photo epoxidation and thermal reactions of safranal can be a significant tool for the design of drugs to act as anticancer agents and potent chemoprevention. Safranal was subjected to oxidation reactions either thermally using m-chloroperbenzoic acid or photochemically with hydrogen peroxide. Photo chemically and thermally oxidation reaction gave the corresponding monoepoxy together with diepoxy derivatives. The primary tested of epoxide derivatives showed a moderate degree of DNA alkylation. Studies on the antimicrobial, especially Methicillin resistant *Staphylococcus aureus* (MRSA), showed high activity of safranal diepoxide (3) against the growth of bacteria Methicillin resistant *Staphylococcus aureus* (MRSA) more than safranal (1) and monoepoxide (**2**) respectively.

The epoxidation products were tested against bacterium Methicillin resistant *Staphylococcus aureus* (MRSA).

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1. Introduction

Saffron has been used since early times as a medicinal plant and a cooking spice (Rios et al., 1996; Malathi et al., 2014; Khayyat, 2017). A monoterpene glycoside precursor of safranal is the main component of volatile oil which is responsible for the aroma (Lozano et al., 2000; Carmona et al., 2007; Maggi et al., 2011). Aqueous extract of saffron could inhibit cyclophosphamide, cisplatin, mitomycin-C, and urethane induced alterations in lipid peroxidation (Samarghandian and Borji, 2014; Koul and Abraham 2017). Several studies showed that saffron has an antioxidant activity and There are many analytical studies that have been conducted to study the characteristics of many potential biologically active compounds that are found in saffron (Martinez et al., 2001; Ali et al., 2002; Ochiai et al., 2004; Premkumar et al., 2003; Sadeghnia et al., 2005; Boroushaki et al., 2007). Natural deglycosylation of picrocrocin will yield safranal. In order to preserve saffron, Dehydration is not the only important process as it is actually important to release the safranal from picrocrocin via enzymatic activity. The reaction yields safranal and D-glucose (John et al., 2010). Various methods of extraction have been used to extract the essential oils from plant material such as microsimultaneous hydrodistillation extraction (Kanakis et al., 2004), vacuum headspace (Tarantilis and Polissiou, 1997). Many chromatographic analytical techniques such as gas liquid chromatography have been used to quantify safranal (Kanakis et al., 2004; Maggi et al., 2009). It has be proven that Safranal has a high antioxidant potential (Assimopoulou et al., 2005; Kanakis et al., 2004), as well as cytotoxicity towards certain cancer cells in vitro (Escribano et al., 1996).

Safranal is a protective agent against gentamicin-induced nephrotoxicity in rat (Boroushaki, and Sadeghnia, 2009) and was able to protect kidney against hexachlorobutadiene-induced nephron toxicity and ischemia/reperfusion injury in rat (Sadeghnia et al., 2005; Boroushaki et al., 2007). A number of dietary, monoterpenes were shown to act in chemoprevention and chemotherapy of different types of cancers in animals effectively, at cellular level, and in human clinical trials (Crowell, 1999; Carnesecchi, 2001). However, plant monoterpenes are subjected to oxidation when they are exposed to air. Oxidation is increased by irradiation (Saddig and Khayyat, 2010), chemical catalysts (Meou et al., 1999) or heat (Elgendy and Khayyat, 2008). The photo

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binding and intercalation activities of monoterpenes to DNA were intensively investigated (Knobler et al., 1988; Niccolai et al., 1990), nevertheless, although epoxides can be efficient DNA-alkylating agents (Elgendy and Fadaly, 2002; Khayyat, 2012). Little is known about such activity for the naturally occurring safranal epoxides. In view of the potential epoxy-biological interest in monoterpenes, this work investigated in detail the epoxidation reactions of safranal and evaluated the antimicrobial activity of the products.

2. Methods and materials

2.1. Chemistry

Safranal was purchased from Fluka. IR spectra were performed on a NICOLET Is50 FT-IR spectrophotometer. ^{1}H NMR & ^{13}C NMR spectrum were obtained in $CDCl_3$ solution with a Brucker Ascend TM 850 MHz apparatus. Thin layer chromatography (TLC) and preparative layer chromatography (PLC): Polygram SIL G/W 254, Mecherey-Nagel. A sodium lamp (Phillips G/5812 SON) was used for photo-irradiation reactions. Gas chromatography-mass spectroscopy GC-MS was performed using a Hewlett–Packard 5890 series II chromatograph equipped with a 5972 series mass selective detector (MSD) in the electron impact mode (70 eV). Evaporation of final product solutions was done by rotatory evaporator (at 20 °C/15 torr).

2.2. Thermally epoxidations with m-chloroperbenzoic acid

A solution of 10 mmol of 80% *m*-chloroperbenzoic acid was carefully added in a dropwise manner over a period of 15 min to a solution of 5 mmol of compound **I** in 25 ml of chloroform at 0 °C. The reaction mixture was stirred at room temperature under nitrogen, the progress of the reaction being monitored by TLC and peroxide test with a 10% solution of KI. The mixture was then carefully washed with a saturated aqueous solution of $NaHCO_3$ (3 × 10 ml) and distilled water (3 × 10 ml). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure at room temperature, and the residue was subjected to column chromatography on silica gel using petroleum ether (bp 60–80 °C)/ethyl acetate (9:2) as eluent to isolate 0.52 g of mixture **2** and **3** with ratio = 65:35, overall yield (70%), which can be separated in pure form (Elgendy and Khayyat, 2008).

2.3. Photochemical epoxidation with hydrogen peroxide

A 30% solution of hydrogen peroxide, 2.5 ml, was carefully added dropwise over a period of 5 min to a solution of 5 mmol of safranal (**1**) in 25 ml of ethanol under stirring at 0 °C. The mixture was irradiated with a sodium lamp for 50 h under nitrogen. The mixture was then evaporated under reduced pressure at room temperature, the gummy residue was treated with 25 ml of chloroform, and the extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using petroleum ether (bp 60–80 °C)/ethyl acetate (9:2) as eluent to isolate: 0.16 g of mixture **2** and **3** with ratio = 65:35, overall yield (50%), which can be separated in pure form as a viscous oils (Khayyat and Elgendy, 2017).

2.4. Spectroscopic data

2,6,6-Trimethylcyclohexa-1,3-diene-1-carbaldehyde **(1):** Colorless oil, $C_{10}H_{14}O$ (*M* 150.21). ^{1}H NMR spectrum, δ, ppm: 1.19 s (6H, $C^{7,8}H_3$), 2.15 d.d (2H, 5-H, *J* = 11, 14 Hz), 2.17 s (3H, C^9H_3), 5.93 d (1H, 3-H, *J* = 10 Hz), 6.16 d.t (1H, 4-H, *J* = 5, 10 Hz), 10.14 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 17.4 (C_9), 25.9 ($C_{7,8}$), 32.3 (C_6), 40.7 (C_5), 129.6 (C_4), 134.1 (C_3), 137.1 (C_2), 146.6 (C_1), 191.3 (CO). GC-MS data: retention time 13.2 min; *m*/*z* (*I*rel, %): 150 (70) $[M]^+$, 135 (10) $[M^+\text{-}CH_3]$, 121 (80) $[M^+\text{-}C_2H_5]$, 107 (1 0 0) $[M^+\text{-}C_2H_3O]$, 91 (90) $[M^+\text{-}C_3H_7O]$, 79 (15) $[M^+\text{-}C_4H_7O]$, 41 (7) $[C_3H_5]^+$.

2,2,6-Trimethyl-7-oxabicyclo[4.1.0]-hept-4-ene-1-carbaldehyde **(2):** Colorless oil, $C_{10}H_{14}O_2$ (*M* 166.21). ^{1}H NMR spectrum, δ, ppm: 1.00 s (3H, C^7H_3), 1.01 s (3H, C^8H_3), 1.5 s (3H, C^9H_3), 1.84 d.d (1H, 3-H, *J* = 2,8 Hz), 2.00 d.d (1H, 3-H, *J* = 2,8 Hz), 5.6 d.d (1H, 4-H, *J* = 7,8 Hz), 5.7 d (1H, 5-H, *J* = 7 Hz), 9.61 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 19 (C_9), 23.6 (C_7), 24.0 (C_8), 39.0 (C_2), 39.5 (C_3), 45.0 (C_6), 95.0 (C_1), 125.8 (C_4), 132.0 (C_5), 200.0 (CO). GC–MS data: retention time 13.93 min; *m*/*z* (*I*rel, %): 166 (35) [*M*]+, 150 (20) [*M* + -O], 135 (10) [*M*+ – CH_3O], 121 (9) $[M^+\text{-}CHO_2]$, 109 (5) $[M^+\text{-}C_3H_5O]$, 95 (50) $[M^+\text{-}C_3H_3O_2]$, 82 (35) $[C6H10]^+$, 70 (48) $[C5H10]^+$; 41 (1 0 0) $[C3H5]^+$.

2,5,5-Trimethyl-3,8-dioxa-tricyclo[5.1.0.02,4]octane-4-carbalde hyde **(3):** Colorless oil, $C_{10}H_{14}O_3$ (*M* 182.21). ^{1}H NMR spectrum, δ, ppm: 1.00 s (3H, C^7H_3), 1.01 s (3H, C^8H_3), 1.21 s (3H, C^9H_3), 1.31 d.d (1H, 3-H, *J* = 2,8 Hz), 1.60 d.d (1H, 3-H, *J* = 2,8 Hz), 2.62 m (1H, 4-H), 3.2 d (1H, 5-H, *J* = 8 Hz), 9.62 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 24.7 (C_7), 24.9 (C_8), 26.1 (C_2), 30.9 (C_9), 39.6 (C_3), 45.1 (C_4), 67.4 (C_5), 67.5 (C_6), 90.9 (C_1), 203.0 (CO). GC–MS data: retention time, min: 16.45–16.85; *m*/*z* (*I*rel, %): 183 (10) $[M^++1]$, 182 (6) $[M^+]$, 166 (5) $[M^+\text{-O}]$, 150 (3) $[M^+\text{-}O_2]$, 137 (15) $[M^+\text{-}CHO_2]$, 121 (15) $[M^+\text{-}CHO_3]$, 109 (30) $[M^+\text{-}C_3H_5O_2]$, 82 (20) $[C_6H_{10}]$+, 43 (1 0 0) $[C_3H_7]$+.

2.5. Antibacterial activity

The agar well diffusion method was employed for the determination of antibacterial activities of the tested compounds on bacterium (MRSA) (Collins et al., 1989). The result of antibacterial is reported in Table 1 and Fig. 1.

3. Result and discussion

3.1. Chemistry

Crocus sativus L. is the botanical name of saffron which belongs to the family Iridaceae. The order of the saffron is Asparagales and it belongs to the class Liliopsida and division Magnoliophyta (Caballero-Ortega et al., 2007; John et al., 2010).

Safranal **(1)** is the main component of saffron oil was epoxidized using *m*-chloroperbenzoic acid (mcpba) at room temperature to give a mixture of 2,2,6-trimethyl-7-oxabicyclo[4.1.0]-hept-4-e ne-1-carbaldehyde **(2)** and diepoxy derivative **(3)**, in the yields of 65 and 35% respectively. This mixture can be separated in pure forms (Scheme 1). On the other hand, **1** was epoxidized with hydrogen peroxide in presence of sodium lamp at room temperature to give 2,2,6-trimethyl-7-oxabicyclo[4.1.0]-hept-4-ene-1-car baldehyde **(2)** and diepoxy derivative (2,5,5-Trimethyl-3,8-dioxa-tricyclo[5.1.0.02,4]octane-4-carbaldehyde (**3**), in the yields of 65 and 35% respectively. This mixture can be separated in pure forms (Scheme 2).

Table 1
Effect of the tested compounds (Safranal, photo epoxidation and Thermal epoxidation) against *Staphylococcus aureus*on Mueller Hinton media.

No.	Treatment	Inhibition zone diameter (mm)
a	Control	–
b	Safranal (**1**)	27.00
c	Epoxide (**2**)	33.00
d	Epoxide (**3**)	35.00

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