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Original article

Gamma Ray-Inducible alpha-Santalene in Lavender Leaves and Its Anti-Inflammatory Effects on LPS-Stimulated RAW 264.7

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ABSTRACT Lavender essential oil is known to exhibit various beneficial effects on the human body; however, its pharmacological anti-inflammatory properties have not been extensively studied. In this study, we performed profiling analysis of volatile sesquiterpenes produced by lavender (*Lavandula angustifolia* L.) leaves in response to ionizing γ-radiation, and evaluated the anti-inflammatory effects of α-santalene, which is induced by γ-irradiation. Following γ-irradiation of lavender leaves, the relative abundance of sesquiterpene hydrocarbons, including α-santalene, α-bergamotene, *epi*-β-santalene, and β-farnesene, increased by more than 160% at 1,000 Gy, with levels at 0 Gy set as 100%. In contrast, the proportion of total monoterpene hydrocarbons was reduced to less than 0.7-fold at 1,000 Gy. Furthermore, α-santalene, the most prominently increased compound following γ-irradiation, significantly inhibited nitric oxide (NO) production in the murine macrophage cell line RAW 264.7, to a greater extent than the anti-inflammatory effects observed for α-santalol. Collectively, our results demonstrate that α-santalene, a γ-ray-inducible volatile compound in lavender leaves, exhibits inhibitory effects on NO production. These findings suggest that α-santalene may be a promising candidate for the development of therapeutics targeting inflammatory diseases.

Key words: α-Santalene, Anti-inflammatory effect, γ-Irradiation, Lavender leaf, Volatile sesquiterpenes

1. Introduction

Terpenoids constitute a major class of secondary metabolites in plants that play pivotal roles in physiological adaptation to environmental fluctuations [1,2]. Considerable research efforts have been directed toward the identification of pharmacologically active terpenoids from medicinal plants. Among these, lavender (*Lavandula angustifolia* L.) has garnered significant attention due to its well-documented anti-inflammatory and antimicrobial activities. Traditionally, lavender is employed in the management of dermatological disorders, gastrointestinal ailments such as irritable bowel syndrome, and sleep disturbances. Essential oils derived from lavender are extensively utilized in aromatherapy, where their volatile constituents interact with the olfactory system, subsequently modulating the limbic structures of the brain and mediating diverse therapeutic outcomes [3]. Recent investigations have highlighted the potential anticancer properties of lavender extracts, demonstrating cytotoxic effects against human lung and prostate cancer cell lines [4,5]. However, the majority of existing studies have focused on the extraction, compositional analysis, and therapeutic applications of essential oils, with relatively limited exploration of the underlying biochemical mechanisms or the response of lavender secondary metabolites to ionizing radiation [6-9]. Although there have been studies examining the alterations in volatile compound profiles in response to various bioactive molecules, phytohormones, and environmental stressors, the impact of ionizing radiation on the volatile metabolome of lavender remains unexplored. Within the sesquiterpene subclass, santalene and santalol have been recognized for their potent cytotoxic activities, including inhibition of tumor progression [10,11]. Nevertheless, research in this field has predominantly focused on santalol, whereas the pharmacological and biological properties of santalene, particularly in the context of anti-inflammatory activities, remain inadequately investigated [11].

While physiological inflammatory responses are crucial for

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host defense, chronic or excessive inflammation is detrimental, promoting the onset and progression of various pathologies, including malignancies and metabolic diseases [12,13]. Sustained inflammatory states are also implicated in dermatological conditions such as atopic dermatitis and chronic skin infections [14,15]. Accordingly, considerable efforts are currently underway to develop strategies for the selective modulation of maladaptive inflammatory responses [16]. Conventional anti-inflammatory therapies, including glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs), are widely adopted in clinical practice but are associated with numerous adverse effects, notably metabolic disturbances and cardiovascular complications when administered long-term [17-20]. These limitations underscore the necessity for the discovery of natural compounds with effective anti-inflammatory potential and more favorable safety profiles.

In this study, we analyzed the compositional dynamics of volatile sesquiterpenes in lavender leaves following γ-irradiation to identify individual components exhibiting radiation-induced accumulation. Our results identified α-santalene as a major γ-ray-inducible sesquiterpene hydrocarbon. Furthermore, we evaluated the anti-inflammatory efficacy of α-santalene using a murine macrophage cell model.

2. Materials and Methods

2.1. Chemical materials

Fetal bovine serum (FBS), Dulbecco's modified Eagle's medium (DMEM), and penicillin-streptomycin (10,000 U mL^{-1}) were purchased from Gibco (Life Technologies Corp., MA, USA). Lipopolysaccharide (LPS, from escherichia coli O111:B4), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), and Griess reagent [1% (w/v) sulfanilamide in 5% (v/v) phosphoric acid with 0.1% (w/v) naphthylethylenediamine-HCl] were purchased from Sigma-Aldrich Corp. (St. Louis, USA).

2.2. Plant material and γ−irradiation

Lavender (*Lavandula angustifolia* L.), two months old, was obtained from a Jeongeup-si lavender farm (Herb ONE, Jeonbuk-do, Republic of Korea, 35°57'21.1"N 126°88'75.5"E), supported by the Medicinal Resource Research Institute (35°77'04.4"N 127°37'81.8"E). The lavender plants were propagated by cuttings, transferred to fresh potting soil, and grown for an additional two months at 22°C with 55–60% relative humidity under constant white light of 100–120 μmol photons m^{-2} s^{-1} and a photoperiod of 16 h light/8 h dark. For γ-irradiation, the fourth to sixth needle leaves at each branch positioned in the apical region were collected. Ten to twelve leaves were harvested and weighed (~500 mg fresh weight). The leaves were transferred into a 20 mL glass vial containing 0.5 mL of sterile distilled water. The vials were exposed to γ-rays at doses of 50, 200, 500, and 1,000 Gy for 4 h, which were generated from a 3 kCi ^{60}Co source at the Advanced Radiation Technology Institute (ARTI, Jeonbuk-do, Republic of Korea). Lavender leaves without γ-irradiation were used as a control (0 Gy).

2.3. GC–MS analysis of headspace volatile compounds

The γ-irradiated lavender leaves were incubated in a growth room for 24 h after exposure to various doses of γ-ray (50, 200, 500, and 1,000 Gy). The headspace volatiles were collected for 1 h at 22°C using a solid-phase microextraction (SPME) fiber coated with polydimethylsiloxane (df 100 μm, needle size 24 Ga; Supelco, PA, USA). The samples were analyzed using a gas chromatography-mass spectrometry (GC–MS) system (GCMS-7890A/5975C; Agilent, CA, USA) equipped with a DB-5MS capillary column (0.25 mm i.d. × 30 m length, 0.25 μm film thickness; Agilent). High-purity helium was used as the carrier gas and maintained at a flow rate of 1 mL min^{-1}. The temperature of the GC injector was set at 180°C. The temperature program for GC–MS analysis was as follows: initial temperature 80°C, held for 3 min; ramped up to 240°C at 10°C min^{-1}, held for 3 min; ramped up to 300°C at 20°C min^{-1}, held for 3 min. For the mass spectral detector, the temperature conditions of the transfer line, quadrupole, and ion source were set at 280, 150, and 230°C, respectively, with an ionization potential of 70 electron volts (eV) and a scan range of 50 to 350 atomic mass units. The following libraries and software were used for the GC–MS identification of terpene compounds: Wiley Registry 12th Edition, NIST 2020 Mass Spectral Libraries, and Mass Spectrometry Program version 2.3 (https://chemdata.nist.gov/dokuwiki/). For identification of α-santalene, comparative analysis of GC retention indices was performed using the Kovats index, calculated for all volatile compounds using a series of C7–C30 n-alkanes (Cat#49451-U, Sigma) [21]. The abundance of each compound in percentage was estimated relative to the total peak area of all identified terpenoids. The content of representative terpenoids was quantified by calibration curves of standard chemicals, using α-santalene (Cat#S115065, TRC, Ontario, Canada) as a standard compound for sesquiterpene hydro-

carbons. The quantification was corrected using 1-bromodecane (Cat#145785, Sigma) as an internal standard. All analyses were performed in triplicate.

2.4. Cell culture and cell viability assay

The macrophage cells (RAW 264.7) used in this study were purchased from the American Type Culture Collection (ATCC). These cells were cultured under high humidity conditions in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin (10,000 U mL^{-1}) at a temperature of 37°C in a 5% CO_2 atmosphere. The cells were subcultured every two days. To assess the cytotoxicity of volatile compounds using the MTT assay, RAW 264.7 cells were seeded into 96-well plates at a density of 1×10^5 cells per well, 24 h prior to the experiment. The cells were then cultured for an additional 24 h in DMEM supplemented with 10% FBS. Once cell confluency reached more than 80% of the well area, the compounds (α-santalene and α-santalol) were added at concentrations of 5, 10, and 20 μM. The cells were subsequently cultured for an additional 24 h in DMEM without FBS. The supernatant was discarded, and MTT reagent (5 mg mL^{-1}) was added at 10 μL per well. The samples were then incubated for 3 h. The formazan crystals that formed were dissolved in 100 μL of DMSO and the mixture was incubated for an additional 15 min. The absorbance was measured using a multi-functional microplate spectrophotometer at a wavelength of 570 nm. The results were expressed as percentages relative to the untreated control samples.

2.5. Measurement of nitric oxide

The levels of nitric oxide (NO) released into the cell culture medium were measured using Griess reagent. On the day before the experiment, RAW 264.7 cells at a density of 2×10^5 cells per well were seeded in 24-well plates. Once cell confluency reached more than 80% of the well area, lipopolysaccharide (LPS) was added to the experimental groups at a concentration of 0.1 μg mL^{-1} along with each compound at concentrations of 5, 10, and 20 μM. The cells were then cultured for an additional 24 h. The supernatant from these samples was reacted with Griess reagent in a 1 : 1 ratio and incubated at room temperature (RT) for 10 min. Subsequently, the absorbance was measured using a multi-functional microplate spectrophotometer at a wavelength of 540 nm. LPS treatment (0.1 μg mL^{-1}) was set as the positive control group. The concentrations of NO were determined by comparing the readings against standard curves generated from different concentrations of sodium nitrite.

2.6. Data analysis

Each datum was obtained from three independent samples conducted simultaneously for error analysis. The averages were calculated with standard deviations and correlations for several experimental conditions. Statistical analysis was carried out using PASW Statistics version 18 software (Chicago, IL, USA) [22] by one-way ANOVA with Tukey's and Duncan's tests for honestly significant differences. A p-value < 0.05 was considered significant.

3. Results and Discussion

3.1. GC–MS analysis of volatile sesquiterpenes in γ-irradiated lavender leaves

To identify volatile sesquiterpenes whose content increases upon γ-irradiation in lavender leaves, we analyzed whether significant alterations in the abundance of volatile terpenes occur following γ-irradiation. Under normal conditions (0 Gy), lavender leaves mainly produced six sesquiterpenes, excluding those with a content of less than 0.4% (Fig. 1a). The extracted ion current (EIC) profile of lavender leaves irradiated with γ-rays at a dose of 200 Gy showed a significant increase in α-santalene content. The abundance of most volatile sesquiterpenes also increased with γ-irradiation. The α-santalene identified in lavender leaves eluted at the same retention time (11.67 min) as the commercially available α-santalene standard (Fig. 1a). The EI mass spectra from both the lavender-extracted α-santalene and the commercial standard were identical, each showing a base peak at *m/z* 93 and a molecular ion at *m/z* 204, in good agreement with the mass spectral library (Fig. 1b).

3.2. Changes in the content of α-santalene after γ-irradiation

To determine the quantitative changes in α-santalene after γ-irradiation, the relative proportions and absolute amounts of α-santalene and other sesquiterpene hydrocarbons (including α-bergamotene, α-humulene, *epi*-β-santalene, and β-farnesene) in lavender leaves exposed to various γ-ray doses (ranging from 50 to 1,000 Gy) were measured. The relative proportion of total sesquiterpene hydrocarbons increased in a dose-dependent manner from 29.0% at 0 Gy to 48.2% at 1,000 Gy: (*Z*)-α-bergamotene (Peak 1, 2.8-fold increase), α-santalene (Peak 2, 1.6-fold increase), (*E*)-α-bergamotene (Peak 3, 1.6-fold increase), *epi*-β-

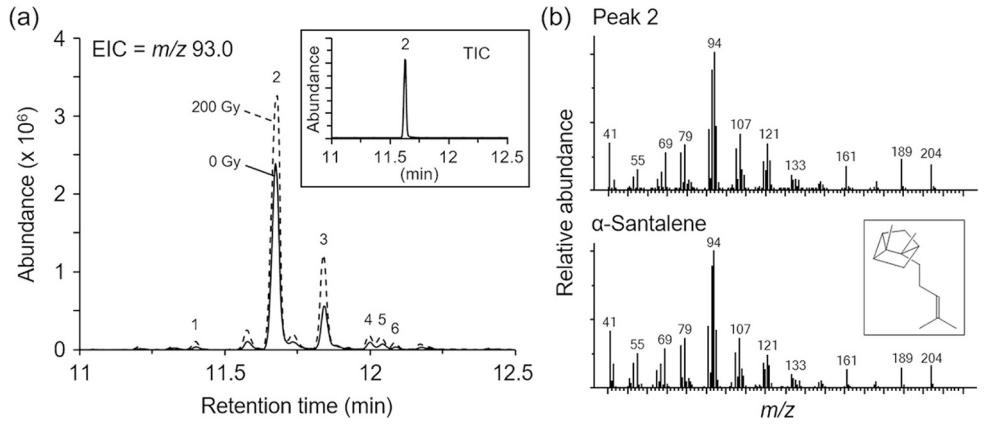

Fig. 1. GC–MS analysis of volatile terpenoids in lavender leaves and identification of α-santalene induced by γ-irradiation. (a) Extracted ion current (EIC) chromatograms at *m/z* 93.0 after exposure to 0 or 200 Gy of γ-rays, and total ion current (TIC) chromatogram of authentic standard α-santalene (inset). Six sesquiterpene hydrocarbons were identified as follows: 1, (*Z*)-α-bergamotene; 2, α-santalene; 3, (*E*)-α-bergamotene; 4, α-humulene; 5, *epi*-β-santalene; 6, (*E*)-β-Farnesene. (b) Positive electron ionization (EI+) mass spectrum of α-santalene compared with the authentic standard, with its chemical structure shown in the inset.

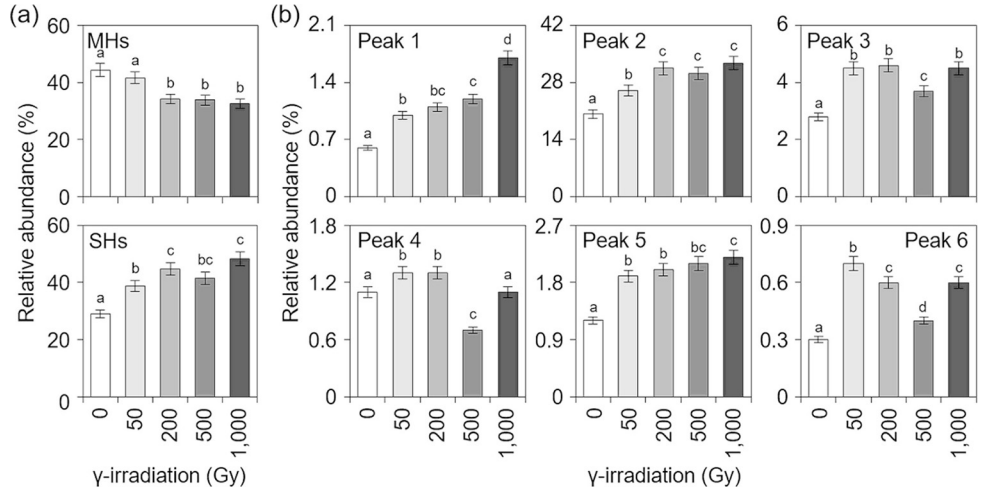

Fig. 2. Relative chemical proportions of volatile sesquiterpene hydrocarbons from lavender leaves after γ-irradiation. Ten to twelve leaves (~500 mg fresh weight) from each lavender plant were placed in a 20 mL glass vial, and volatiles were analyzed by SPME–GC–MS. (a) Relative chemical proportions of monoterpene hydrocarbons and (MHs) and sesquiterpene hydrocarbons (SHs). (b) The peak area of each compound, (*Z*)-α-bergamotene (1), α-santalene (2), (*E*)-α-bergamotene (3), α-humulene (4), *epi*-β-santalene (5), (*E*)-β-farnesene (6), was converted to a percentage relative to the total area of all identified terpenoid peaks. Values are presented as means±SD (n=3). Different letters above bars indicate significant differences ($p<0.05$) by one-way ANOVA followed by Duncan's multiple range test.

santalene (Peak 5, 1.8-fold increase), and (*E*)-β-farnesene (Peak 6, 2.0-fold increase) (Fig. 2a, 2b). Conversely, the proportion of total monoterpene hydrocarbons decreased from 44.4% at 0 Gy to 32.7% at 1,000 Gy (Fig. 2a). Notably, the proportion of α-santalene increased more than 1.5-fold at 50 Gy (Fig. 2b, Peak 2).

We further quantified α-santalene and (*E*)-α-bergamotene after γ-irradiation. Quantitative analysis revealed that amounts of α-santalene and (*E*)-α-bergamotene significantly increased after exposure to 200 Gy of γ-irradiation: α-santalene increased from 2.30 μg at 0 Gy to 5.22 μg at 200 Gy, and (*E*)-α-bergamotene from 0.25 μg at 0 Gy to 0.71 μg at 200 Gy. However, this increasing pattern was not dose-dependent, as the highest levels were observed at 200 Gy (Fig. 3). These findings indicate that γ-irradiation effectively alters the terpenoid chemical composition of lavender leaves [10,23]. Previous reports have shown that α-santalol and α-santalene, which are abundant in various *Santalum* species, exhibit significant anticancer effects both

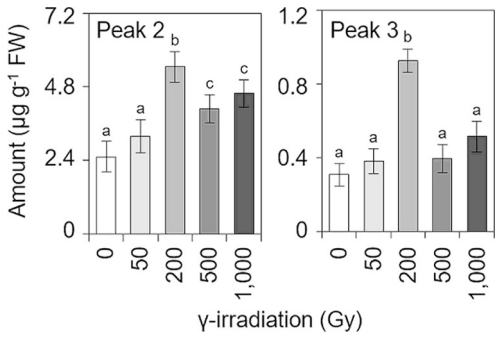

Fig. 3. Quantification of representative volatile sesquiterpene hydrocarbons in lavender leaves after γ-irradiation. The amounts of α-santalene (Peak 2) and (*E*)-α-bergamotene (Peak 3) were calculated using calibration curves from authentic standards. Values are presented as means±SD (n=3). Different letters above bars indicate significant differences ($p<0.05$) by one-way ANOVA followed by Duncan's multiple range test. FW, fresh weight.

in vitro and *in vivo* [10,24]. The α-santalol is synthesized via oxidation of α-santalene, catalyzed by cytochrome P450 monooxygenases (CYPs), and is known for its anti-inflammatory and anticancer activities [25-27].

3.3. Anti-inflammatory effect of α-santalene

To investigate whether α-santalene, the precursor of α-santalol, possesses anti-inflammatory properties, we first performed a cell viability test, as no prior data on α-santalene was available. The α-santalol, a well-known anti-inflammatory agent, was used as a control. The effect of each compound on the viability of RAW 264.7 cells was assessed via an MTT assay. The cell viability of the untreated control was set to 100%, and those of α-santalene and α-santalol were expressed as a percentage relative to this control. At concentrations of 5, 10, and 20 μM, the cell viability for α-santalene was 100.4±1.9, 98.9±3.0, and 94.6±4.2%, respectively. For α-santalol, the values were 100.1±2.8, 96.9±2.0, and 99.2±3.5%. No significant differences were observed between the treated groups and the control (Fig. 4a). To assess the effects of each compound on nitric oxide (NO) production in RAW 264.7 cells stimulated with lipopolysaccharide (LPS), we conducted NO assay. The NO production level in the LPS-only treated control was 38.5±1.2 μM. All treatment groups (α-santalene and α-santalol) exhibited a significant decrease in NO production compared to the control (Fig. 4b). Specifically, NO levels at concentrations of 5, 10, and 20 μM for α-santalene were reduced to 28.5±0.3, 24.7±0.5, and 21.8±0.6 μM, respectively. For α-santalol, NO levels were 31.8±0.6, 28.8±0.3, and 26.7±0.5 μM at the same concentrations. These results indicate that 5 μM of α-santalene reduced NO production by approximately 25.9% relative to the LPS-treated group, and 20 μM of α-santalene led to a reduction of about 43.3%, demonstrating a significant anti-inflammatory effect. Notably, α-santalene exhibited a higher inhibition rate of NO production than α-santalol at the same concentrations, despite α-santalol being a well-established anti-inflammatory compound in sandalwood oil [11,28-30]. Since α-santalene is a simple sesquiterpene without a hydroxyl group (-OH), its polarity, capacity to bind to target proteins, and intracellular activity may differ from those of α-santalol. Sesquiterpenols with a hydroxyl group (-OH) have polarity and hydrogen bonding ability, and are well known to be involved in anti-inflammatory and cell membrane/protein interactions [31,32]. Cedrol is an example of

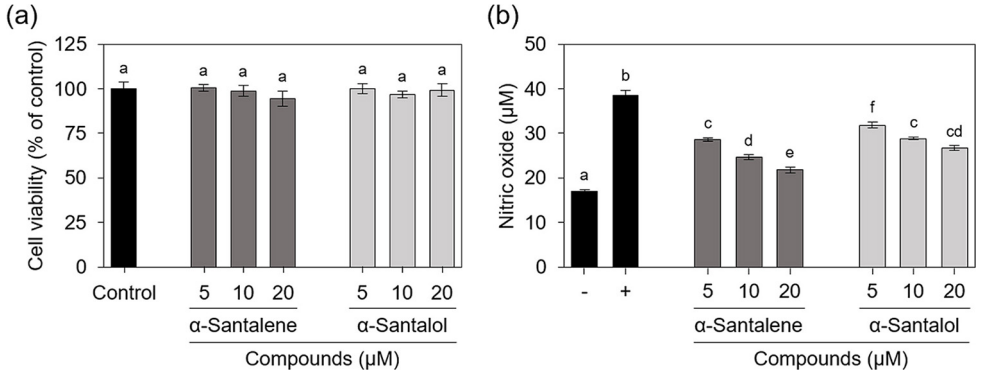

Fig. 4. Effect of α-santalene on LPS-induced RAW 264.7 cells. (a) Cell viability was assessed by MTT assay after 24 h of treatment with each sample. (b) Effect on NO production by LPS-activated RAW 264.7 cells. The cells were treated with both the samples and LPS (0.1 μg mL^{-1}) for 24 h, and nitrite content in the culture medium was analyzed. Values are presented as means±SD (n=3). Different letters above bars indicate significant differences ($p<0.05$) by one-way ANOVA followed by Tukey's honestly significant difference (HSD) test. FW, fresh weight.

a sesquiterpenol that changes the composition of cell membrane compositions while also inhibiting mTOR, AKT, and NF-κB signaling [33]. More research is required to determine how α-santalene [a sesquiterpene without a hydroxyl group (-OH)] contributes to the anti-inflammatory mechanism. It is expected that α-santalene will serve as the foundation for a new anti-inflammatory mechanism.

4. Conclusion

In this study, we investigated the anti-inflammatory effects of α-santalene, a sesquiterpene hydrocarbon isolated from lavender leaves, and evaluated its potential as a therapeutic agent. Our results demonstrated that α-santalene significantly inhibited lipopolysaccharide (LPS)-induced nitric oxide (NO) production in RAW 264.7 macrophage cells, indicating pronounced anti-inflammatory activity. Notably, γ-irradiation was effective in increasing the content of α-santalene and other sesquiterpene hydrocarbons in lavender leaves. Furthermore, α-santalene exhibited a stronger inhibitory effect on NO production compared to α-santalol, a recognized anti-inflammatory compound. Collectively, these findings suggest that α-santalene may serve as a valuable candidate for the development of novel anti-inflammatory therapeutics. However, additional studies are warranted to further elucidate its mechanisms of action, including its effects on inflammatory mediators such as iNOS and COX-2, as well as its regulation of NF-κB signaling pathways. With continued research, α-santalene holds promise as a potential therapeutic agent not only for inflammatory conditions but also for cancer treatment.

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