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IN VIVO WOUND HEALING AND *IN VITRO* ANTI- ANTIOXIDANT ACTIVITY EVALUATION OF *COTULA CINEREA*

Zineb Lakache[1*], Mohcene Sadallah[2], Hamza Aliboudhar[3], Hinda Hacib[1], Hassina Tounsi[1] and Abdelkrim Kameli[1]

[1]*Laboratory of Ethnobotanyand Natural Substances, ENS-Kouba, Algiers*
[2]*Department of Biology, ENS-Kouba, Algiers*
[3]*USTHB, Laboratory of Functional Organic Analysis, Faculty of Chemistry, University of Sciences and Technology Houari Boumediene, El Bab-Ezzouar, Algiers, Algeria*

The objective of this research was to identify the primary constituents of the essential oil obtained from Cotula cinerea (Delile) Vis. through the process of hydrodistillation. Additionally, the study aimed to explore the oil's in vivo wound healing properties and its in vitro antioxidant capabilities. Several compounds were identified in the essential oil, including thujone, santolina triene, camphor, and 1,8-cineole. To assess its wound healing potential, the essential oil was topically applied to induced wounds in mice, resulting in a notable acceleration of wound healing and repair, with a reported rate of 93.2 ± 0.7%. Furthermore, the research included an evaluation of the essential oil's analgesic activity, which was assessed by administering intraperitoneal injections of acetic acid to mice. Moreover, the antioxidant activity of the essential oil was assessed through the ferric reduction antioxidant power and DPPH scavenging assay. The findings from these antioxidant tests revealed that the essential oil extracted from Cotula cinerea exhibited the ability to reduce iron and scavenge DPPH radicals effectively. These results underscore the bioactive characteristics of Cotula cinerea essential oil and its potential for synergistic effects. Consequently, Cotula cinerea shows promise as a natural source of biologically active compounds with therapeutic potential for wound healing. These discoveries suggest that Cotula cinerea could serve as a viable alternative to synthetic wound treatment medications in the future pharmaceutical industry.

Keywords: *Cotula cinerea; antioxidant, wound healing*

INTRODUCTION

Throughout history, plants and their bioactive substances have been utilized as traditional medicine to treat various diseases. In present times, the use of plants for medicinal purposes continues to be prevalent in different cultures[1-3]. One region that stands out for its rich biodiversity of medicinal plants is the Southeast region of Algeria. Among the numerous plant species found in this area, *Cotula cinerea*, a member of the *Asteraceae* family, grows naturally and is recognized for its medicinal properties. *Cotula cinerea* is well-suited to arid environments and is commonly found in sandy and desert areas[4,5]. It is a compact, annual plant that typically emerges following the rainy season. With its woolly appearance, it reaches a height ranging from 5 to 15 cm. The plant's stems of *Cotula cinerea* can either be upright or spreading, and its leaves are thick, whitish, and woolly, featuring three to five obtuse teeth at the top. At the tip of short stems, small yellow-gold pompom-like flowers are produced[6]. This plant, belonging to the *Asteraceae* family and specifically the Anthemideae tribe, possesses a valuable chemical composition characterized by the presence of flavonoids, sesquiterpene lactones, and polyacetylenes. *Cotula cinerea* is known

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*Corresponding author: Zineb Lakache, E-mail: lakache.zineb@gmail.com

to contain various secondary metabolites, making it a valuable source of natural compounds for traditional medicine[7-10].

There has been a lack of extensive research on the antioxidant and wound healing properties of extracts derived from *Cotula cinerea*. In this study, our main objective is to analyze the chemical composition of the essential oil extracted from the aerial parts of *Cotula cinerea* and assess its wound healing and antioxidant activities. Through this research, we aim to enhance our understanding of the pharmacological and medicinal properties of *Cotula cinerea* oil, with a specific focus on its potential role in promoting wound healing.

MATERIALS AND METHODS

Chemicals

The compounds used in the study, including ketamine, xylazine, aspirin were obtained from Sigma (Sigma-Aldrich, Germany).

Vegetal material

The aerial parts of the *Cotula cinerea* plant were collected from the Ghardaïa region in Southeast Algeria. The plant material was identified by Professor Toumi from the Department of Biological and Environmental Sciences, ENS Kouba, Algeria. After collection, the plant material was naturally air-dried in a dark area at room temperature.

Hydrodistillation extraction

The essential oil of *Cotula cinerea* was extracted using the hydrodistillation method, specifically the Clevenger method. The plant material was mixed with water in a flask and left for a period of two hours. Following this, the oil was separated from the water through simple decantation, without the use of any organic solvents. To ensure proper preservation, the extracted oil was stored in a tightly closed brown vial in a dark and cool place at a temperature of 4 °C.

Chemical composition

The chemical composition analysis of the essential oil of *Cotula cinerea* was conducted using Gas Chromatography-Mass Spectrometry (GC/MS) with an Agilent GC-FID system '7890A/5977B MSD' equipped with a non-polar fused-silica-capillary column (HP5MS) having dimensions of 30 m x 0.25 mm x 0.25 µm film thickness. For the GC analysis, a volume of 0.2 µL of the essential oil was injected into the splitless GC inlet, which was maintained at a temperature of 250 °C. The column temperature program started at 60 °C and was held for 8 minutes, followed by an increase of 4 °C per minute until reaching 250 °C, which was then held for 25 minutes. The ionization mode used was electronic impact at 70 eV.

The identification of the chemical constituents was performed by comparing the mass spectral fragmentation patterns with those stored in the databases Adams 2017, NIST 2014, and Wiley. Additionally, the retention indices of the volatile extract constituents were compared with published index data to aid in identification.

Evaluation of Antioxidant Activity

DPPH radical scavenging activity

To assess the DPPH free radical activity, we utilized the procedure described by Musa et al. [11]. Briefly, different concentrations of the extract were mixed with a methanol solution containing DPPH (0.04%,). After a duration of thirty minutes, the absorbance of the sample was determined at 517 nm. Butylated hydroxytoluene (BHT) and Ascorbic acid reference standards were employed as comparative references. The percentage of inhibition activity was determined using the following equation:

$$\% \text{ Inhibition} = (Ac - As/Ac) \times 100$$

In the provided equation, Ac represents the absorbance of the control, and As represents the absorbance of the sample solution. The antiradical activity of the samples was measured by determining their IC_{50} value, which indicates the concentration of the sample required to neutralize 50% of the DPPH radicals.

Reducing power

The method used to measure the reducing power was based on the procedure developed by Yen and Chen [12]. In brief, different concentrations of the essential oil were mixed

with 2.50 mL of a 0.2 M sodium phosphate buffer (pH = 6.6) and 2.50 mL of 1% potassium ferricyanide (K_3Fe $(CN)_6$). The mixture was then incubated in a water bath at 50 °C for 20 minutes. Afterwards, 2.50 mL of 10% trichloroacetic acid were added, followed by centrifugation at 3000 rpm for 10 minutes. The resulting supernatant (2.50 mL) was combined with 2.50 mL of distilled water and 0.50 mL of 0.1% ferric chloride solution, and the absorbance was measured at 700 nm. BHT and Ascorbic acid served as reference standards.

Preparation of topical formulations

To prepare the cream, a mixture of 5 g of beeswax and 10 ml of soya oil was heated using a bain-marie setup, creating a liquid mixture. The essential oil was then added to the cream (beeswax and soya oil) until it reached a concentration of 8%. The resulting topical formulations were appropriately packaged, labeled, and stored at a temperature of 4 °C until they were ready for use.

Evaluation of Wound Healing Activity

Animals

Swiss albino mice (24), weighing between 20–25 grams, were acquired from the Pasteur Institute in Algiers. The mice were housed in standard cages under controlled environmental conditions, including a temperature of 25 ± 1 °C and a 12-hour light-dark cycle. To allow for acclimatization, the mice were given a week in the laboratory environment and provided with unrestricted access to both water and a standard pellet diet. All animal experiments were conducted in strict adherence to ethical protocols for laboratory animal care.

Wound healing evaluation

In this study, the mice were initially anesthetized with ketamine (100 mg/kg) and xylazine (10 mg/kg) through intraperitoneal injection to create wounds. The dorsal region of each mouse was shaved, and four wounds were created using a 5 mm punch, with approximately 1 cm spacing between each wound. Following the surgery, the mice were individually housed to prevent any interference with the wound healing process[13]. A total of 24 mice were randomly divided into four groups, with six to eight mice in each group.

- **Group 1:** The untreated group.
- **Group 2:** Received a commercial ointment of madecassol cream.
- **Group 3:** Received a cream containing 8% essential oil of *Cotula cinerea*.
- **Group 4:** Received a cream containing beeswax and soya oil.

All mice received daily topical treatment using sterile swabs for a duration of 13 days. Throughout this period, wound healing progress was evaluated by measuring the wound closure. The ImageJ software was utilized for this purpose, calculating the percentage of wound closure using the following formula:

Percentage of wound closure =
100-[(Initial wound area - Current wound area) / Initial wound area] x 100.

This measurement allowed for the assessment of wound healing progress over time.

Acute toxicity

In this experiment, different concentrations of the essential oil of *Cotula cinerea* (400 and 600, and 1000 mg/kg) were tested by diluting them in a physiological saline solution (0.9% NaCl). The study involved five groups, with each group consisting of six mice. The first group served as the untreated and received only the physiological saline solution orally. The other groups were administered varying concentrations of the methanolic extract of *Cotula cinerea*.

After administration, the mice were closely observed for a duration of 72 hours to assess any signs of toxicity and monitor the mortality rate. This observation period allowed for the evaluation of potential adverse effects or harm caused by the different concentrations of the essential oil[14].

Statistical study

The data was summarized using mean values accompanied by their corresponding standard deviations. To assess the presence of significant differences among groups, a one-way analysis of variance (ANOVA) test was conducted.

RESULTS AND DISCUSSION

Hydrodistillation extraction

The essential oil derived from the aerial parts of *Cotula cinerea* using the hydrodistillation method was found to have a yellowish-brown color. The yield of the essential oil obtained was 0.42%, indicating the proportion of oil obtained relative to the starting material.

Chemical composition

The essential oil obtained from the aerial parts of *Cotula cinerea* through hydro-distillation was subjected to GC-MS analysis, which identified a total of 29 components. These components accounted for approximately 98.57% of the total oil. The composition of the essential oil, along with their corresponding retention indices and relative area percentages, is presented in **(Table 1)**. The major compound found in the essential oil was thujone, constituting 34.02% of the oil. Other significant components included santolina triene (16.25%), camphor (10.47%), 1,8 cineol (7.19%), *cis*-verbenyl acetate (4.29%), *cis* chrysanthenol (3.15%), α-terpineol (3.06%), α-pinene (2.82%), santolina alcohol (2.88%), and camphene (2.25%). The remaining components, including α-thujene, borneol, terpinen-4-ol, and linalyl acetate, were present in concentrations below 1% in the essential oil. The identified components can be categorized as oxygenated monoterpenes (62.72%), monoterpenes hydrocarbons (34.9%), and sesquiterpene hydrocarbons (0.95%) within the aerial parts of the plant.

Table 1 : Chemical composition of the *Cotula cinerea* essential oil.

Compound[a]	**RI**[b]	**RI**[c]	**Peak area (%)**[d]
Santolina triene	910	908	16.25
α-Thujene	931	929	1.73
α-Pinene	939	934	2.82
Camphene	953	944	2.25
β-Pinene	980	971	0.32
α- Terpinene	1018	1011	0.85
Limonene	1031	1025	0.14
1,8 Cineol	1033	1032	7.19
Santolina alcohol	1035	1034	2.88
y-Terpinene	1062	1051	0.47
Linalool	1098	1092	0.59
Thujone	1114	1119	34.02
Camphor	1143	1145	10.47
Cis Chrysanthenol	1163	1164	3.15
Borneol	1165	1168	1.34
Terpinen-4-ol	1177	1179	1.08
α-Terpineol	1189	1191	3.06
Carvacrol methyl ether	1245	1248	0.89
Linalyl acetate	1257	1263	1.21
Cis-Verbenyl acetate	1280	1285	4.29
Bornyl acetate	1287	1289	1.27
Carvacrol	1298	1304	0.11
Neryl acetate	1365	1374	0.85
Geranyl acetate	1383	1386	0.39
β -Elemene	1389	1391	0.32
Caryophyllene	1418	1420	0.16
Germacrene D	1480	1486	0.35
Caryophyllene oxide	1583	1587	0.12
Grouped compounds			**34.9**
Monoterpene hydrocarbons			**62.72**
Oxygenated monoterpenes			**0.95**
Sesquiterpene hydrocarbons			
Total Identified (%)		**98,57**	

aCompounds identified according their families on HP-5MS column; bRetention indices with respect to C5–C28 n-alkanes calculated on non-polar HP5-MS capillary column; cRetention indices given in literature (NIST, Wiley or ADAMS on non-polar HP-MS or DB5-MS capillary column); [d]Percentage calculated from the peaks areas of GC chromatogram on non-polar HP5-MS capillary column.

Antioxidant activity evaluation

The antioxidant power of the essential oil of *Cotula cinerea* was assessed using the FRAP and DPPH assays **(Table. 2)**. The essential oil of *Cotula cinerea* exhibited a moderate reducing power in comparison to ascorbic acid. The results from the DPPH assay indicated that ascorbic acid had an IC_{50} value of 0.13± 0.001 mg/mL, which was lower than the IC_{50} values obtained for the essential oil of *Cotula cinerea* (5.362±0.142 mg//mL) and BHT (0.019± 0.001 mg//mL).

Table 2: Antioxidant activity of *Cotula cinerea* essential oil.

	IC_{50} (mg/ml)	
	DPPH	**FRAP**
Essential oil	5.362±0.142	0.179±0.018
BHT	0.019± 0.001	0.013 ± 0.002
Ascorbic acid	0.13± 0.001	0.007 ± 0.001

Would healing evaluation

The study evaluated wound healing progress by measuring wound closure, which is the percentage reduction in wound area over time. The experimental groups were compared over a 13-day treatment period, and the findings are depicted in **Fig. 1**. On day 6, groups treated with madecassol cream and treated with 8% *Cotula cinerea* cream exhibited significantly higher percentages of wound closure compared to the untreated group and group treated with cream. Notably, wounds treated with *Cotula cinerea* cream showed accelerated closure after 6 days of treatment **(Fig. 1 and Fig. 2)**. By day 9, wounds treated with 8% *Cotula cinerea* cream achieved a greater percentage of wound closure (93.2 ± 0.7%) compared to the untreated group (62.3 ± 1.4%) and the cream group (63.4 ± 1.9%).

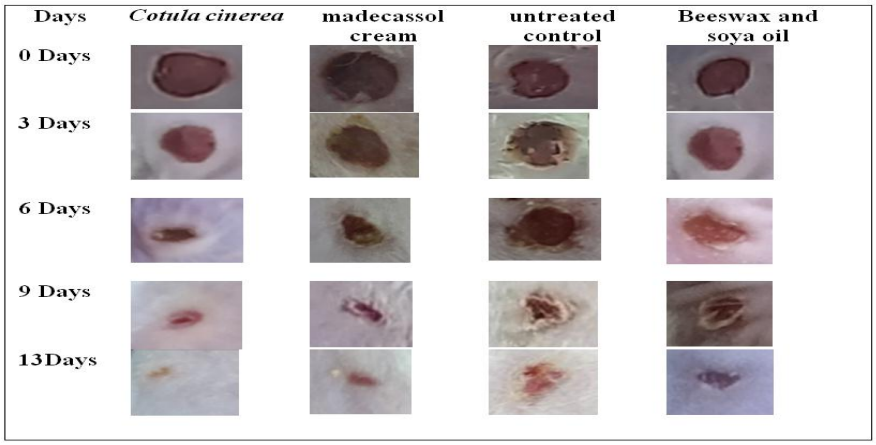

Fig. 1: Photograph of mouse wound sites following topical application of *Cotula cinerea* essential oil cream, madecassol cream, and beeswax and soya oil cream.

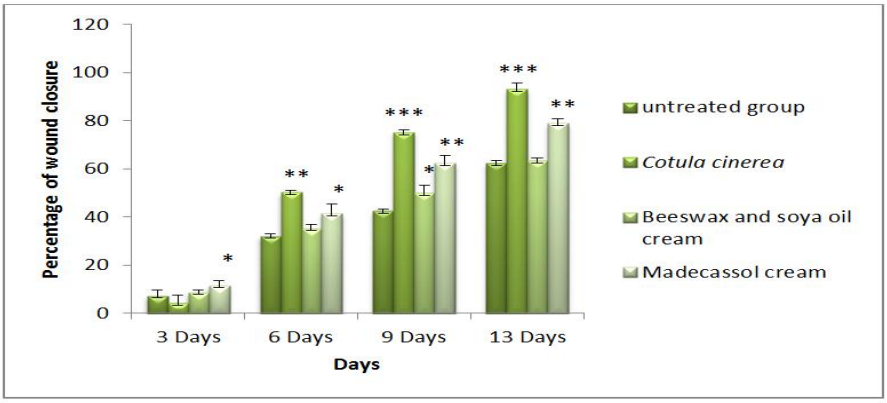

Fig. 2: Wound closure percentage in experimental mouse groups treated with *Cotula cinerea* essential oil cream, madecassol cream, untreated control, and beeswax and soya oil cream over treatment days.* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ are considered significant, compared to the control.

Acute toxicity

The results of the study revealed that the essential oil of *Cotula cinerea* did not induce any signs of toxicity or mortality in mice across multiple trials. This was observed even when the essential oil was administered orally at concentrations of 1000 mg/kg. The absence of toxicity or mortality suggests that the essential oil of *Cotula cinerea*, at the tested concentrations, did not have any harmful effects on the mice during the experimental period.

Discussion

Chemical composition

Cotula cinerea collected in the region of Ghardaïa (Southeast Algeria) yielded 0.41% of essential oil. The chemical analysis using GC/MS revealed the presence of 29 chemical compounds during the flowering period. The dominant compounds were thujone (34.02%), followed by santolina triene (16.25%), camphor (10.47%), 1,8 cineol (7.19%), and cis-Verbenyl acetate. These findings are in line with a previous study conducted by Ghouti et al[8], which also observed α-thujone as the predominant compound (32.35%) in *Cotula cinerea*. The analysis of two *Cotula cinerea* essential oils using GC/MS revealed the identification of 23 chemical compounds at the Beni Guecha station, comprising 96.94% ± 2.35 of the total oil. Notably, the analyzed samples exhibit distinct differences in their chemical compositions. These oils are characterized by elevated levels of oxygenated monoterpenes, with concentrations of 1,8-cineole, camphor, trans-thujone, cis-chrysanthenol, and terpinen-4-ol reaching significant proportions, accounting for 78% and 41% of the composition, respectively [15].

The composition of essential oils is complex, which poses challenges in explaining their activity patterns. Previous studies have demonstrated the antioxidant activity of specific phenolic compounds and other pure substances. When it comes to essential oils, their antioxidant power is often attributed to concepts such as synergism, antagonism, and additive effects[17,18]. However, it is crucial to acknowledge that the chemical composition of the essential oil and its antioxidant activity can be affected by multiple factors. One significant factor is the extraction method employed, such as hydrodistillation, which has the potential to cause the degradation of bioactive compounds. During the process of hydrodistillation, thermal degradation, hydrolysis, and solubilization of bioactive compounds in water can take place, resulting in alterations in their antioxidant capacity[17].

Antioxidant activity

The moderate antioxidant activity of the *Cotula cinerea* essential oil observed in the two assays can be attributed to the higher concentration of oxygenated monoterpenes present in the essential oil, which promote its ability to scavenge free radicals. However, the sesquiterpene hydrocarbons and their oxygenated derivatives exhibited low antioxidant activity[19].

The observed antioxidant activity in this study can be attributed to the presence of specific components, namely thujone, 1,8-cineol, and santolina triene, which are present in relatively high percentages in the essential oil. Terpenes such as pinene, limonene, myrcene, sabinene, and terpinolene are known for their antioxidant properties, although their low percentage in our essential oils may have contributed to the observed antioxidant power[20]. Essential oils are complex mixtures, and their activity patterns are challenging to explain due to this complexity. Previous studies have demonstrated the antioxidant activity of specific phenolic compounds and other pure substances. However, when referring to the antioxidant power of EOs, concepts such as synergism, antagonism, and additivity often come into play [17, 18]. In general, the antioxidant activity of EOs depends on the presence of phenolic compounds and their ability to react with chain-carrying peroxyl radicals, as well as the stability of the resulting phenoxyl radicals[17].

Wound healing evaluation

Various monoterpenes are being studied for their potential wound healing properties. These compounds are believed to promote wound healing through multiple mechanisms of action. One such mechanism is their ability to inhibit the growth of microorganisms through antimicrobial activity. This is achieved by interfering with the RNA and protein biosynthesis of microorganisms. Another

mechanism is their anti-inflammatory activity, which involves reducing the production of certain pro-inflammatory cytokines, such as IL-6 and TNF-α in mast cells[21]. Monoterpenes also inhibit the release of LTC4, which is involved in the inflammatory response, and affect the release of TXB2. Additionally, monoterpenes possess antioxidant properties, which help provide photoprotective effects and inhibit the production of free radicals induced by UVB radiation. They are generally characterized by their low toxicity, making them a suitable choice for therapeutic purposes. Moreover, monoterpenes may also affect the activity of macrophage migration inhibitory factor (MIF) and promote fibroblast growth, which play key roles in immune regulation and wound healing[6,8,21].

Furthermore, prominent essential oils have been recognized for their antioxidant and anti-inflammatory properties. Compounds like α-thujone, β-thujone, 1,8-cineole, camphor, and borneol have been identified as key contributors to the anti-inflammatory effects of these oils. Their presence in essential oils plays a significant role in reducing inflammation and combating oxidative stress. These compounds offer promising potential as therapeutic agents for managing inflammatory conditions due to their antioxidant and anti-inflammatory properties[22]. α-Terpineol demonstrated wound healing effects and exhibited anti-inflammatory activity through multiple mechanisms[23]. α-Terpineol inhibits the cyclooxygenase (COX) enzyme and production of interleukins (IL), contributing to its anti-inflammatory properties[24,25].It acts as an NF-κB inhibitor, leading to the down-regulation of IL-1β and IL-6 expression. Furthermore, α-Terpineol reduces the production of tumor necrosis factor-alpha (TNF-α) and nitric oxide (NO). Additionally, it selectively inhibits ovine COX-2 activity inhibits neutrophil influx, and displays strong antimicrobial and antifungal effects[26,27].

Besides its antioxidant properties, 1,8-cineole has demonstrated anti-inflammatory effects. It functions as an inhibitor for several inflammatory markers, including TNF-α, IL-6, IL-8, LTB 4, PGE 2, and IL-1β. Additionally, it down-regulates the 5-lipoxygenase (LOX) and cyclooxygenase (COX) pathways, which play crucial roles in the inflammatory response[28,29].

The presence of multiple compounds within the essential oil contributes to its ability to demonstrate antioxidant and anti-inflammatory effects, as well as facilitate wound healing. It is important to acknowledge that the article may identify additional constituents that play a role in the observed plant activities. Therefore, exploring and studying these identified compounds can provide further understanding of the mechanisms involved and the potential collective impact of various constituents in the essential oil.

Cotula cinerea is a plant that contains a significant amount of phenolic compounds, and it exhibits remarkable anti-inflammatory capabilities. These properties are closely linked to its ability to promote wound healing[6,8]. The findings of the current study indicate that the wound healing activity of *Cotula cinerea* is primarily attributed to its anti-inflammatory and pro-angiogenic properties. Furthermore, the plant extract influences the extracellular matrix by enhancing collagen production, which contributes to its wound healing effects.

Conclusion

The central objective of this study was to explore the relationship between the chemical composition and the efficacy of essential oil extracted from the aerial parts of *Cotula cinerea*, with a particular emphasis on its potential as a wound-healing and antioxidant agent. The results of this research offer compelling proof that the essential oil derived from this plant could serve as a valuable natural alternative within the pharmaceutical industry, complementing modern medical approaches.

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التئام الجروح في الجسم الحي وتقييم النشاط المضاد للأكسدة في المختبر لنبات الكوتولا الرمادية

زينب لكاش[1*] – محسن سعد الله[2] – حمزة علي بودحار[3] – هندة حسيب[1]– حسينة تونسي[1] – عبد الكريم كاملي[1]

[1]مختبر علم النبات العرقي والمواد الطبيعية، المدرسة العليا للأساتذة ، القبة ،الجزائر

[2]قسم علم الأحياء، المدرسة العليا للأساتذة ، القبة ،الجزائر

[3]مختبر التحليل العضوي الوظيفي ، كلية الكيمياء ، جامعة العلوم والتكنولوجيا هواري بومدين ، باب الزوار ، الجزائر العاصمة ، الجزائر

كان الهدف من هذا البحث هو تحديد المكونات الأولية للزيت العطري الذي تم الحصول عليه من **الكوتولا الرمادية** (دلهي) فس. من خلال عملية التقطير المائي. بالإضافة إلى ذلك ، تهدف الدراسة إلى استكشاف خصائص التئام الجروح في الجسم الحي والخصائص المضادة للأكسدة في المختبر. تم تحديد العديد من المركبات في الزيت العطري ، بما في ذلك الثوجون و سانولينا ترايين والكافور و ١و٨ سنيول. لتقييم إمكانية التئام الجروح ، تم تطبيق الزيت العطري موضعيا على الجروح المستحثة في الفئران ، مما أدى إلى تسارع ملحوظ في التئام الجروح وإصلاحها ، بمعدل ٩٣.٢ ± ٠.٧٪. علاوة على ذلك ، تضمن البحث تقييما للنشاط المسكن للزيت العطري ، والذي تم تقييمه عن طريق إعطاء الحقن داخل الصفاق لحمض الأسيتيك للفئران. علاوة على ذلك ، تم تقييم النشاط المضاد للأكسدة للزيت العطري من خلال قوة مضادات الأكسدة للحد من الحديديك وفحص كسح DPPH. كشفت نتائج هذه الاختبارات المضادة للأكسدة أن الزيت العطري المستخرج من الكوتولا الرمادية أظهر القدرة على تقليل الحديد والتخلص من جذور DPPH بشكل فعال.

تؤكد هذه النتائج على الخصائص النشطة بيولوجيا لزيت الكوتولا الرمادية الأساسي وإمكاناته للتأثيرات التآزرية. وبالتالي ، فإن الكوتولا الرمادية تعتبر مصدرا طبيعيا واعدا للمركبات النشطة بيولوجيا مع إمكانات علاجية لالتئام الجروح. تشير هذه الاكتشافات إلى أن الكوتولا الرمادية يمكن أن يكون بمثابة بديل قابل للتطبيق لأدوية علاج الجروح الاصطناعية في صناعة الأدوية المستقبلية.