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Histological Study and Chemical Composition of *Apium graveolens*: In Vivo Antimicrobial Activity

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ABSTRACT

The purpose of the current investigation is to evaluate the methanolic extract from *Apium graveolens* seeds for chemical composition and in vivo antimicrobial activity, supported by a histological study. The chemical profile of the methanolic extract was identified using high-performance liquid chromatography diode array detector analysis. The toxicity and antimicrobial effects of the methanolic extract were examined through in vivo experiments on rats weighing 220 ± 5 g. The histological study was conducted using the rats' ileum. The methanolic extract (80%) contained sinapic acid (49.9%), ascorbic acid (25.4%), butylated hydroxyanisole acid (6.1%), and quercetin (8.2%), with a yield ratio of 11.74%. The dose of 50 mg/kg of the methanolic extract did not lead to animal lethality or toxicity symptoms. Two days after treatment, the blood cultures of all females treated with the methanolic extract at 50 mg/kg showed sterility (100%). The same result appeared on the fifth day after treatment in all males of the same group. Histopathological examination revealed normal and well-preserved architecture of the ileum in both sexes. The study concludes that the methanolic extract of *Apium graveolens* possesses significant antimicrobial capacity.

KEYWORDS

Anatomopathology, celery, chemical compounds, enteric infection, HPLC, rats

CITATION

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1. Introduction

Enteric infections are a growing public health problem, posing a critical threat across the world.

One particular international public health concern is the struggle against *Escherichia coli* (*E. coli*) infections, which cause intestinal diseases and bleeding. Such bacteria, which can be found in food and drinking water, can cause acute intestinal inflammation and chronic diarrhea (Pokharel *et al.*, 2023 and Xiao *et al.*, 2022). *E. coli* is the most common gram-negative bacterium associated with bloodstream infections (Kolesnichenko *et al.*, 2021). Such infections are thought to be responsible for more than 2 million deaths per year (Cheng et al., 2024). The use of antibiotherapy has been crucial in preventing microbial infections. Nevertheless, the global expansion of antibiotic resistance highlights the need for novel therapies.

A new supply of natural antimicrobial substances is provided by medicinal plants, which are important in addressing basic health demands. Furthermore, several natural materials, including essential oils originating from edible and medicinal plants, spices, and herbs have been declared to possess antimicrobial potency and perform as natural antimicrobials against a variety of pathogenic microbes, as well as food spoilage (Khalil *et al.*, 2015). *Apium graveolens*, popularly known as celery, belongs to the family Apiaceae, which primarily consists of aromatic plants, including the genus Apium. These plants are grown worldwide for their petioles, bulbous roots, seeds, and green leaves (Mezeyova *et al.*, 2018 and Roslon *et al.*, 2010) and possess in vitro antimicrobial properties (Salehi et al., 2019). Indeed, in some investigations, *A. graveolens* has shown modest antibacterial efficacy against multi-drug-resistant *Salmonella typhi* (Al-Aboody, 2021; Rani and Khullar, 2004). Other studies have reported that methanol is the best solvent for extracting antimicrobial compounds from Apium plants (Edziri *et al.*, 2012 and Penna *et al.*, 2001). Moreover, recent research has revealed positive antibacterial effects of these plants against methicillin-resistant *Staphylococcus aureus* in vitro and in vivo (Prakoso *et al.*, 2020).

According to the literature, however, no in vivo studies have been conducted on the antimicrobial activity of the methanolic extract of *A. graveolens* seeds from the Mascara region in western Algeria. The objective of this investigation is to study the polyphenolic profile of the methanolic extract of *A. graveolens* seeds, evaluate its in vivo antimicrobial activity against intestinal infection induced by the pathogen *E. coli*, and conduct a histological study.

2. Materials and Methods

2.1. Sampling:

For the present investigation, *Apium graveolens* seeds (Figure 1) were collected in May 2021from El Maarif in the Tighennif plain, which extends over an area of 108 km^2 and is located 20.70 km from Mascara in western Algeria (latitude 35°24′55.56 N; longitude 0°19′46.72 E) (Figure 2). The plant materials were authenticated by experts for the present research.

Figure 1: Seeds of *Apium graveolens*

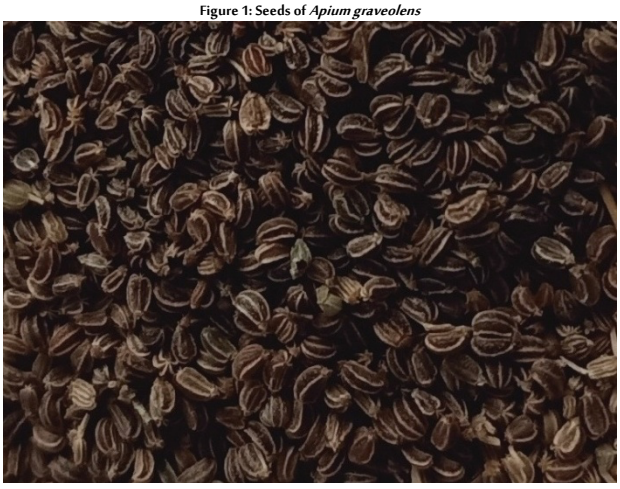

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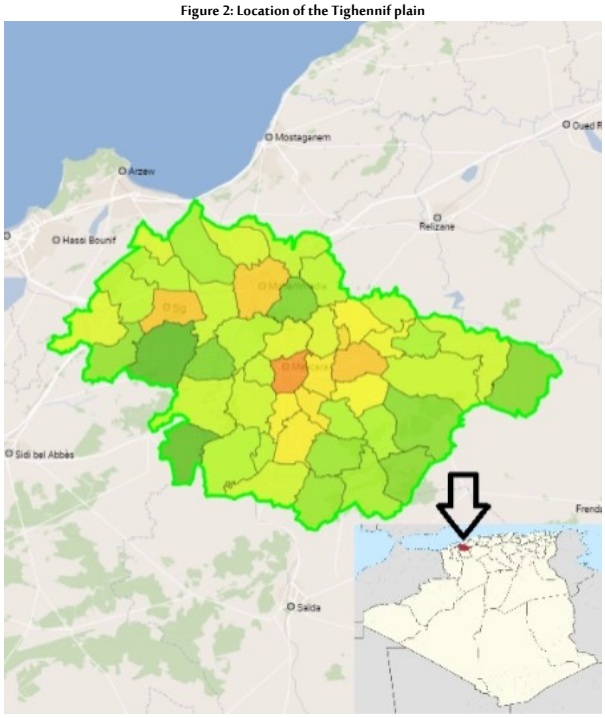
Figure 2: Location of the Tighennif plain



2.2. Bacterial Strains:

The pathogenic agent *Escherichia coli* (*E. coli* ATCC 25922) utilized in this investigation was acquired from the Faculty of Nature and Life Sciences at the University of Mostaganem, Algeria. To validate the test microorganism and test its susceptibility, the VITEK microbial identification system adapted by bioMérieux (bioMérieux, France) was chosen.

2.3. Extraction and Preparation of Plant Sample:

The dried plant materials were macerated with 500 ml of methanol (80%) for 24 h at room temperature. The extract was filtered and dried at a temperature of 40 °C under reduced pressure (Chouikh *et al.*, 2020). The crude extract was lyophilized and maintained at 4 °C for further analysis (ElNaker *et al.*, 2021).

2.4. High Performance Liquid Chromatography Diode Array Detector (HPLC-DAD) Analysis:

Following the aim of evaluating the polyphenolic profile of the tested extract, the analysis was performed using HPLC identification with the YL9100 HPLC system (Young Lin, Anyang, Korea). The HPLC instrument was supplied with a C18 column and diode array detector. The mobile phase consisted of acidified water at 1% formic acid/acetonitrile, and methanol was applied as a solvent. The extract concentration was 5 mg/ml, and the composites were detected at 254 nm under a flow rate of 1 ml/min with a gradient mode; injection volumes were then set at 20 µl. The identification and quantification of phytochemical constituents were assessed by comparison with standards. The quantity of each phytocomponent was expressed based on peak area without correction factors.

2.5. Experimental Animals:

The experimental animals utilized in this research were Wistar rats of both sexes weighing 220 ± 5g. These test rats were raised in the Animal Care Facility of the Faculty of Nature and Life Sciences, Mustapha Stambouli University, Mascara, Algeria.

Animals were housed under optimal standard conditions of temperature (25 ± 2 °C) and relative humidity (60%–70%) with a nychthemeral rhythm (12 h light/dark cycle); standard food and water were given adlibitum. All experimental studies were performed following an overnight fast, but free water access was available. The test animals were assigned at random to several groups to conduct the different experiments.

All experimental processes and approaches adopted in this investigation were conducted according to the ethical standards of the Organization for Economic Cooperation and Development and in compliance with Algerian Law Number 12-235/2012, which is crucial for safeguarding animals used in scientific research.

2.6. Acute Toxicity:

The study aimed to investigate the toxic effects of the methanolic extract acquired from *A. graveolens* seeds in Wistar rats (weighing 220 ± 5g) based on the criteria established by the Organization for Economic Cooperation and Development (OECD, 2008).Two groups were used: The first group (n = 6) received normal saline (9%) orally (p.o.) and served as a control group (CG), whose behavior was to be compared to that of rats from the other group. The second group (n = 6) received individual doses of the methanolic extract of *A. graveolens* seeds (AGM) (50 mg/kg) p.o. (AGMG).

After treatment, the animals were fasted for 2 hours, after which food was made available. To conduct this experiment, the test animals were selected at random. They were observed over 7 days for mortality, changes in skin color, membranes, and pupils, body posture, movement, rearing, tremors, and absorption, as well as the effects of the dose on pain, touch sensitivity, righting reflex, and dietary behavior.

2.7. In Vivo Antimicrobial Activity:

The methanolic extract was tested for its antimicrobial properties on an *E. coli*-induced intestinal infection model. A total of 18 rats were divided randomly into three groups (n = 6), which were designated as follows: The negative control group (NCG) received sterile normal saline (9%); the positive control group (PCG) was treated with a standard antibiotic (4 mg/kg of amoxicillin and clavulanic acid) administered p.o.; and the tested group (CSAG) was administered a dose of 50 mg/kg body weight of *A. graveolens* seed methanolic extract (AGM) p.o.

Forty eight hours before the administration of treatment, all animals were given 1ml of saline solution containing 10^8cfu/ml of *E. coli* in the exponential phase intraperitoneally and then placed in various cages. After 24 hours, blood cultures were conducted to ensure that the animals were infected. After 72 hours, blood cultures were conducted for all groups. This process was carried out regularly after 48, 72, and 144 hours (Yunana *et al.*, 2018). This investigation was conducted under aseptic conditions.

2.8. Histological Study and Preparation of Samples:

After 7 days of experiment, a histological evaluation was conducted on all experimental animals. They were anesthetized, then sacrificed, and the ileum of each was removed. The ileum was kept in a 10% formalin buffer solution. Samples were dehydrated with increasing alcohol percentages from 50% to 99.6% and cleared in xylene; they were then embedded in paraffin using an embedding machine.

After this, blocks of paraffin-embedded samples were sectioned using a rotary ultramicrotome, distributed onto glass slides, and dried overnight. They were stained with hematoxylin and eosin for further microscopic analysis. Microphotography was conducted using Leica Microsystems (Leica Microsystems, Wetzlar, Germany).

3. Results and Discussion

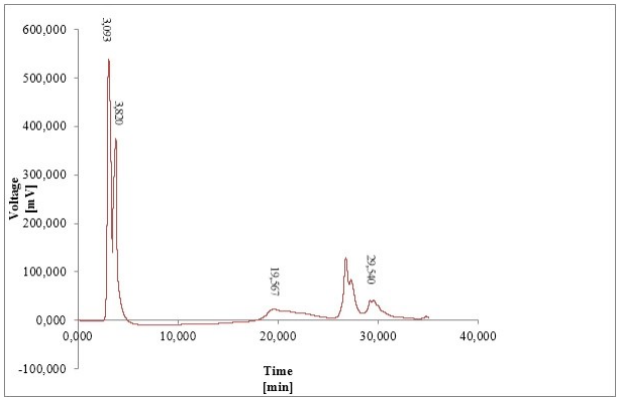
3.1. Yield and AGM Chemical Composition:

The yield value of AGM was 11.74%, higher than the 8.4% obtained by Minaiyan et al. (2021). Seasonal and geographical variables and the postharvest procedure, as well as the extraction solvent, affect the yield percentage (Burdejova *et al.*, 2023). The HPLC analysis of the AGM revealed many phytochemicals, of which the most significant were sinapic acid (49.9%), ascorbic acid (25.4%), quercetin (8.2%), and butylated hydroxyanisole acid (6.1%). This chemical composition is not present in the celery seed ethanol extract and celery seed ethyl acetate fraction identified by gas chromatography-mass selective detector (Kim *et al.*, 2021). However, sinapic acid and quercetin were found in *A.graveolens* seed extract as profiled by Ghoname *et al.* (2023). The phytochemistry of *A. graveolens* is known to be impacted by various factors, including the plant parts (leaves, stem, or seeds), climatic conditions, geographic location, agronomic applications, time and stage of harvest, and postharvest treatment (Chaudhry *et al.*, 2022; Malhotra, 2006 and Sorour *et al.*, 2015) (Table 1, Figure 3).

Table 1: Chemical composition of the methanolic extract of *A. graveolens* seeds.

Peak	Retention Time (min)	Area (%)	Compound Name
1	3.093	49.9	Sinapic acid
2	3.820	25.4	Ascorbic acid
3	19.567	6.1	Butylated hydroxyanisole acid
4	26.777	7.6	Unknown
5	27.300	2.6	Unknown
6	29.540	8.2	Quercetin
7	34.817	0.2	Unknown
	Total	100.0	

Figure 3. High performance liquid chromatography chromatogram of the methanolic extract of *A. graveolens* seeds.



3.2. Acute Toxicity:

Our findings indicated that the dose of 50 mg/kg of AGM did not result in any animal death or signs of toxicity throughout the experimentation period (Table 2).

Table 2: Extract effect on acute toxicity.

Parameters	CG	AGMG
Alertness	usual	usual
Restlessness	usual	usual
Grooming	usual	usual
Touch response	usual	usual
Pain response	usual	usual
Tremors	usual	usual
Writhing reflux	usual	usual
Salivation	usual	usual
Pupils	usual	usual
Urination	usual	usual
Food intake	usual	usual
Water intake	usual	usual
Convulsion	usual	usual
Writhing	usual	usual
Gripping	usual	usual
Skin color	usual	usual
Fur shedding/density	usual	usual
Corneal reflex	usual	usual
Mortality	no mortality	no mortality

CG: control group; AGMG: group received the methanolic extract of *A.graveolens* seeds.

3.3. Antimicrobial Activity Evaluation:

Blood cultures of the NCG (males and females) revealed an intense bacterial culture during the first four samples, followed by a slight decrease in the last sample. However, blood cultures of the PCG showed an intense bacterial culture in males and a slightly less intense bacterial culture in females on day D'0. A continuous decrease in bacterial intensity was observed in all specimens of the PCG across the rest of the experiment.

Observation of the blood cultures of the CSAG indicated an intense bacterial culture in both sexes in the first sample. In the males of this group, a significant decrease in the number of bacterial colonies was detected in the two subsequent blood samples (D'3 and D'5). In D'6 and D'7, the blood cultures were sterile. In the females of the group, blood cultures showed sterility from the second blood sample onward. The sterility of the blood cultures carried out for the CSAG from the second sample for females and the fourth sample for males suggests, when compared to the PCG, that the components of AGM are more powerful than the tested antibiotic (Table 3).

Numerous epidemiological investigations have demonstrated that the genus Apium contributes significantly to avoiding microbial proliferation thanks to its antibacterial and antifungal properties (Kooti and Daraei, 2017). The crude extracts of *A. graveolens* show notable bactericidal activity against several gram-positive, -negative, and fungal strains. It has been demonstrated that plant extracts' potency and their bioactive components, especially flavonoids, have antimicrobial properties (Al-Aboody, 2021).

Indeed, the outcomes seen here accord with those of Uddin et al.(2015), performed in vitro, which demonstrated that *A. graveolens* extracts had strong antimicrobial effects and exhibited good efficacy against *E. coli*, *S. aureus*, *S. typhi*, *B. subtilis*, and *P. aeruginosa*. Flavonoids, alkaloids, and saponins are phytoconstituents of *A.graveolens* extract that contribute to its antibacterial activity. Flavonoids' antibacterial effects can be attributed to a number of processes, including energy metabolism suppression, nucleic acid production, and cytoplasmic membrane function, while bacterial cell membrane permeability is correlated with saponins (Khotimah *et al.*, 2020).

Due to its hydroxyl group's action on bacterial membranes, quercetin is a flavonoid that demonstrates antibacterial activity against a variety of gram-positive and gram-negative bacteria. Quercetin was found to be a potent antibacterial agent in vitro against isolates of *E. coli* that produced OXA-48 β-lactamase by lowering the minimum inhibitory concentrations of imipenem and piperacillin when used in combination (Majumdar and Mandal, 2024). By modulating the activity of adenosine triphosphate, this phytocomposite inhibits the growth of *E. coli* (Qi *et al.*, 2022).

Moreover, the structural integrity of the bacterial cell wall and cell membrane was compromised by quercetin, which made these more permeable. The cell's endochylema contents were discharged, which altered adenosine triphosphate activity. In fact, quercetin impacted protein expression in the cell, reduced bacterial protein production, and ultimately caused cell lysis and death (Wang et al., 2018). In addition, quercetin breaks or modifies plasma membranes, prevents population intervention pathways, stops bacterial adhesion, and inhibits efflux pumps, which interrupt the synthesis of nucleic acids (Qi *et al.*, 2022).

Studies conducted in vitro and in vivo have revealed that vitamin C works against clinical isolates of *E. coli* as an antibacterial and anti-biofilm agent (Hassuna *et al.*, 2023).

The antibacterial action of sinapic acid against *E. coli* and *S. aureus* is substantial. It contributes to the suppression of the NorA efflux pump,

since it has the highest affinity for the protein NorA and forms meaningful interactions, including hydrogen bonds with tyrosine (Singh *et al.*, 2022).

Table 3: Detection of *E. coli* in blood cultures.

Group	Sex	D'0	D'3	D'5	D'6	D'7
NCG	Male	++++	++++	++++	++++	+++
	Female	++++	++++	++++	++++	+++
PCG	Male	++++	++	++	+	–
	Female	+++	++	++	+	–
CSAG	Male	++++	+	+	–	–
	Female	++++	–	–	–	–

++++: too numerous to count; +++: numerous; ++: moderate; +: low; –: sterile.
NCG: negative control group (infected); PCG: positive control group (infected; treated with antibiotics); CSAG: infected group treated with the methanolic extract of *A.graveolens* seeds.

3.4. Histological Study:

The anatomopathological study of the ilea of the NCG in males and females indicated intense inflammation marked by an inflammatory infiltrate containing eosinophilic polynuclear leukocytes and lymphocytes, vascular congestion, and remodeling of lymph nodes, which reflects ileitis; this was probably a consequence of the induced intestinal infection. This could then be expected, through bacterial invasion, to translocate to target organs, such as the liver, spleen, and general blood circulation.

Microscopic examination of the ileum in rats from the PCG revealed an inflammatory infiltrate and vascular congestion in both sexes. In addition, the histological architecture of this group was modified by a well-marked cellular necrosis of the villi. These results show that the antibiotic had an oxidative effect, causing cell necrosis. Subsequently, it caused a modification in the architecture of the ileum by affecting the intestinal microbial flora and the immune system of the ileum in general, resulting in an imbalance and the persistence of inflammation. This led to other complications and pathologies.

Ileum histology of the CSAG, however, showed a normal and well-preserved morphological appearance similar to that of the neutral control group, with normal mucosa and epithelial tissue and well-preserved architecture and relief of the villi, as well as a normal chorion, seat of a slight infiltrate, which is normal in males, and no visible vascular congestion or necrotic remodeling in males or females, representing no inflammation. This appearance was more conspicuous than that of the PCG, which suggests, firstly, that the extract treated the infection and, secondly, that it protected the organ against lesions, destruction, and cellular necrosis. Indeed, it stimulated its functioning and its microbial flora by improving the immune system, fighting against the pathogen, treating inflammation, and fighting cellular oxidation (Figure 4).

Recent research has examined the anti-inflammatory potential of chemicals extracted from Apium plants (Al-Asmari *et al.*, 2017; Powanda and Rainsford, 2011; Vahidi *et al.*, 2019 and Ziyan *et al.*, 2007). One of these chemicals is quercetin, whose anti-inflammatory effect was demonstrated by its decreasing the production of inflammatory molecules such as nuclear factor-kappa B (NF-ĸB), reactive C-protein, activator protein 1, mitogen-activated protein kinase, reactive nitric oxide synthase, and cyclooxygenase-2 (Aghababaei and Hadidi, 2023).

Moreover, due to the presence of vitamins, including vitamin C and vitamin A, *A. graveolens* can positively affect the immune system (Sowbhagya, 2014). A recent study demonstrated the antioxidant and anti-inflammatory qualities of ascorbic acid in treating urinary tract infections induced by *E. coli*, with significant increases in antioxidants (glutathione and total antioxidant capacity) and decreases in inflammatory mediators (malondialdehyde and NF-ĸB) (Hassuna *et al.*, 2023). Furthermore, sinapic acid suppresses the signaling of activating transcription factor 2 protein and NF-ĸB by targeting transforming growth factor beta-activated kinase 1 (Jang *et al.*, 2023).

These findings also align with the histological results obtained in the CSAG, where ileitis, the inflammation of the ileum, was not visible.

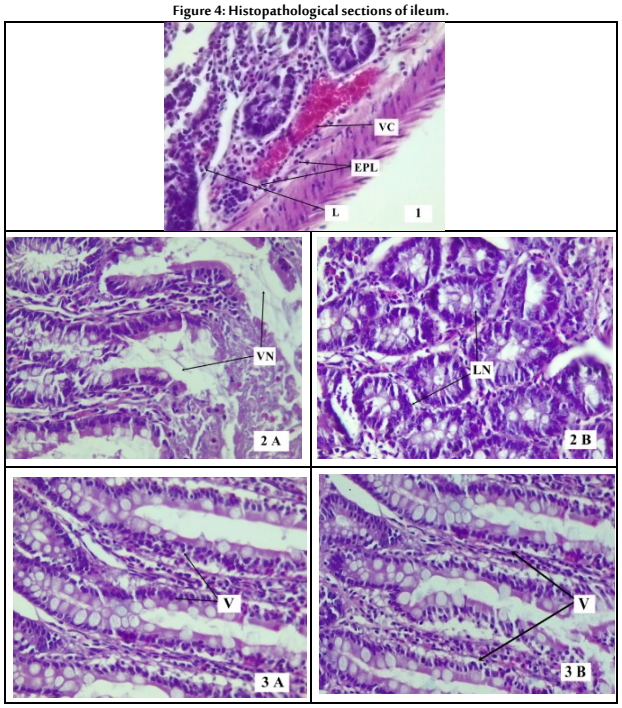
Plants of the genus Apium are rich in flavonoids and phenolic components, which are principally responsible for antioxidant activity. Numerous studies have been performed to demonstrate that the seeds, roots, and leaves of Apium plants possess antioxidant capacities both in vitro and in vivo (Al-Asmari *et al.*, 2017; Liu *et al.*, 2020). Recent investigations have revealed that celery leaves, as compared to petioles, are an excellent source of natural antioxidants and free radical scavengers (Liu et al., 2020). Flavonoids and phenolic chemicals found in celery extract prevent reactive oxygen species (ROS) from being produced during inflammation (Hussain *et al.*, 2016).

Quercetin is the most potent natural antioxidant. It has been shown that quercetin exhibits antioxidant properties as an ROS scavenger (Aghababaei and Hadidi, 2023). By controlling glutathione levels, it can strengthen the body's antioxidant systems (Qi *et al.*, 2022). Furthermore, quercetin can reduce oxidative stress in A549 cells by modifying the expression of genes linked to antioxidants (Qi *et al.*, 2022).

In addition to ascorbic acid, a reducing agent that may decrease and neutralize ROS, including hydrogen peroxide, sinapic acid is a promising antioxidant that efficiently reduces oxidative stress indicators in plasma and tissues while increasing non-enzymatic antioxidants in plasma (Nithya and Subramanian, 2017).

Such data explain the absence of cellular necrosis, the preservation of the villus structure, and the well-maintained architecture of the ileum in the CSAG. They thus confirm the antioxidant effect of this extract.

Figure 4: Histopathological sections of ileum.



(1) Negative control group (infected); (2) positive control group (infected; treated with antibiotics), (A) male; (B) female; (3) infected group treated with the methanolic extract of *A. graveolens* seeds, (A) male; (B) female (Hematoxylin and eosin staining x 100). VC: vascular congestion; L: lymphocytes; EPL: eosinophilic polynuclear leukocytes; VN: villi necrosis; V: villi; LN: lymphatic nodes.

4. Conclusion

This study revealed that the methanolic extract of *A.graveolens* seeds was a rich source of various bioactive molecules (sinapic acid

[49.9%], ascorbic acid [25.4%], butylated hydroxyanisole acid [6.1%], and quercetin [8.2%]). *A. graveolens* seed extract harvested from western Algeria was found to be completely safe and non-toxic at the dose of 50 mg/kg. Furthermore, the in vivo study showed that this extract was 100% effective in treating *E. coli*-induced intestinal infection in the treated animals.

The efficiency of this extract could be associated with the various phytochemicals found in the plant. This result is confirmed and validated by the application of this plant in treating various microbial infections in traditional medicine. *Apium graveolens* is an antimicrobial agent that could be used as an antibiotic or a natural antimicrobial ingredient in the antibiotic industry. This plant also possesses anti-inflammatory and antioxidant properties, which qualify it as an excellent therapeutic substance.

This study suggests that future research should be designed to investigate the effect of other extraction solvents and techniques on the phytocomposition of this plant and evaluate its antimicrobial activity in vitro and in vivo in treating infections and combating antibiotic resistance. Additionally, clinical trials should be devised with large sample numbers and extended follow-up periods to explore the extract's applicability and acquire relevant clinical data, including toxicity, to evaluate its specific therapeutic dosage and improve its application in patients.

Biographies

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Prof. Sonnet graduated from Caen University in 1997 with a Ph.D. in Medicinal Chemistry. From 1997 to 1998, he worked as a Postdoctoral Research Assistant in Synthetic Organic Chemistry at Montreal University. In 1998, he started as an Assistant Professor of Medicinal Chemistry at the UPJV Faculty of Pharmacy. In 2004, he was promoted to professor. He has led the AGIR research team since 2018. His research area is the development of antibacterial and antimalarial medicines.

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