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Title: The Miracle from Pistachio Shell: Natural Healing Gel

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INTRODUCTION

A B S T R A C T

This project examines studies on wound healing processes and the materials used. Wounds are classified into two types: acute and chronic. Acute wounds heal quickly, while chronic wounds heal slowly or recur. The wound healing process occurs in four stages: hemostasis, inflammation, proliferation, and maturation. Various wound dressings are used to accelerate healing. Modern wound dressings such as hydrocolloids, alginates, and hydrogels support healing by providing a moist environment.
Antibacterial, antioxidant, and anti-inflammatory substances are also crucial in wound healing processes. Extracts obtained from the outer shell of pistachios possess antibacterial and antioxidant properties, making them a potential candidate for medical applications. The study highlights the sustainable recycling of pistachio shells for the production of an antibacterial gel. This approach is significant in terms of waste management and environmental protection.
In the gel production process, chemical components such as carbomer, triethanolamine, and propylene glycol were used. Carbomer acts as a thickening agent, while triethanolamine serves as a neutralizer. The extraction process was applied to obtain extracts from pistachio shells. This project not only contributes to the reutilization of waste but also promotes innovation in the medical field by utilizing natural resources.

1. Wounds

A wound is defined as damage occurring on the skin surface or internal tissues of the body due to the impact of a blow, trauma, sharp or piercing object, or the effect of chemical, thermal, or biological agents reacting with the skin or body. The formation of a wound disrupts the integrity of the skin or body and typically triggers natural healing processes such as hemostasis (cessation of bleeding), inflammation, and proliferation (tissue regeneration) [4]Wounds are classified into two categories based on their etiology: acute and chronic [1].

1.1 Acute Wounds

An acute wound is a clean wound that occurs due to trauma or surgery and generally responds well to the healing process[2]. These wounds result from the loss of integrity in the skin and body tissues due to trauma, surgical intervention, or infection. Acute wounds can heal with medical intervention or first aid. In most cases, wound dressings are applied to the

1.2 Chronic Wounds

Chronic wounds are wounds that do not heal or heal very slowly due to a persistent factor, and they often recur [3].Because these wounds tend to repeat, the risk of infection is higher, and their treatment is more complex. Chronic wounds require more advanced care

and longer treatment periods compared to acute wounds.

2. Wound Healing Methods

Wound healing methods may vary depending on the shape, size, depth, or location of the wound. If the wound is small enough and not in a vital area of the body, no dressing is required, and the body can heal the wound through its natural healing processes. The stages of natural wound healing are divided into four phases: hemostasis (stopping the bleeding through clotting), inflammation (the formation of immune cells that cleanse damaged cells from harmful microorganisms), proliferation (the formation of new tissues and blood vessels), and maturation (the strengthening of newly formed tissues) [4].

If the wound is more severe, first aid should be applied to prevent infection. This can include alcohol, antiseptic solutions, gels, and dressing. If medical intervention is required, stitches may be applied to the damaged area, tissue adhesives can be used, antibiotics may be administered, or wound dressings may be applied. In addition to these treatments, alternative methods can also be used for wound tissue healing.

3. Wound Dressings

Wound dressings cover the damaged area, protecting the injured tissue from external factors, and, if appropriately designed, can activate cell production in the damaged area, thereby contributing to the healing process[1]. It has been observed that creating a warm and moist environment on the damaged tissue leads to faster and more successful wound healing. To achieve these optimal healing conditions, modern wound dressings have been developed. Since wounds come in various types, multiple types of wound dressings are available to suit different needs.

3.1 Wound Dressings Based on the Material They Are Made Of

Hydrocolloid Dressings: Hydrocolloids are wound care products made from substances that form gels, flexible materials, and adhesives, combined to create thin layers. Upon contact with the wound, they swell over time and form a gel, creating a moist environment conducive to healing. These dressings help reduce pain during the healing process and prevent foreign particles from coming into contact with the wound [1].

Alginate Dressings: Alginate dressings, due to their high liquid absorption capacity, form a strong hydrophilic gel when they come into contact with wound exudate (fluid). This gel formation creates an optimal, warm, and moist environment for wound healing [1]. Additionally, these dressings have antibacterial properties that help prevent infection.

Hydrogel Dressings: Hydrogels are gels that contain a high amount of water in their structure. These dressings have high absorption capacity and do not stick to the wound surface [1]. They also have a pain-relieving effect and, due to their moist nature, cool the wound area, providing comfort during the healing process.

3.2 Wound Dressings Based on Their Physical Forms

Foams: Foam dressings are flexible, highly absorbent, soft, and porous materials [1]. When placed on a moist wound surface, they absorb wound exudate due to their capillary effect. When applied to a dry surface, the structure helps reduce moisture loss and prevents the damaged area from drying out.

Transparent Films: Films are highly flexible, which makes them comfortable for the patient. They serve as a barrier, preventing bacteria from contacting the wound. Additionally, they prevent slipping, are waterproof, and allow the passage of

essential gases like carbon dioxide and water vapor, which are crucial for wound healing [1].

3.3 Wound Dressings Based on Active Ingredients

Antibacterial Dressings: The purpose of these dressings is to prevent infection in wounds such as ulcers, surgical incisions, or open wounds [1]. Antibiotics can be impregnated into wound dressings to provide antibacterial properties. These dressings prevent the growth of bacteria in the wound bed, thus reducing the risk of infection.

Dressings Containing Growth Factors: While antibacterial dressings fight infection and assist with wound healing, they do not contribute physiologically to the healing process. Growth factors, on the other hand, promote cell division, which accelerates the healing of the wound and the closure of damaged tissue. These substances are impregnated into dressings and work effectively in environments that are conducive to wound healing [1].

Dressings Containing Vitamins and Minerals: Like other active ingredients, vitamins and minerals play an essential role in wound healing. In particular, vitamins A, C, E, and minerals like zinc and copper are crucial for effective healing. For this reason, these vitamins and minerals can be integrated into wound dressings to support and enhance the healing process [1].

4. Antimicrobials

Antimicrobial refers to substances or treatments that kill or inhibit the growth of microorganisms such as bacteria and viruses [6]. Antimicrobials, widely used in fields like healthcare and agriculture, play a vital role in treating infections in wounds. Antibiotics are examples of antimicrobial substances that are effective against bacteria, fungi, parasites, and viruses [7]. Additionally, antimicrobial substances such as disinfectants and antiseptic solutions can also be used to combat microorganisms. These substances are indispensable in various fields and are crucial in the fight against diseases.

5. Antioxidants

Free radicals are molecules that arise due to external factors and can interact with biological materials in the body and cells, causing damage. Antioxidants, or the antioxidant defense system, exist to prevent the damage that free radicals may cause [8]. If free radicals are not neutralized by antioxidants, oxidative stress occurs, leading to tissue damage. Oxidative stress can contribute to the development of various diseases such as cancer, hypertension, asthma, diabetes, and more [9].

6. Anti-inflammatory

Anti-inflammatory substances are those that reduce or even prevent inflammation in the body. Inflammation is the body's natural defense response to injury, infection, or other factors. However, excessive or chronic inflammation can damage tissues and lead to various diseases [10].

7. Pistachio (Pistacia Vera)

Pistachio (Pistacia vera), especially grown in the Southeastern Anatolia Region of Turkey, provides a significant source of income to the country through its exports [11]. For example, in 2023, Turkey exported pistachios worth $151.6 million to other countries [12]. However, the pistachio’s value is not limited to its financial contribution from exports. In this research, it has been observed that the extract obtained from the outer shell of fresh pistachios shows antibacterial properties through bacterium cultivation experiments. Additionally, other studies have identified antioxidant and other beneficial properties in the soft shell of fresh pistachios. Based on these findings, it has been established that pistachios can be utilized not only in trade but also in the medical field.

7.1 Pistachio Outer Shell

Generally, consumers focus on eating the nut of the pistachio, and therefore the outer shell does not attract much attention. However, as mentioned earlier, the outer shell is actually one of the most valuable parts of the pistachio. In addition to being consumed as a snack, pistachios can also be used for medicinal purposes. This is due to research findings showing that the outer shell of pistachios contains biological activities such as antibacterial, antioxidant, anti-inflammatory, hypoglycemic, and anti-atherogenic properties. When consumed in reasonable amounts, the fats in the shell can be beneficial for health [13].

8. Carbomer

Carbomer, also known as polyacrylic acid, is an organic compound with the formula $C_3H_4O_2$ [14]. Carbomers are compounds that can be used for thickening or gel-forming purposes. These substances are commonly found in pharmaceutical and cosmetic products. Examples include eye drops, skin creams, and similar cosmetic products. Carbomer also has properties such as pH regulation.

8. Triethanolamine

Triethanolamine, commonly referred to as TEA in the chemical industry, is a compound with the formula $C_6H_{15}NO_3$. It is used in the manufacturing of products such as paper, ink, and certain oils. Additionally, due to its dense and viscous structure, it is also used in the production of shaving foam. Beyond its other properties, triethanolamine can be used to neutralize carbomer. [15]

9. Propylene Glycol

Propylene glycol, also known as propanediol, is a colorless, odorless, and viscous compound. It is widely used in many processed products because it helps maintain their consistency, moisture, and texture. Propylene glycol can function as an emulsifier, binding substances like water and oil that typically do not mix. Additionally, it is used as an anti-caking agent and moisturizer. This compound can be found in a variety of products, including cosmetics, pet foods, bath products, sauces, pharmaceuticals, and more. [16]

10. Extraction

Extraction is a process used to obtain a specific substance from a mixture in its pure form. This process is typically carried out using a separating funnel. A solvent (such as alcohol, water, etc.) is added to the mixture intended for extraction, and the mixture is shaken. To adjust air pressure, the stopcock should be opened carefully. As a result of these steps, the organic phase is separated, dried, or evaporated to obtain the desired pure compound. [17]

METHOD

1.Problem Definition

The aim of this study is to determine whether the extract obtained from the shells of pistachios has antimicrobial properties and to evaluate its effectiveness against *E. coli* bacteria when incorporated into a hydrogel formulation. The pistachio shells were separated.

2.Hypothesis

The extract obtained from pistachio shells possesses antimicrobial properties, and when integrated into a hydrogel, it can maintain these properties and inhibit the growth of *E. coli* bacteria.

3. Materials and Methods

3.1. Materials

- Pistachio shells

- Solvent (e.g., ethanol or methanol)
- *Escherichia coli* culture
- Carbomer (3.5 g)
- Triethanolamine (25 drops)
- Propylene glycol (13.3 g)
- Distilled water (200 mL)
- Ethyl alcohol (2 mL)
- Disk diffusion plates and appropriate agar medium
- Microbiological equipment (laminar flow cabinet, incubator, etc.)

3.2. Methods

The extraction procedure began with cleaning and drying the pistachio shells to ensure the removal of any impurities. The extract was then obtained using an appropriate solvent, such as by employing the cold extraction method for 48 hours. Once the extraction was complete, the solvent was evaporated under vacuum conditions to concentrate the extract for further use.

For the antimicrobial activity test using the disk diffusion method, the *E. coli* culture was first spread evenly onto an appropriate agar medium. A specific volume of the extract, such as 20 µL, was then applied to a sterile disk and placed onto the prepared agar plate. The plates were incubated at 37°C for 24 hours to allow microbial growth and interaction with the extract. After the incubation period, the inhibition zone diameters were carefully measured to assess the antimicrobial activity of the extract.

In the hydrogel preparation process, 3.5 grams of carbomer were added to 200 mL of distilled water and left to swell for 24 hours to ensure proper hydration. After swelling, the carbomer was treated with 25 drops of triethanolamine and thoroughly mixed to achieve neutralization. To enhance the formulation, 2 mL of ethyl alcohol, 13.3 grams of propylene glycol, and 20 mL of pistachio extract were incorporated into the mixture, resulting in a homogeneous hydrogel.

Finally, the antimicrobial properties of the hydrogel formulation were tested using the disk diffusion method. The prepared hydrogel was applied onto agar plates in the same manner as the extract. Discs containing the hydrogel were placed onto the *E. coli* culture and incubated at 37°C for 24 hours. After incubation, the inhibition zone diameters were measured, and the results were recorded to evaluate the antimicrobial effectiveness of the hydrogel formulation.

FINDINGS

1.Antimicrobial Activity of Pistachio Extract:

In tests conducted using the disk diffusion method, the pistachio shell extract demonstrated a significant antimicrobial effect against *E. coli* bacteria. The inhibition zone diameter created by the extract was measured at 3 cm. This result confirms that the extract has the ability to inhibit bacterial cell growth.

2.Integration of Pistachio Extract in Hydrogel and Antimicrobial Activity:

Pistachio extract was integrated into a carbomer-based hydrogel matrix, and the antimicrobial activity of the formulation was tested using the disk diffusion method. The inhibition zone diameter formed by the hydrogel was measured at 2.5 cm, compared to the extract's pure form. This result indicates that the hydrogel formulation preserved the antimicrobial activity of the extract, but there was approximately a 16.7% reduction in effectiveness.

3.Comparative Evaluation and Possible Reasons

Decrease in Effectiveness: The smaller inhibition zone diameter created by the hydrogel compared to the pure form of the extract can be explained by the hydrogel matrix potentially limiting the diffusion of the extract or partially reducing the bioavailability of the antimicrobial components.
Hydrogel Matrix: The carbomer and other components of the hydrogel may have slowed the release of the extract. While this could provide an advantage for prolonged effects through controlled release, it may also be a limitation for short-term activity.
Stability of Antimicrobial Compounds: During the integration of the extract into the hydrogel environment, chemical interactions with components like ethanol or triethanolamine could affect the stability or concentration of the active compounds.

4.Importance of the Inhibition Zone

The 3 cm inhibition zone in the pure extract indicates high antimicrobial activity, while the 2.5 cm zone observed in the hydrogel formulation shows that the effect was maintained, but somewhat reduced. Strategies such as improving the homogeneity of the hydrogel formulation or increasing the extract quantity could enhance the inhibition effect.

5. Interpretation of General Findings

These findings indicate that pistachio extract possesses strong antimicrobial potential and that hydrogel formulations can be used as a carrier system for this extract in biomedical applications. However, the slight reduction in the antimicrobial activity of the extract in the hydrogel environment highlights the need for optimization in the hydrogel design.

RESULT AND DISCUSSION

1. Results

In this study, the antimicrobial activity of the pistachio shell extract was tested on *E. coli* bacteria using the disk diffusion method. The pistachio extract formed an inhibition zone of 3 cm on *E. coli*, indicating that the extract has an effective antimicrobial effect. This finding is consistent with similar studies in the literature and supports the presence of biologically active compounds in pistachio extract.

Additionally, the same extract was integrated into a hydrogel formulation and tested. The inhibition zone formed by the hydrogel was measured at 2.5 cm, showing approximately a 16.7% reduction compared to the pure extract. This result suggests that the hydrogel formulation partially preserved the antimicrobial activity of the extract, but with a notable decrease in its effectiveness.

2. Discussion

2.1 Effect Of Hydrogel Formulation

The observed loss of activity after integrating pistachio extract into the hydrogel can be attributed to several factors. First, the structural properties of the hydrogel can affect the release rate of the extract. Carbomer-based gels, by increasing viscosity, may slow the release of the extract, which can prevent the effect from manifesting quickly. This slowed release could limit the short-term effectiveness of the formulation, making it a disadvantage for conditions requiring immediate treatment. However, for long-term effects, this controlled release could be beneficial.

2.2 Chemical Interactions and Stability

The components of the hydrogel, particularly substances like ethanol and triethanolamine, may interact with the active compounds in the pistachio extract. These interactions could affect the stability and biological activity of the extract. Phenolic compounds and other antimicrobial compounds in the extract may experience a loss in solubility and stability within the hydrogel. However, a more detailed investigation of these

interactions could help optimize the formulation and improve its effectiveness.

2.3 Decrease in Efficacy and Shrinkage of the Inhibition Zone:

The observed decrease in the inhibition zone after integrating the extract into the hydrogel may also be related to the uneven distribution of the extract on the surface of the hydrogel or limited solubility. The matrix structure of hydrogels, particularly in preventing the rapid release of antimicrobial compounds, might have made it more difficult for active components to interact with microorganisms. This could explain why a smaller inhibition zone was formed compared to the pure extract.

2.4 Suggestions for Future Studies:

Formulation Optimization: Changes can be made in the design of the hydrogel. By using different polymeric materials (e.g., alginate, chitosan), it may be possible to increase the controlled release of the extract. Long-Term Efficacy Tests: Longer release tests can be conducted to assess the hydrogel's release over time and its efficacy. This would be important for evaluating the long-term effects of the hydrogel.
Testing on Different Microorganisms: In this study, tests were conducted only on *E. coli*. The effectiveness of the extract and hydrogel can be tested on different pathogenic bacteria (e.g., *S. aureus*, *P. aeruginosa*) to expand the spectrum of activity.
Active Ingredient Characterization: Chemical characterization of the active components in the pistachio extract should be performed, and detailed analyses (e.g., GC-MS or HPLC) should be carried out to identify these compounds. This will help in better understanding the biological activity of the extract.

2.5 Conclusion:

The pistachio shell extract is effective as an antimicrobial agent in its direct form, but it has partially lost its activity within the hydrogel formulation. However, the hydrogel formulation can be considered a potential carrier system, particularly for controlled release and long-term effects. This study is an important step toward enhancing the biomedical applicability of pistachio extract, and it is believed that further research could further increase this potential.

Suggestions

To enhance the effective release of the extract in hydrogels, different polymer structures (e.g., alginate or chitosan) could be used. Long-term release and activity studies should be conducted to evaluate whether the antimicrobial effect is sustained over time. Additionally, disk diffusion results can be tested on different bacterial species to broaden the activity spectrum.

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