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Review Article

Application Of Phytosome In Wound Healing: A Comprehensive Review

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ABSTRACT

Wound healing is a crucial physiological process involving complex cellular and molecular mechanisms. Conventional treatments often struggle with limited drug bioavailability, stability, and side effects. Phytosome technology offers an innovative solution to enhance the efficacy of phytoconstituents in wound healing. This review explores the application of phytosomes in wound care, focusing on their mechanisms of action, specific phytoconstituents used, clinical evidence, and future directions. Phytosome-based formulations, such as those containing curcumin, quercetin, and resveratrol, have demonstrated improved wound healing through enhanced bioavailability, antioxidant, anti-inflammatory, and antimicrobial activities.

INTRODUCTION

Wound healing is a complex and dynamic biological process involving multiple cellular and molecular mechanisms aimed at repairing damaged tissue. This process can be triggered by various forms of injury, such as cuts, burns, surgical incisions, ulcers, or chronic wounds. It typically progresses through four overlapping and well-coordinated phases: hemostasis, inflammation, proliferation, and remodeling. Despite significant advancements in wound care, managing wounds effectively remains a challenge, especially in cases of chronic wounds, diabetic ulcers, and infected wounds. Chronic wounds, such as pressure ulcers, venous leg ulcers, and diabetic foot ulcers, affect millions of people worldwide, leading to a significant socioeconomic burden. These wounds often fail to heal within the expected timeframe, primarily due to impaired blood flow, prolonged inflammation, infection, and oxidative stress [1,2].

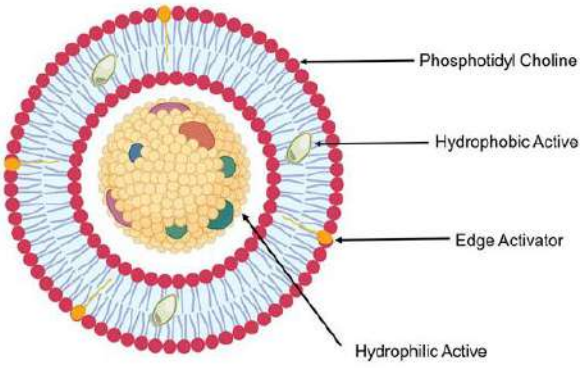

Figure 1: Structure of Phytosome

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Conveund treatments include the use of antiseptics, antibiotics, synthetic dressings, and surgical interventions. However, these methods have limitations such as poor penetration, limited drug bioavailability, side effects, and the development of antimicrobial resistance. For instance, topical antibiotics might not reach deeper tissue layers effectively, and oral antibiotics often fail to maintain sufficient local drug concentrations at the wound site. Moreover, the prolonged use of synthetic drugs can lead to delayed wound healing due to cytotoxic effects on regenerating cells [3]. Given these chthere has been increasing interest in exploring alternative therapies based on natural plant-derived compounds, also known as phytoconstituents. These compounds, including flavonoids, terpenoids, alkaloids, polyphenols, and saponins, possess a wide range of pharmacological properties beneficial for wound healing, such as anti-inflammatory, antioxidant, antimicrobial, and angiogenic effects. However, the clinical application of these phytoconstituents is limited due to their poor solubility, low bioavailability, rapid metabolism, and instability under physiological conditions [4-6].

Phytosome Technovel Approach

To overcome the limitations of traditional drug delivery systems, **phytosome technology** has emerged as an innovative approach to enhance the therapeutic potential of phytoconstituents. The term "phytosome" refers to a complex formed by the interaction between phytoconstituents (active plant extracts) and phospholipids, typically phosphatidylcholine. This interaction results in a lipid-compatible molecular complex that can efficiently penetrate biological membranes, enhancing the solubility, stability, and bioavailability of the encapsulated phytoconstituents [7]. Phytosomes differ from conventiomes in that the phytoconstituents are chemically bonded to phospholipids rather than being merely encapsulated within the lipid bilayer. This unique structural arrangement offers several advantages, including improved membrane permeability, enhanced absorption, and prolonged retention of the active compounds at the site of action. As a result, phytosomes have shown increased therapeutic efficacy in various preclinical and clinical studies compared to traditional herbal extracts and liposome-based formulations [8].

For example, **curcumin**, a well-known polyphenourcuma longa (turmeric), possesses strong anti-inflammatory, antioxidant, and antimicrobial properties. However, its clinical utility is hampered by poor water solubility and low systemic bioavailability. The formulation of curcumin as a phytosome complex significantly enhances its absorption and tissue distribution, making it more effective in promoting wound healing. Clinical studies have demonstrated that curcumin phytosomes accelerate wound closure, reduce oxidative stress, and enhance tissue regeneration in various wound models, including diabetic ulcers and burn wounds [9,10].

Similarly, **quercetin**, a flavonoid found in many fruits and vegetibits potent antioxidant and anti-inflammatory activities that are beneficial for wound healing. Quercetin phytosomes have been developed to enhance its poor solubility and bioavailability. Studies have shown that quercetin phytosomes promote faster epithelialization, reduce inflammation, and enhance collagen deposition in wound healing models. These benefits highlight the potential of phytosome technology to address the limitations of conventional therapies and provide an effective alternative for wound care [11-13].

Advantages of Using Phytosome Technology in Wound Care

Phytosome-basivery systems offer several advantages over traditional formulations in wound healing, including:

1. **Improved Bioavailability**: The complexation of phytoconstituents with phospholipids enhances their solubility and absorption, leading to higher bioavailability and better therapeutic outcomes.
2. **Enhanced Stability**: Phytosomes protect the encapsulated phytoconstituents from degradation due to environmental factors such as light, heat, and oxidation, thereby improving their stability and shelf life.
3. **Sustained Release**: Phytosome formulations provide a controlled release of active compounds, allowing for prolonged therapeutic effects and reducing the need for frequent application.
4. **Targeted Delivery**: The lipid-based nature of phytosomes enhances their penetration through biological membranes, enabling targeted delivery of the active compounds to the deeper layers of the wound tissue, where they can exert their therapeutic effects more effectively [14,15].

Phytosome Structure in Drug Delivery Systems

Phytosome technology is an advanced drug delivery system specifically designed to improve the bioavailability and therapeutic efficacy of plant-derived phytoconstituents. The unique structure of phytosomes distinguishes them from conventional delivery systems like liposomes and polymeric nanoparticles. This section delves into the detailed structural aspects of phytosomes and their significance in enhancing drug delivery, particularly in the context of wound healing.

1. Components of Phytosome Structure

Phytosomes are formed by complexation between two main components:

- **Phytoconstituents (Active Plant Extracts):** These include bioactive compounds like flavonoids (quercetin, silybin), polyphenols (curcumin, resveratrol), terpenoids, and glycosides. These molecules are chosen for their pharmacological benefits in wound healing, including anti-inflammatory, antioxidant, and antimicrobial properties. However, their therapeutic potential is often limited by poor water solubility, low permeability, and rapid metabolism.
- **Phospholipids:** Phosphatidylcholine is the most commonly used phospholipid in phytosome formulations. It consists of:
- **Hydrophilic Head:** The polar head group interacts with the polar phytoconstituent through hydrogen bonds or electrostatic interactions.
- **Hydrophobic Tails:** The non-polar fatty acid chains interact with lipid environments, enhancing membrane permeability and the solubility of the complex.

2. Formation of the Phytosome Complex

The formation of a phytosome involves the molecular complexation of a phytoconstituent with phospholipids. Unlike liposomes, where the active compound is merely encapsulated, in phytosomes, the phytoconstituent is chemically or physically bound to the phospholipid. This interaction involves non-covalent bonds such as hydrogen bonding, van der Waals forces, or electrostatic interactions between the polar head of the phospholipid and the phytoconstituent. This results in a **molecular complex** where the phytoconstituent becomes an integral part of the lipid-compatible bilayer, increasing its affinity for biological membranes and enhancing absorption.

3. Structural Features of Phytosomes

Phytosomes exhibit distinct structural features:

- **Monolayer Structure:** Phytosomes typically form a monolayer structure, where the phytoconstituent is conjugated with the hydrophilic head of the phospholipid. This structure mimics the natural cell membrane, facilitating better integration and absorption in the body.
- **Size and Morphology:** Phytosomes are nanosized particles, generally ranging from

100 to 200 nm in diameter. Their small size and spherical or ellipsoid shape contribute to enhanced penetration into biological tissues, such as skin layers in wound healing applications.

- **Complexation Ratio:** The typical ratio of phytoconstituent to phospholipid in a phytosome formulation is 1:1 or 1:2 by weight. This ratio ensures optimal interaction and stability of the complex [16,17].

4. Mechanism of Action in Drug Delivery

The unique structure of phytosomes offers several advantages in drug delivery, especially for enhancing the bioavailability of poorly soluble phytoconstituents:

- **Enhanced Lipid Solubility:** The complexation of hydrophilic phytoconstituents with phospholipids increases their lipid solubility, improving absorption through the lipid bilayers of cell membranes. This feature is particularly beneficial in topical wound healing formulations, where skin penetration is critical.
- **Improved Membrane Permeability:** Phytosomes exhibit enhanced permeability due to their lipid-compatible structure, which mimics cell membranes. This allows the phytoconstituent to be absorbed more efficiently across biological barriers such as the skin and gastrointestinal tract.
- **Protection from Degradation:** The phospholipid complex protects sensitive phytoconstituents from degradation by enzymes, light, heat, and oxidation. This enhanced stability is crucial in maintaining the therapeutic efficacy of the active compound during storage and upon application to the wound site.
- **Controlled Release:** The molecular bonding between the phytoconstituent and phospholipid allows for a controlled release of the active compound, providing sustained therapeutic effects over time. This is particularly advantageous in wound healing, where prolonged activity is needed to support the repair process [18].

5. Structural Advantages in Wound Healing

The structural properties of phytosomes make them especially suitable for wound healing applications:

- **Enhanced Skin Penetration:** The lipid-compatible nature of phytosomes facilitates deeper penetration into the skin layers, delivering the active phytoconstituent directly to the site of injury. This targeted delivery enhances the local therapeutic effects, promoting faster wound closure and tissue regeneration.
- **Reduced Inflammation:** The improved bioavailability of anti-inflammatory phytoconstituents, such as curcumin and quercetin, helps in effectively reducing inflammation at the wound site. The complexation with phospholipids ensures that these compounds remain stable and active over a prolonged period.
- **Antioxidant Protection:** The enhanced stability of phytoconstituents within the phytosome complex helps in preserving their antioxidant properties. This is crucial in wound healing, where oxidative stress can delay the repair process. By reducing oxidative stress, phytosome-based formulations promote a healthier wound environment and faster healing [19]

6. Comparison with Other Delivery Systems

Table 1: Comparison with Other Delivery Systems

Feature	Phytosome	Liposome	Polymeric Nanoparticles
Encapsulation	Phytoconstituents bonded to phospholipids	Encapsulated in lipid bilayer	Encapsulated in polymer matrix
Bioavailability	Higher, due to direct interaction with phospholipids	Moderate	High, but dependent on polymer type
Size	100-200 nm	50-500 nm	10-200 nm
Membrane Permeability	High, due to lipid compatibility	Moderate	Variable
Stability	High, protected from degradation	Moderate, prone to oxidation	High, depending on polymer type

The comparison highlights the structural and functional advantages of phytosomes over traditional liposomes and polymeric nanoparticles, particularly in enhancing bioavailability and stability [20].

The Wound Healing Process

Wound healing is a highly dynamic and complex process involving the coordinated action of various cellular and molecular mechanisms. It aims to restore the integrity and functionality of the injured tissue. This process can be broadly categorized into four distinct but overlapping phases: **hemostasis**, **inflammation**, **proliferation**, and **remodeling**. Understanding these phases is crucial for developing effective therapeutic interventions, including advanced drug delivery systems like phytosomes, which can enhance wound healing outcomes.

1. Hemostasis Phase

The hemostasis phase is the immediate response to tissue injury and aims to stop bleeding. It begins within seconds to minutes following an injury and involves:

- **Vasoconstriction:** Blood vessels constrict to reduce blood flow at the wound site.
- **Platelet Activation:** Platelets adhere to the exposed collagen of damaged blood vessels and release clotting factors. This leads to the formation of a platelet plug.
- **Coagulation Cascade:** A series of enzymatic reactions involving clotting factors result in the formation of fibrin, a protein that stabilizes the platelet plug and forms a blood clot.
- **Fibrin Matrix Formation:** The fibrin clot serves as a provisional matrix, preventing blood loss and providing a scaffold for incoming cells involved in wound healing.

This phase is critical as it provides the initial barrier to microbial invasion and creates a foundation for the subsequent healing phases.

2. Inflammation Phase

The inflammation phase is characterized by the recruitment of immune cells to the wound site. It typically lasts from 1 to 5 days and serves to clear debris, pathogens, and damaged cells. Key events include:

- **Vasodilation and Increased Permeability:** Following hemostasis, blood vessels dilate, increasing blood flow and vascular permeability. This allows immune cells, nutrients, and growth factors to reach the wound site.
- **Immune Cell Recruitment:** Neutrophils are the first responders, arriving at the wound site to phagocytose debris and pathogens. They release reactive oxygen species (ROS) and proteases to eliminate bacteria. This is followed by the recruitment of macrophages, which play a pivotal role in phagocytosis and the secretion of pro-inflammatory cytokines.
- **Macrophage Activation:** Macrophages transition from a pro-inflammatory (M1) phenotype to an anti-inflammatory (M2)

phenotype, promoting tissue repair. They release growth factors such as transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), and interleukin-10 (IL-10).

- **Oxidative Stress and ROS:** Although ROS help to control infection, excessive oxidative stress can damage surrounding healthy tissue, impairing the healing process.

The inflammation phase is crucial for preventing infection and preparing the wound bed for new tissue formation. However, chronic or excessive inflammation can delay wound healing and is a common issue in chronic wounds such as diabetic ulcers.

3. Proliferation Phase

The proliferation phase focuses on the formation of new tissue and typically lasts from 4 to 21 days. It involves several key processes:

- **Angiogenesis:** New blood vessels are formed from existing ones, driven by angiogenic factors such as VEGF. This revascularization ensures an adequate supply of oxygen and nutrients to the healing tissue.
- **Fibroplasia and Collagen Synthesis:** Fibroblasts migrate to the wound site, synthesizing extracellular matrix (ECM) components like collagen and elastin. Collagen provides structural integrity and strength to the newly formed tissue.
- **Granulation Tissue Formation:** The combined action of fibroblasts, endothelial cells, and newly formed blood vessels leads to the development of granulation tissue, a highly vascularized and cellular tissue that fills the wound bed.
- **Epithelialization:** Keratinocytes migrate across the wound surface, covering the wound with a new layer of epithelium. This process is essential for re-establishing the skin barrier function.
- **Wound Contraction:** Myofibroblasts, which are specialized fibroblasts with contractile properties, play a role in wound contraction. They reduce the wound size by pulling the edges together.

The proliferation phase is a critical period in wound healing, as it restores the integrity of the injured tissue. However, poor vascularization or fibroblast function can impair this phase, leading to delayed healing.

4. Remodeling (Maturation) Phase

The remodeling phase is the final stage of wound healing and can last from several weeks to months, or even years, depending on the wound's severity. This phase involves:

- **Collagen Remodeling:** The initially deposited collagen (type III) is replaced by the stronger, more resilient type I collagen. This process increases the tensile strength of the tissue.
- **Matrix Metalloproteinases (MMPs) Activity:** MMPs are enzymes that degrade excess ECM components, helping to remodel the tissue. Their activity is tightly regulated to prevent excessive degradation.
- **Vascular Regression:** The newly formed blood vessels regress, reducing the vascular density as the tissue matures.
- **Scar Formation:** The final healed tissue forms a scar, which is usually less flexible and has a different texture compared to normal skin. Scarring results from the incomplete regeneration of the original skin architecture, as hair follicles, sweat glands, and nerve endings may not fully regenerate [21-25].

While the remodeling phase restores tissue strength and integrity, it rarely achieves the same level of strength and function as the original tissue, making the area prone to re-injury.

Plants Bioactive Compounds in Promoting Wound Repair

Various plant bioactive compounds and their effects on wound healing. The table includes information on the bioactive compound, plant source, wound model used, mechanism of action, and main findings.

Table 2: Plant Bioactive Compounds in Promoting Wound Repair

Bioactive Compound	Plant Source	Wound Model	Mechanism of Action	Main Findings	Reference
Curcumin	*Curcuma longa*	Excision wound in rats	Anti-inflammatory, antioxidant, promotes collagen synthesis	Enhanced wound contraction, reduced inflammation	[26]
Quercetin	*Allium cepa*	Diabetic wound in mice	Antioxidant, angiogenesis, fibroblast proliferation	Improved collagen deposition, wound contraction	[27]
Aloe Vera Extract	*Aloe barbadensis*	Burn wound in rabbits	Anti-inflammatory, fibroblast activity, epithelialization	Faster re-epithelialization, reduced scar tissue	[28]
Resveratrol	*Vitis vinifera*	Incision wound in rats	Anti-inflammatory, antioxidant, vascularization	Enhanced tensile strength, reduced oxidative stress	[29]
Silymarin	*Silybum marianum*	Excision wound in rats	Antioxidant, collagen synthesis, inflammation reduction	Faster contraction, increased collagen content	[30]
Madecassoside	*Centella asiatica*	Diabetic wound in rats	Anti-inflammatory, fibroblast proliferation, angiogenesis	Improved healing rate, reduced inflammation	[31]
Berberine	*Berberis vulgaris*	Diabetic ulcer in mice	Antimicrobial, antioxidant, granulation tissue formation	Decreased bacterial load, enhanced wound closure	[32]
Asiaticoside	*Centella asiatica*	Excision wound in rabbits	Collagen synthesis, fibroblast proliferation	Increased tensile strength, collagen content	[33]
EGCG	*Camellia sinensis*	Burn wound in rats	Antioxidant, anti-inflammatory, fibroblast migration	Faster wound closure, reduced scar formation	[34]
Thymoquinone	*Nigella sativa*	Excision wound in mice	Anti-inflammatory, antimicrobial	Faster closure, reduced inflammation, lower microbial load	[35]
Chitosan-Quercetin	*Allium cepa*	Diabetic wound in rats	Antioxidant, vascularization, controlled release	Enhanced healing, reduced oxidative damage	[36]
Emodin	*Rheum palmatum*	Burn wound in rats	Antimicrobial, anti-inflammatory	Enhanced healing, reduced bacterial infection	[37]
Apigenin	*Chamomilla recutita*	Excision wound in rats	Anti-inflammatory, antioxidant	Faster epithelialization,	[38]

				reduced inflammation	
Hesperidin	*Citrus sinensis*	Diabetic wound in mice	Antioxidant, collagen synthesis	Enhanced granulation tissue, increased collagen	[39]
Baicalin	*Scutellaria baicalensis*	Incision wound in mice	Anti-inflammatory, fibroblast proliferation	Improved tensile strength, faster closure	[40]
Genistein	*Glycine max*	Burn wound in rats	Estrogenic activity, antioxidant	Accelerated healing, reduced oxidative stress	[41]
Betulinic Acid	*Betula alba*	Incision wound in rats	Antioxidant, anti-inflammatory	Faster wound healing, improved tensile strength	[42]
Ginsenoside Rb1	*Panax ginseng*	Diabetic wound in mice	Anti-inflammatory, angiogenesis	Enhanced healing, reduced inflammatory markers	[43]
Catechin	*Camellia sinensis*	Excision wound in rats	Antioxidant, fibroblast activation	Improved collagen deposition, faster healing	[44]
Luteolin	*Olea europaea*	Burn wound in mice	Anti-inflammatory, antioxidant	Reduced inflammation, enhanced re-epithelialization	[45]
Rutin	*Ruta graveolens*	Diabetic wound in rats	Antioxidant, collagen synthesis	Enhanced wound contraction, increased hydroxyproline content	[46]
Glycyrrhizin	*Glycyrrhiza glabra*	Incision wound in rabbits	Anti-inflammatory, immunomodulatory	Faster healing, reduced inflammation	[47]
Escin	*Aesculus hippocastanum*	Excision wound in mice	Anti-inflammatory, reduces edema	Improved wound healing, reduced swelling	[48]
Apocynin	*Picrorhiza kurroa*	Diabetic wound in mice	Antioxidant, inhibits NADPH oxidase	Reduced oxidative stress, enhanced closure	[49]
Boswellic Acid	*Boswellia serrata*	Incision wound in rats	Anti-inflammatory, antimicrobial	Faster healing, reduced scar tissue	[50]
Gallic Acid	*Terminalia chebula*	Burn wound in rats	Antioxidant, anti-inflammatory	Enhanced re-epithelialization, reduced oxidative damage	[51]
Oleuropein	*Olea europaea*	Diabetic wound in mice	Antioxidant, collagen synthesis	Improved granulation tissue formation	[52]

Ursolic Acid	*Rosmarinus officinalis*	Incision wound in rabbits	Anti-inflammatory, promotes fibroblast proliferation	Increased tensile strength, faster healing	[53]
Shikonin	*Lithospermum erythrorhizon*	Burn wound in mice	Anti-inflammatory, antimicrobial	Faster healing, reduced microbial load	[54]
Propolis Extract	*Apis mellifera*	Excision wound in rats	Antimicrobial, promotes collagen deposition	Enhanced wound contraction, reduced infection	[55]
Naringenin	*Citrus paradisi*	Diabetic wound in mice	Antioxidant, anti-inflammatory	Improved healing rate, reduced inflammation	[56]
Harpagide	*Harpagophytum procumbens*	Burn wound in rats	Anti-inflammatory, antioxidant	Enhanced wound closure, reduced scar tissue	[57]
Xanthohumol	*Humulus lupulus*	Excision wound in mice	Anti-inflammatory, antioxidant	Faster healing, reduced oxidative stress	[58]

This comprehensive list demonstrates the effectiveness of various plant bioactive compounds in promoting wound healing through different mechanisms, such as reducing inflammation, enhancing collagen synthesis, improving angiogenesis, and providing antimicrobial effects.

CONCLUSION:

Phytosome technology has emerged as a promising approach in wound healing, offering significant advantages over conventional delivery systems. By improving the bioavailability, stability, and targeted delivery of plant-derived bioactive compounds, phytosomes enhance the therapeutic effects of natural ingredients commonly used in wound care. These advantages include enhanced skin penetration, reduced inflammation, and accelerated tissue regeneration through mechanisms such as collagen synthesis and fibroblast proliferation. Numerous studies have highlighted the potential of phytosomes in promoting wound healing, with compounds such as curcumin, Centella Asiatica, aloe vera, and quercetin showing positive outcomes in preclinical and clinical settings. Phytosome formulations, including creams, gels, ointments, and wound dressings, have demonstrated improved healing rates, reduced scarring, and prevention of infection, making them ideal for treating various types of wounds, including burns, chronic wounds, and diabetic ulcers. Despite the promising results, challenges such as the scalability of phytosome production, regulatory hurdles, and the need for further clinical studies remain. However, the ongoing research and development in phytosome technology suggest that it has the potential to revolutionize wound care, offering safer, more effective, and targeted treatments for faster wound healing. In conclusion, phytosome-based formulations represent a cutting-edge advancement in the field of wound healing, combining the healing power of natural compounds with the precision and efficacy of modern drug delivery systems. As research progresses, phytosome technology holds the potential to significantly improve outcomes in wound management, benefiting both patients and healthcare providers alike.

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