Review

Garlic Oil and Manuka Honey-Based Nanoemulsion Systems for Antimicrobial Therapy: Current Insights and Future Perspectives

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Abstract:
Garlic oil and Manuka honey are natural antimicrobial agents widely recognized for their therapeutic potential. Garlic oil contains sulfur-based compounds responsible for antimicrobial activity, while Manuka honey exhibits unique antibacterial properties due to methylglyoxal content. However, their pharmaceutical application is limited by poor solubility, instability, and formulation challenges. Nanoemulsion-based drug delivery systems provide an effective approach to enhance stability, bioavailability, and antimicrobial efficacy. This review focuses on formulation strategies, characterization, antimicrobial mechanisms, applications, challenges, and future perspectives of garlic oil and Manuka honey-based nanoemulsion systems. The synergistic effect of these natural components makes them promising candidates for topical antimicrobial therapy, especially in acne management.

Keywords: Garlic oil, Manuka honey, Nanoemulsion, Antimicrobial therapy, Polyherbal formulation

Introduction

The increasing prevalence of microbial resistance has created a demand for alternative therapeutic approaches using natural products. Garlic (*Allium sativum*) and Manuka honey are well-known for their antimicrobial and healing properties. Garlic oil contains sulfur compounds such as allicin, which exhibit broad-spectrum antimicrobial activity. Manuka honey, derived from *Leptospermum scoparium*, possesses strong antibacterial activity due to methylglyoxal.

Despite their advantages, both agents face challenges such as poor solubility, instability, and formulation difficulties. Nanoemulsion systems have emerged as an effective drug delivery platform to enhance the therapeutic performance of such natural compounds.

In addition to antimicrobial resistance, there is an increasing demand for biocompatible and patient-friendly topical formulations in dermatological therapy. Conventional antimicrobial agents often lead to side effects such as irritation, dryness, and resistance upon prolonged use. In this context, polyherbal approaches combining natural actives like garlic oil and Manuka honey offer a safer and more effective alternative. The integration of these bioactives into advanced delivery systems such as nanoemulsions not only enhances their physicochemical stability but also improves skin penetration and therapeutic performance. Furthermore, nanoemulsion-based systems provide a platform for controlled and sustained release, thereby reducing dosing frequency and improving patient compliance. This makes them particularly suitable for chronic skin conditions such as acne vulgaris, where long-term treatment is required.

Garlic Oil: Composition and Properties

Garlic oil, obtained from *Allium sativum*, is rich in biologically active sulfur-containing compounds that are primarily responsible for its therapeutic effects. The major constituents of garlic oil include allicin, diallyl disulfide, diallyl trisulfide, and other organosulfur compounds formed during the enzymatic conversion of alliin by the enzyme alliinase. Among these, allicin is considered the most active component, exhibiting potent antimicrobial, antioxidant, and anti-inflammatory properties. Garlic oil is characterized by its strong pungent odor, high volatility, and lipophilic nature, which contributes to its poor aqueous solubility. It demonstrates broad-spectrum antimicrobial activity against bacteria, fungi, and viruses by disrupting microbial cell membranes and inhibiting essential enzymatic processes. Additionally, garlic oil possesses antioxidant activity that helps in reducing oxidative stress and promoting healing. However, its instability, especially in the presence of heat and light, and its strong odor limit its direct pharmaceutical application, necessitating the use of advanced delivery systems such as nanoemulsions to enhance its stability and therapeutic efficacy.

Manuka Honey: Composition and Therapeutic Properties

Manuka honey is a unique type of honey derived from the nectar of the *Leptospermum scoparium* plant and is widely recognized for its exceptional antimicrobial and therapeutic properties. Unlike conventional honey, its antibacterial activity is primarily attributed to the presence of methylglyoxal (MGO), along with other bioactive components such as hydrogen peroxide, phenolic compounds, flavonoids, and organic acids. These constituents contribute to its broad-spectrum antimicrobial activity against a variety of pathogenic microorganisms. Manuka honey also exhibits significant anti-inflammatory, antioxidant, and wound healing properties, making it highly valuable in dermatological applications. Its high osmolarity and low pH further enhance its antimicrobial effectiveness by creating an unfavorable environment for microbial growth. However, its high viscosity and hydrophilic nature can limit its uniform incorporation into topical formulations. Therefore, advanced drug delivery systems such as nanoemulsions are employed to improve its dispersion, stability, and therapeutic performance, particularly in combination with lipophilic agents like garlic oil for synergistic effects.

Limitations of Garlic Oil and Manuka Honey

Despite their significant therapeutic potential, both garlic oil and Manuka honey exhibit certain limitations that restrict their direct application in pharmaceutical formulations. Garlic oil is highly volatile, possesses a strong pungent odor, and exhibits poor aqueous solubility due to its lipophilic nature, which can affect patient acceptability and formulation stability. Additionally, it is chemically unstable and prone to degradation when exposed to heat, light, and oxygen. On the other hand, Manuka honey, although rich in antimicrobial components, has high viscosity and a hydrophilic nature, which can lead to difficulties in uniform formulation and controlled drug release. The compatibility of garlic oil and Manuka honey in a single formulation also presents a challenge due to their differing physicochemical properties, particularly in oil and aqueous phases. Furthermore, issues such as potential microbial contamination, stability during storage, and variability in natural product composition may affect reproducibility and efficacy. These limitations highlight the need for advanced delivery systems, such as nanoemulsions, to improve stability, bioavailability, and overall therapeutic performance.

Nanoemulsion Systems

Nanoemulsion systems are advanced colloidal drug delivery systems consisting of two immiscible liquids, typically oil and water, stabilized by a combination of surfactants and co-surfactants. These systems are characterized by their nanoscale droplet size, generally ranging from 20 to 200 nm, which imparts unique physicochemical properties such as high surface area, enhanced solubility, and improved stability. Nanoemulsions can be formulated as oil-in-water (O/W), water-in-oil (W/O), or bicontinuous systems depending on the composition and intended application. Due to their small droplet size and kinetic stability, nanoemulsions are particularly suitable for delivering lipophilic compounds like garlic oil while also accommodating hydrophilic components such as Manuka honey. This makes them an ideal platform for developing polyherbal formulations with enhanced therapeutic efficacy. Furthermore, nanoemulsion systems improve drug penetration through biological membranes and provide controlled release, thereby enhancing bioavailability and clinical effectiveness.

Key Features of Nanoemulsion Systems

- Droplet size in the range of 20–200 nm
- High surface area leading to improved drug absorption
- Ability to incorporate both hydrophilic and lipophilic agents
- Enhanced physical stability compared to conventional emulsions
- Transparent or translucent appearance

Advantages in Drug Delivery

- Improved solubility of poorly water-soluble drugs
- Enhanced bioavailability and therapeutic efficacy
- Better skin penetration for topical applications
- Controlled and sustained drug release
- Improved patient compliance

Table 1: Components of Polyherbal Nanoemulsion

Component	Function
Garlic oil	Antimicrobial agent
Manuka honey	Antibacterial and healing agent
MCT oil/IPM	Carrier oil
Tween 80	Surfactant
PEG 400	Co-surfactant
Water	Aqueous phase

Methods of Preparation

Nanoemulsions can be prepared using a variety of techniques broadly classified into high-energy and low-energy methods, depending on the desired droplet size, formulation stability, and scalability. In the case of polyherbal systems containing garlic oil and Manuka honey, the selection of an appropriate method is crucial to ensure uniform dispersion of both lipophilic and hydrophilic components. High-energy methods utilize mechanical devices to reduce droplet size through intense shear forces, whereas low-energy methods rely on the physicochemical properties of the system for spontaneous formation. The preparation process typically involves the formation of a coarse emulsion followed by size reduction to achieve nanoscale droplets. Optimization of formulation parameters such as oil-to-surfactant ratio, mixing speed, temperature, and composition plays a significant role in determining the stability and performance of the nanoemulsion.

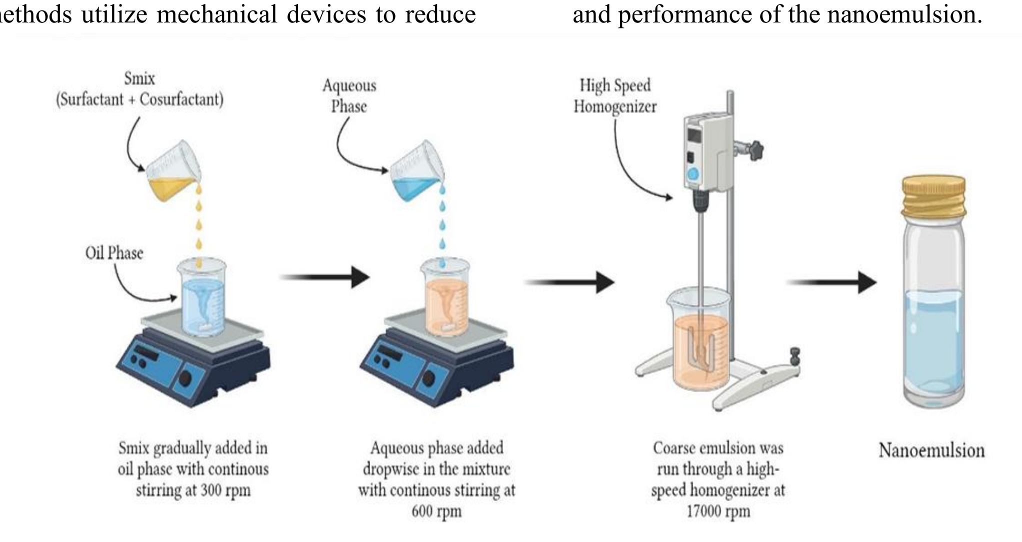

Figure 1: Schematic representation of nanoemulsion preparation (modified by authors)

Common Methods of Preparation

1. Ultrasonication Method

- Involves the use of ultrasonic waves to reduce droplet size
- Oil phase (garlic oil + carrier oil) is mixed with surfactant and co-surfactant
- Aqueous phase containing Manuka honey is added slowly under stirring
- The mixture is subjected to probe sonication to form nano-sized droplets

Advantages:

- Produces uniform and small droplets
- Suitable for laboratory-scale preparation

2. High-Pressure Homogenization

- Pre-emulsion is passed through a high-pressure homogenizer
- Intense shear, turbulence, and cavitation reduce droplet size
- Multiple cycles may be required for optimal size reduction

Advantages:

- Suitable for large-scale production
- Produces highly stable nanoemulsions

3. Spontaneous Emulsification (Low-Energy Method)

- Oil phase is mixed with surfactant and co-surfactant (Smix)
- Aqueous phase is added dropwise under mild stirring
- Nanoemulsion forms spontaneously due to interfacial turbulence

Advantages:

- No external energy required
- Cost-effective and simple

Important Formulation Parameters

- Oil to surfactant ratio (Smix ratio)
- Temperature of preparation
- Mixing speed and time
- Order of addition of components

Characterization of Nanoemulsion

Characterization of nanoemulsion systems is essential to evaluate their physicochemical properties, stability, and performance. These parameters help in determining the suitability of the formulation for therapeutic applications. Proper characterization ensures reproducibility and quality of the nanoemulsion system, especially in polyherbal formulations where multiple active components are involved.

Key Characterization Parameters

1. Droplet Size and Polydispersity Index (PDI)

- Measured using dynamic light scattering (DLS)
- Indicates average droplet size and uniformity
- Smaller droplet size enhances penetration and stability

2. Zeta Potential

- Measures surface charge of droplets
- Indicates stability of nanoemulsion
- Higher absolute value suggests better stability

3. pH Measurement

- Determines suitability for topical application
- Should be compatible with skin pH (approximately 5–7)

4. Viscosity

- Evaluates flow behaviour of formulation
- Important for topical application and spreadability

Stability Studies

- **Centrifugation Test:** Detects phase separation
- **Freeze–Thaw Cycles:** Evaluates resistance to temperature variation
- **Storage Stability:** Monitors changes over time

Additional Evaluation Parameters

- Spreadability
- Drug content
- In vitro release studies

Antimicrobial Mechanism of Garlic Oil and Manuka Honey-Based Nanoemulsion

The antimicrobial activity of garlic oil and Manuka honey-based nanoemulsion is attributed to the combined and synergistic effects of their bioactive constituents along with the enhanced delivery provided by the nanoemulsion system. Garlic oil contains sulfur-rich compounds such as allicin, which interact with microbial cell components, while Manuka honey exhibits antibacterial activity mainly due to methylglyoxal and hydrogen peroxide. When incorporated into a nanoemulsion system, the small droplet size significantly increases surface area, facilitating better interaction with microbial cells and improved penetration across biological membranes. This results in enhanced antimicrobial efficacy compared to conventional formulations. The nanoemulsion system also ensures controlled release of active components, prolonging their activity at the target site and reducing microbial resistance.

Mechanism of Action of Garlic Oil

- **Disruption of Cell Membrane:**
  Allicin interacts with lipid bilayers, causing structural damage and loss of membrane integrity
- **Enzyme Inhibition:**
  Sulfur compounds react with thiol groups of microbial enzymes, inhibiting essential metabolic pathways
- **Oxidative Stress Induction:**
  Generates reactive oxygen species leading to cellular damage
- **Inhibition of DNA and Protein Synthesis:**
  Interferes with replication and protein formation

Mechanism of Action of Manuka Honey

- **Methylglyoxal (MGO) Activity:**
  Disrupts microbial cellular functions and protein structure
- **Hydrogen Peroxide Production:**
  Contributes to antibacterial activity
- **Osmotic Effect:**
  High sugar concentration draws water out of microbial cells, causing dehydration
- **Low pH Environment:**
  Inhibits microbial growth

Role of Nanoemulsion System

- **Enhanced Surface Area:**
  Nano-sized droplets increase contact with microbial cells
- **Improved Penetration:**
  Facilitates deeper entry into microbial membranes
- **Sustained Release:**
  Provides prolonged antimicrobial activity
- **Improved Stability:**
  Protects active compounds from degradation

Synergistic Antimicrobial Effect

- Combined action of garlic oil and Manuka honey enhances efficacy
- Targets multiple microbial pathways simultaneously
- Reduces likelihood of resistance development
- Improves overall therapeutic outcome

Applications of Garlic Oil and Manuka Honey-Based Nanoemulsion

Garlic oil and Manuka honey-based nanoemulsion systems have gained considerable attention due to their enhanced antimicrobial efficacy, improved stability, and better skin penetration. The synergistic combination of these natural bioactives, along with the advantages of nanoemulsion delivery, makes them highly suitable for a wide range of pharmaceutical and biomedical applications. These systems are particularly effective in topical drug delivery, where localized action, controlled release, and improved patient compliance are essential. The incorporation of both lipophilic (garlic oil) and hydrophilic (Manuka honey) components in a single nanoemulsion system allows for multifunctional therapeutic effects, including antimicrobial, anti-inflammatory, and wound healing activities.

Topical Applications in Dermatology

- **Acne Vulgaris Management:**
  Reduces bacterial load (*Cutibacterium acnes*), controls sebum, and decreases inflammation
- **Skin Infections:**
  Effective against bacterial and fungal infections of the skin
- **Wound Healing:**
  Promotes tissue regeneration, reduces infection, and accelerates healing

Antibacterial Applications

- **Broad-Spectrum Activity:**
  Effective against Gram-positive and Gram-negative bacteria
- **Drug-Resistant Strains:**
  Potential activity against resistant pathogens such as MRSA
- **Enhanced Efficacy via Nanoemulsion:**
  Improved penetration increases antibacterial performance

Antifungal Applications

- Effective against fungal infections such as dermatophytosis

- Inhibits fungal growth and spore formation
- Useful in topical antifungal formulations

Cosmeceutical Applications

- Used in herbal creams, gels, and lotions
- Improves skin health and appearance
- Provides antioxidant and anti-aging benefits

Food and Pharmaceutical Preservation

- Natural preservative due to antimicrobial activity
- Prevents microbial contamination
- Extends shelf life of products

Advantages in Application

- **Targeted Delivery:**
  Acts directly at the site of infection
- **Improved Patient Compliance:**
  Reduced dosing frequency and better acceptability
- **Reduced Side Effects:**
  Natural origin minimizes irritation compared to synthetic drugs

Challenges and Limitations

Despite the promising therapeutic potential of garlic oil and Manuka honey-based nanoemulsion systems, several challenges must be addressed to ensure their successful formulation and clinical application. The combination of lipophilic garlic oil and hydrophilic Manuka honey in a single system presents formulation complexities, particularly in achieving uniform dispersion and long-term stability. Additionally, factors such as odor, viscosity, and variability in natural product composition can affect product acceptability and reproducibility. Stability-related issues, including phase separation and droplet growth, may also compromise the effectiveness of the nanoemulsion. Furthermore, concerns regarding surfactant safety, scale-up feasibility, and regulatory approval pose additional hurdles in translating these systems from laboratory to commercial use.

Formulation Challenges

- **Compatibility Issues:**
  Difficulty in combining oil-based garlic and aqueous Manuka honey in a stable system
- **Droplet Stability:**
  Risk of coalescence, flocculation, and Ostwald ripening
- **Viscosity Control:**
  High viscosity of honey affects formulation consistency

Physicochemical Challenges

- **Instability of Garlic Oil:**
  Susceptible to degradation by light, heat, and oxygen
- **Strong Odor:**
  Garlic oil odor affects patient acceptability
- **Variability in Natural Products:**
  Composition of honey and garlic may vary with source

Safety and Toxicity Concerns

- **Surfactant Irritation:**
  High concentration of surfactants may cause skin irritation
- **Allergic Reactions:**
  Natural products may trigger sensitivity in some individuals

Industrial and Regulatory Challenges

- **Scale-Up Difficulties:**
  Maintaining uniform droplet size in large-scale production
- **Cost of Production:**
  High-quality Manuka honey is expensive
- **Regulatory Approval:**
  Standardization and quality control are required

Future Perspectives

The development of garlic oil and Manuka honey-based nanoemulsion systems holds significant promise for advancing antimicrobial therapy, particularly in dermatological applications. Future research should focus on optimizing formulation strategies to overcome existing limitations and enhance therapeutic outcomes. The integration of advanced technologies and natural bioactives offers opportunities for the development of innovative, safe, and effective drug delivery systems. With increasing interest in herbal and nanotechnology-based therapies, these systems have the potential to be translated into clinically effective and commercially viable products.

Conclusion

Garlic oil and Manuka honey-based nanoemulsions represent a promising polyherbal approach for antimicrobial therapy. The synergistic combination enhances antimicrobial activity while improving stability and bioavailability. These systems have significant potential in topical applications, especially for acne management. Further studies are required for clinical validation.

Moreover, the integration of natural bioactive agents such as garlic oil and Manuka honey into nanoemulsion-based delivery systems represents a significant advancement in the field of herbal drug delivery. This approach not only enhances the therapeutic efficiency of individual components but also provides a synergistic effect that can be highly beneficial in managing microbial infections. The growing preference for natural, safe, and effective formulations further supports the potential of such polyherbal nanoemulsion systems in modern healthcare. With continued research, optimization, and clinical validation, these formulations may emerge as viable alternatives to conventional antimicrobial therapies, offering improved efficacy, reduced side effects, and better patient compliance. This review provides a foundation for future development of polyherbal nanoemulsion-based therapeutics.

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