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MICROEMULSIONBASED DELIVERY SYSTEMS FOR PHYTOCHEMICAL COMPOUNDS: FORMULATION STRATEGIES AND BIOMEDICAL APPLICATIONS

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ABSTRACT

The study demonstrates how phytochemical compounds protect bioactive compounds from degradation while enhancing their drug delivery ability. The research establishes microemulsion-based systems as effective delivery systems which enhance phytochemical bioactive compounds through improved solubilization and stability and absorption. The current review presents major phytochemical categories with their physicochemical characteristics and describes microemulsion systems through their thermodynamic stability and phase behaviour and surfactant selection and pseudo-ternary phase diagram construction. The study evaluates critical characterization parameters which include droplet size and polydispersity index and zeta potential and encapsulation efficiency and stability assessment. Microemulsions improve drug delivery through better bioactive protection and greater membrane penetration ability, and they provide both controlled and prolonged drug release. The research demonstrates how phytochemical-loaded microemulsions achieve better pharmacokinetics and deeper tissue penetration and greater therapeutic efficacy than their free compound counterparts. The study demonstrates how microemulsions facilitate drug delivery for anticancer therapies and antimicrobial treatments and transdermal medicine. The technology shows good development progress but suffers from problems in making stable products and producing items in bulk and using surfactants which have safety risks and obtaining permission from regulatory bodies. The successful development of biomedical therapeutics requires research on biocompatible materials together with targeted delivery systems and clinical testing.

Keywords: *Phytochemicals; Microemulsion; Nano drug delivery; Bioavailability enhancement; Thermodynamic stability; Encapsulation efficiency; Controlled release; Pharmacokinetics.*

INTRODUCTION

Phytochemicals are naturally occurring bioactive compounds present in plants that possess diverse therapeutic properties and contribute to the prevention and management of various diseases. They include antioxidants, anti-inflammatory, antimicrobial, and anticancer agents that exert their effects through modulation of molecular and cellular pathways. Phytochemicals are secondary metabolites synthesized by plants as part of their defines and survival mechanisms. In recent decades, they have gained significant attention in pharmaceutical and biomedical research due to their wide range of biological activities and comparatively favourable safety profiles over synthetic drugs [1].

Phytochemicals are broadly classified into flavonoids, terpenoids, phenolic acids, alkaloids, glycosides, tannins, and lignans. These compounds exert therapeutic effects by regulating oxidative stress, inflammatory mediators, cellular signalling pathways, gene expression, and immune responses [2]. Among them, flavonoids and phenolic compounds are particularly noted for their strong antioxidant activity through free-radical scavenging and metal chelation, thereby protecting cells from oxidative damage [3]. Epidemiological and experimental studies associate phytochemical-rich diets with a reduced risk of chronic diseases, including cancer, cardiovascular disorders, neurodegenerative diseases, diabetes mellitus, and inflammatory conditions. Their anti-inflammatory effects are mainly mediated through inhibition of key pathways such as nuclear factor-kappa B (NF-κB) and cyclooxygenase (COX). In addition, many phytochemicals exhibit anticancer activity by inducing apoptosis, inhibiting cell proliferation, regulating the cell cycle, and suppressing angiogenesis and metastasis [4]. Antimicrobial activity has also been reported, offering potential alternatives amid rising antimicrobial resistance. Despite promising preclinical outcomes, clinical translation of phytochemicals remains limited due to poor solubility, low bioavailability, rapid metabolism, and chemical instability, highlighting the need for advanced drug delivery approaches. Many phytochemicals are hydrophobic and exhibit poor aqueous solubility, resulting in inadequate dissolution in gastrointestinal fluids. Since dissolution is essential for absorption, low solubility leads to poor and variable oral bioavailability. Consequently, several phytochemicals fall under BCS Class II or IV, where solubility is a major limiting factor.

Certain phytochemicals also show limited permeability across intestinal membranes due to high molecular weight, multiple hydroxyl groups, and extensive hydrogen bonding. Additionally, efflux transporters may further restrict intracellular accumulation, reducing systemic exposure even after dissolution. Extensive first-pass metabolism significantly limits phytochemical bioavailability. Phase I and Phase II metabolic reactions convert these compounds into hydrophilic metabolites that are rapidly eliminated, resulting in short half-lives and reduced therapeutic effectiveness. Many phytochemicals are chemically unstable and sensitive to light, heat, oxygen, and pH variations. Degradation processes such as oxidation and hydrolysis can reduce pharmacological activity and compromise formulation stability. Microemulsions are thermodynamically stable, isotropic systems composed of oil, water, surfactant, and co-surfactant, with droplet sizes typically in the nanometre range. Their spontaneous formation and high solubilization capacity make them particularly suitable for incorporating lipophilic drugs, thereby enhancing apparent aqueous solubility.

The large interfacial surface area of microemulsions promotes rapid drug dissolution and improved membrane permeability. Surfactants may further enhance drug transport across biological membranes. Additionally, microemulsions can protect drugs from degradation and improve pharmacokinetic performance, making them effective carriers for poorly water-soluble compounds. Microemulsion systems effectively address the major limitations of phytochemicals, including poor solubility, limited permeability, rapid metabolism, and instability. Solubilization within the oil phase enhances drug loading and dissolution, while nanosized droplets improve absorption. Encapsulation protects phytochemicals from chemical and enzymatic degradation, and lipid-based systems may partially bypass first-pass metabolism through lymphatic transport.

Collectively, these advantages result in improved bioavailability and enhanced therapeutic efficacy of phytochemical-based formulations [5].

PHYTOCHEMICAL COMPOUNDS

Classification of Phytochemicals

Phenolic Compounds

Phenolic compounds, commonly known as polyphenols, are plant-derived secondary metabolites widely distributed in fruits, vegetables, cereals, and beverages. Their levels vary depending on plant species, environmental conditions, and processing methods. Structurally, they are characterized by one or more hydroxyl groups attached to aromatic rings and are biosynthesized mainly through the shikimate and phenylpropanoid pathways.

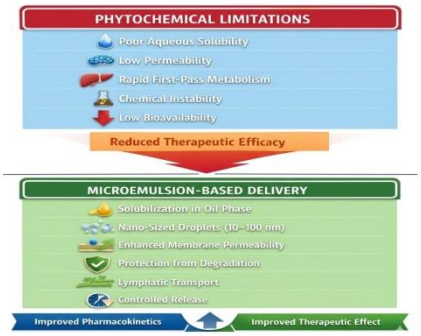


Figure 01: Phytochemical Limitations and Microemulsion-Based Drug Delivery

Based on chemical structure, polyphenols are broadly classified into flavonoids and non-flavonoids. Flavonoids possess two aromatic rings connected by a heterocyclic ring, whereas
non-flavonoids primarily include phenolic acids derived from benzoic and cinnamic acids. Environmental and genetic factors significantly influence their composition in plants.
Polyphenols are extensively studied due to their antioxidant, anti-inflammatory, and antimicrobial properties. They also exhibit immunomodulatory effects by regulating nitric oxide production, cytokine signalling, and inflammatory gene expression, highlighting their relevance in chronic disease prevention.

Flavonoids

Flavonoids are a major subclass of polyphenols widely present in fruits, vegetables, grains, tea, and medicinal plants. Chemically, they possess a C6–C3–C6 structure consisting of two aromatic rings linked by a heterocyclic ring and commonly occur as glycosides.
Based on structural variations, flavonoids are broadly divided into anthocyanins and non-pigmented flavonoids, including flavanones, flavones, flavanols, isoflavones, and flavan-3-ols. These subclasses differ in physicochemical properties, influencing their solubility, stability, and biological behaviour.
Flavonoids are recognized for strong antioxidant activity through free-radical scavenging and metal chelation. Their antioxidant efficacy depends on hydroxylation pattern, conjugation, and glycosylation. In addition, flavonoids exhibit anti-inflammatory, anticancer, antimicrobial, antidiabetic, and cardioprotective effects by modulating cellular signalling pathways and enzyme activity.
Regular intake of flavonoid-rich foods such as fruits, vegetables, tea, and cocoa is associated with reduced risk of chronic diseases. However, their therapeutic efficacy is often limited by poor bioavailability due to low solubility, metabolism, and instability. Consequently, novel delivery systems such as nano emulsions, nanoparticles, and liposomes are being explored to enhance their bioavailability.

Anthocyanins

Anthocyanins are water-soluble flavonoid pigments responsible for red, blue, and purple colours in fruits and flowers. They occur mainly as glycosides of anthocyanidins and are concentrated in fruit skins and peels, where they protect plants from environmental stress.
Major dietary sources include berries, grapes, cherries, and coloured vegetables. Common anthocyanidins include cyanidin, delphinidin, pelargonidin, peonidin, and malvidin. Structural variations influence their colour, stability, and biological activity.
Anthocyanins possess strong antioxidant activity through scavenging reactive oxygen species and inhibiting lipid peroxidation. They also exhibit anti-inflammatory, antidiabetic, cardioprotective, neuroprotective, and anticancer activities. Despite these benefits, their low bioavailability due to poor absorption and rapid metabolism limits therapeutic use, prompting the development of advanced delivery systems.

Tannins

Tannins are high–molecular-weight polyphenolic compounds known for their astringent properties. Based on structure, they are classified into hydrolysable tannins, condensed tannins (proanthocyanidins), and phlorotannin. These structural differences affect their solubility and biological activity.
Dietary sources include fruits, nuts, berries, and tea. Tannins exhibit antioxidant, antimicrobial, anti-inflammatory, anticancer, and neuroprotective effects by modulating oxidative stress and enzyme activity. However, excessive intake may reduce nutrient absorption due to protein and mineral binding, necessitating controlled formulation strategies.

Saponins

Saponins are amphiphilic glycosides composed of a hydrophobic sapogenin linked to hydrophilic sugar chains, giving them surface-active properties. They are classified into triterpenoid and steroidal saponins based on aglycone structure.
Saponins exhibit antioxidant, anti-inflammatory, antimicrobial, anticancer, hepatoprotective, and cardioprotective activities. Their anticancer effects are attributed to apoptosis induction and inhibition of tumour proliferation. However, high doses may cause haemolytic or gastrointestinal effects, highlighting the need for optimized formulations.

Terpenoids

Terpenoids are structurally diverse secondary metabolites derived from isoprene units and classified based on carbon number into mono-, sesqui-, di-, tri-, and tetraterpenoids. They are synthesized via the mevalonate and MEP pathways.
Terpenoids are major constituents of essential oils and pigments and play key roles in plant defines. Pharmacologically, they exhibit antioxidant, anti-inflammatory, antimicrobial, antidiabetic, anticancer, and neuroprotective activities. Their structural diversity and lipophilicity make them valuable lead compounds in drug discovery.

Sterols and Sterolins

Sterols and sterolins, collectively termed phytosterols, are plant-derived lipid compounds structurally similar to cholesterol. Common phytosterols include β-sitosterol, stigmasterol, and camp sterol. Due to structural

similarity with cholesterol, they reduce intestinal cholesterol absorption and improve lipid profiles. Phytosterols exhibit antioxidant, anti-inflammatory, anticancer, antidiabetic, and neuroprotective effects. Glycosylation influences their solubility and bioavailability. Their favourable safety profile supports their use in functional foods and pharmaceutical formulations.

CHEMICAL STRUCTURE AND PROPERTIES

Biological Activities of Phytochemical Compounds

Phytochemicals exhibit diverse biological activities that contribute to disease prevention and health promotion, including antioxidant, anti-inflammatory, anticancer, antimicrobial, wound healing, cardioprotective, neuroprotective, and metabolic regulatory effects.

Antioxidant Activity

Polyphenols and flavonoids effectively neutralize reactive oxygen species, reduce lipid peroxidation, and protect cellular biomolecules, thereby reducing oxidative stress and chronic disease risk.

Anti-Inflammatory Activity

Several phytochemicals suppress inflammatory mediators and protect tissues from inflammation-associated damage, supporting their role in managing inflammatory disorders.

Anticancer Activity

Phytochemicals inhibit tumour growth by inducing apoptosis, regulating cell cycle progression, and suppressing metastasis across various cancer types.

Antimicrobial Activity

Flavonoids, polyphenols, and saponins exhibit broad-spectrum antimicrobial activity by disrupting microbial membranes and inhibiting essential metabolic pathways.

Wound Healing Activity

Certain phytochemicals enhance collagen synthesis, tissue regeneration, and epithelialization, making them useful in wound care and dermatological applications.

Cardioprotective and Metabolic Effects

Phytochemicals regulate lipid metabolism, improve vascular function, and enhance insulin sensitivity, reducing cardiovascular and metabolic disease risk.

Neuroprotective and Anti-Aging Properties

Their antioxidant and anti-inflammatory properties support neuronal protection, cognitive function, and delay age-related degeneration [6].

FUNDAMENTALS OF MICROEMULSION

Definition

Microemulsions are thermodynamically stable, transparent, and isotropic systems composed of oil, water, surfactant, and often a co-surfactant, with droplet sizes typically between 10 and 50 nm. Unlike conventional emulsions, microemulsions form spontaneously and remain stable.

They may exist as oil-in-water (o/w), water-in-oil (w/o), or Bl continuous systems depending on composition. Their properties are influenced by surfactant type, concentration, and electrolytes.

History and Terminology

Microemulsions were first described by Hoar and Schulman in 1943, with the term formally introduced in 1959. Initially explored for enhanced oil recovery, their application has expanded to pharmaceutical drug delivery systems.

Components

Microemulsions consist of:

1. Oil phase – fatty acids and fatty acid esters
2. Surfactants – polysorbates, sorbitan esters, lecithin, ionic surfactants
3. Co-surfactants – short-chain alcohols and polyoxymethylene derivatives
4. Aqueous phase

Classification of Micro Emulsion

According to Winsor, there are four types of micro emulsion phases exists in equilibrium, these phases are referred as Winsor phases.10-13 they are:

- Winsor I (two phase system): upper oil layer exists in equilibrium with lower (o/w) micro emulsion phase
- Winsor II (two phase system): the upper (w/o) micro emulsion exists in equilibrium with lower excess water.
- Winsor III (three phase system): middle bi-continuous phase of o/w and w/o called) exists in equilibrium with upper phase oil and lower phase water.
- Winsor IV (single phase system): it forms homogenous mixture of oil, water and surfactant.

Figure 02: Winsor Phase Types in Microemulsion Systems

Mechanism of Microemulsion Formation

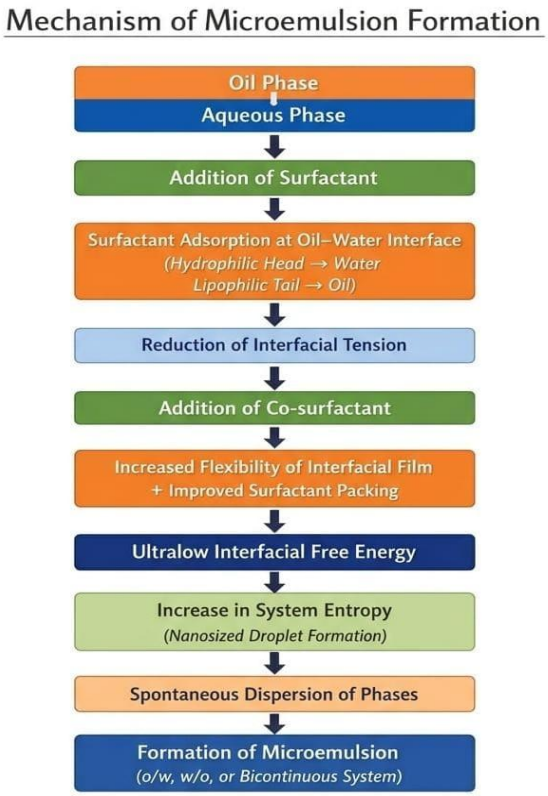


Figure 03: Mechanism of Microemulsion Formation

Formulation and Optimization of Phytochemical-Loaded Microemulsions

Phytochemical-loaded microemulsions were prepared by dissolving the active compound in an appropriate combination of oil, surfactant, and co-surfactant, followed by high-shear homogenization to obtain uniform nanoscale droplets. The formulation process involved separation into two phases: an aqueous phase containing distilled water and co-surfactant, and an oil phase comprising the selected oil, surfactant, phytochemical, and preservative. Both phases were heated separately to ensure complete solubilization. The oil phase was then added dropwise to the aqueous phase under continuous stirring and homogenized at 6000 rpm for 15 minutes. The resulting microemulsion was allowed to cool to room temperature to obtain the final formulation.

Experimental Design and Optimization

Optimization of the microemulsion was carried out using Response Surface Methodology (RSM) based on a Box–Behnken design. Three independent formulation variables-Isopropyl palmitate (A), Span 80 (B), and PEG 400 (C)-were evaluated for their influence on key dependent responses, including drug content, viscosity, and drug release. The experimental design consisted of 13 runs incorporating factorial, axial, and centre points. Mathematical models generated from the design enabled evaluation of individual and interaction effects of formulation variables and facilitated selection of an optimized microemulsion composition.

Selection of Formulation Components

The choice of oil, surfactant, and co-surfactant is critical for the successful development of phytochemical microemulsions, as many phytochemicals exhibit poor aqueous solubility and low bioavailability. The oil phase acts as the primary solubilizing medium for lipophilic phytochemicals such as flavonoids, terpenoids, and polyphenols. Commonly employed oils include medium-chain triglycerides, isopropyl myristate, isopropyl palmitate, oleic acid, and selected natural oils. The surfactant reduces interfacial tension and stabilizes the system; non-ionic surfactants are preferred due to their biocompatibility and lower toxicity. Co-surfactants such as glycols and short-chain alcohols enhance interfacial flexibility, expand the microemulsion region, and promote spontaneous formation.

Importance of Component Screening and HLB System

Solubility screening studies are performed to identify components with maximum phytochemical solubilization capacity. Optimized oil–surfactant–co-surfactant ratios are established using pseudo-ternary phase diagrams to ensure formulation robustness. The hydrophilic–lipophilic balance (HLB) system provides a rational basis for surfactant selection, determining whether oil-in-water or water-in-oil microemulsions are formed. Adjustment of HLB values through surfactant combinations enhances interfacial flexibility, reduces droplet size, and improves stability and bioavailability of phytochemicals [7].

Construction and Interpretation of Pseudo-Ternary Phase Diagram

Pseudo-ternary phase diagrams were constructed to identify the microemulsion existence region and to optimize the proportions of oil, surfactant–co-surfactant mixture, and aqueous phase. The surfactant and co-surfactant were blended in fixed ratios and combined with the selected oil phase, followed by gradual titration with the aqueous phase under continuous stirring. Visual observation was used to identify clear, transparent, and isotropic systems, which were considered indicative of microemulsion formation. The resulting diagrams enabled identification of stable microemulsion regions and guided the selection of optimized compositions with maximum stability and solubilization efficiency for phytochemical incorporation [8].

Drug Incorporation Techniques

Phytochemicals may be incorporated into microemulsions using various techniques, including direct dissolution, solvent evaporation–assisted incorporation, surfactant–co-surfactant loading, oil phase saturation, and post-loading methods. The choice of technique depends on the solubility, lipophilicity, and thermal stability of the phytochemical. Proper selection ensures high drug loading, uniform distribution, and preservation of microemulsion stability [9].

Characterization of Microemulsions

Comprehensive characterization is essential to understand the physicochemical properties, internal structure, and stability of microemulsions. Pseudo-ternary phase diagrams identify microemulsion regions and phase behaviour. Viscosity measurements provide insight into internal structure and suitability for different routes of administration. Electrical conductivity determines the nature of the continuous phase and detects structural transitions [10]. Nuclear magnetic resonance spectroscopy elucidates molecular mobility and internal connectivity. Static and dynamic light scattering techniques are used to assess droplet size and distribution. Microscopy confirms nanoscale morphology and isotropy, while fluorescence studies evaluate droplet diffusion and microenvironment polarity. Interfacial tension measurements reflect solubilization efficiency and spontaneous microemulsion formation [11].

Biomedical Applications of Phytochemical-Loaded Microemulsions

Phytochemicals from medicinal plants exhibit diverse biomedical activities, including anticancer, anti-inflammatory, antimicrobial, wound healing, cardioprotective, neuroprotective, and transdermal effects; however, their clinical application is often limited by poor aqueous solubility, low stability, rapid metabolism, restricted permeability, and low bioavailability. Microemulsion-based drug delivery systems provide an effective strategy to overcome these limitations, as they are thermodynamically stable, isotropic dispersions of oil, water, surfactant, and co-surfactant with nanoscale droplet sizes that enable high solubilization and enhanced membrane permeability. By improving phytochemical solubility and stability, protecting active compounds from degradation, and enabling controlled release and efficient transport across biological barriers, microemulsions significantly enhance therapeutic efficacy, reduce toxicity, and improve the clinical potential of phytochemical-based treatments.

Anticancer Applications

Cancer remains a leading cause of morbidity and mortality worldwide, despite advances in diagnosis and therapeutic interventions. Many phytochemicals, including flavonoids, terpenoids, alkaloids, and polyphenols, exhibit potent anticancer activities such as antioxidant effects, induction of apoptosis, inhibition of angiogenesis, suppression of tumour proliferation, and regulation of the cell cycle. However, their clinical translation is restricted by unfavourable physicochemical properties that limit effective tumour exposure.

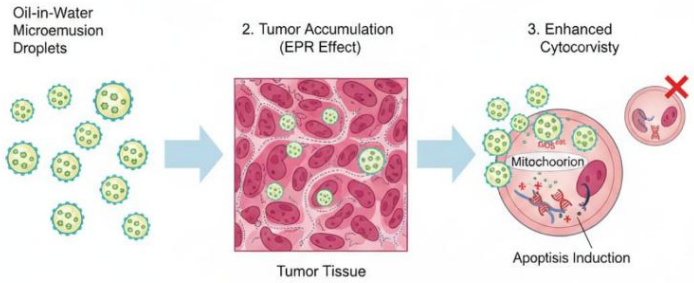


Figure 04: Anticancer Mechanism of Microemulsion Drug Delivery

Microemulsion-based delivery systems address these challenges by enhancing the solubility and stability of anticancer phytochemicals and improving their bioavailability. The nanosized droplets facilitate enhanced tumour penetration and cellular uptake, while controlled release maintains therapeutic drug levels over extended periods. These advantages result in improved anticancer efficacy with reduced systemic toxicity and fewer dose-related adverse effects. Furthermore, microemulsions enable the co-delivery of multiple phytochemicals, supporting synergistic anticancer effects and multi-targeted therapeutic strategies. Collectively, phytochemical-loaded microemulsions represent a promising platform for improving the effectiveness and safety of anticancer therapy [12].

Anti-Inflammatory Applications

Inflammation is a protective physiological response to injury and infection; however, chronic or uncontrolled inflammation contributes to the progression of several diseases, including arthritis, cardiovascular disorders, neurodegenerative diseases, and cancer. Although conventional anti-inflammatory drugs are effective, their long-term use is associated with significant adverse effects, driving interest in safer, plant-derived alternatives.

Phytochemicals possess broad anti-inflammatory activity by inhibiting pro-inflammatory cytokines, suppressing cyclooxygenase and lipoxygenase enzymes, and regulating key signalling pathways such as nuclear factor-kappa B. Despite their therapeutic promise, poor solubility and limited absorption restrict their clinical effectiveness. Microemulsions enhance the solubility, stability, and permeability of anti-inflammatory phytochemicals, resulting in improved absorption and prolonged therapeutic action. Surfactants used in microemulsions further enhance membrane fluidity, facilitating drug transport across biological barriers. These properties make microemulsion-based systems highly suitable for oral, topical, transdermal, and parenteral anti-inflammatory therapy [13].

Wound Healing Applications

Wound healing is a complex and highly regulated biological process involving haemostasis, inflammation, proliferation, and remodelling. Disruption of these stages due to infection, oxidative stress, ischemia, or metabolic disorders can result in delayed or chronic wounds. Conventional wound therapies, while effective, may cause cytotoxicity, microbial resistance, or delayed tissue regeneration, highlighting the need for safer alternatives.

Phytochemicals offer multifaceted wound healing benefits through antioxidant, anti-inflammatory, antimicrobial, and collagen-stimulating activities. However, poor solubility and inadequate skin penetration limit their topical efficacy. Microemulsion systems overcome these barriers by enhancing dermal penetration, protecting phytochemicals from degradation, and maintaining a moist wound environment that supports cellular migration and angiogenesis. The nanoscale droplets increase drug retention at the wound site and ensure sustained release, leading to accelerated wound contraction, improved epithelialization, and enhanced collagen deposition. These features make phytochemical-loaded microemulsions particularly valuable for topical wound management [14].

Table 01: Phytochemical-Loaded Microemulsions for Wound Healing

Phytochemicals	Source	Key Wound Healing Actions	Advantage of Microemulsion	Therapeutic Outcome
Asiatic side	Centella asiatica	Collagen synthesis, angiogenesis	Enhanced skin penetration	Accelerated wound contraction
Aloin	Aloe vera	Anti-inflammatory, epithelialization	Improved stability and spread ability	Faster wound closure
Chrysin	Passionflower, propolis	Antioxidant, anti-inflammatory	Improved solubility and retention	Enhanced collagen deposition
Rutin	Citrus fruit, buckwheat	Antioxidant, angiogenesis	Prolonged local availability	Improved granulation tissue

Thymol/carvacrol	Thyme, oregano oil	Antimicrobial, anti-inflammatory	Reduced volatility, sustained action	Infection control and healing

Antimicrobial Applications

Microbial infections continue to pose a major global health challenge, exacerbated by the rapid emergence of antimicrobial resistance and biofilm-associated infections. Although synthetic antibiotics remain the mainstay of treatment, their limitations include toxicity, resistance development, and reduced efficacy against biofilms [1].

Phytochemicals exhibit broad-spectrum antimicrobial activity through disruption of microbial membranes, inhibition of enzyme systems, interference with nucleic acid synthesis, and suppression of virulence factors. However, volatility, instability, and poor aqueous solubility hinder their therapeutic application. Microemulsions enhance the solubilization and stability of antimicrobial phytochemicals and facilitate close interaction between active compounds and microbial cells. The presence of surfactants enhances penetration into biofilms, while sustained release maintains prolonged antimicrobial activity. These properties make microemulsion-based phytochemical delivery systems promising alternatives for managing resistant and chronic infections [15].

Table 02: Phytochemical-Loaded Microemulsions for Anti-microbial therapy

Phytochemical Class	Representative Compounds	Target Microorganisms	Advantage of Microemulsion	Therapeutic Outcome
Essential oil phenols	Thymol, carvacrol	Bacteria, fungi	Improved solubility and stability	Enhanced antimicrobial activity
Flavonoids	Quercetin, chrysin, rutin	Resistant bacteria	Enhanced penetration and retention	Reduced microbial load
Phenolic acids	Gallic acid, ferulic acid	Gram-positive bacteria	Sustained release	Prolonged antimicrobial effect
Terpenoids	Ursolic acid, betulinic acid	Bacteria and fungi	Improved dispersion	Increased microbial membrane disruption
Terpenoids	Ursolic acid, betulinic acid	Bacteria and fungi	Improved dispersion	Increased microbial membrane disruption

Cardioprotective Applications

Cardiovascular diseases represent a major global health burden, driven by oxidative stress, chronic inflammation, endothelial dysfunction, lipid peroxidation, and apoptosis of cardiac cells. Phytochemicals have demonstrated cardioprotective effects through antioxidant, anti-inflammatory, lipid-lowering, anti-platelet, and endothelial-protective mechanisms. Despite these benefits, poor solubility, extensive first-pass metabolism, and low bioavailability limit their therapeutic translation [16].

Microemulsions enhance the solubility, stability, and absorption of cardioprotective phytochemicals, improving systemic exposure and therapeutic efficacy. Controlled release properties help maintain consistent plasma concentrations, which are essential for long-term cardiovascular protection. By improving pharmacokinetic profiles and reducing dose requirements, microemulsion-based delivery systems offer safer and more effective strategies for both preventive and therapeutic cardiovascular applications [17].

Table 03: Phytochemical-Loaded Microemulsions for Cardioprotective Applications

Phytochemical	Type of Microemulsion	Route of Administration	Cardiovascular Model	Key Findings	Study Type
Resveratrol	Oil-in-water	Oral	Endothelial dysfunction	Enhanced bioavailability and antioxidant activity	Preclinical
Quercetin	Bicontinuous	Oral	Oxidative stress-induced CVD	Reduced lipid peroxidation	Preclinical
Quercetin	Oil-in-water	Oral	Atherosclerosis model	Improved lipid profile and vascular protection	Preclinical
Catechins	Oil-in-water	Oral	Myocardial dysfunction	Improved mitochondrial function and cardiac protection	Preclinical
Coenzyme Q10	Water-in-oil	Oral	Cardiovascular oxidative stress	Enhanced absorption and cardioprotective effect	Preclinical

Neuroprotective Applications

Neurodegenerative diseases are characterized by progressive neuronal loss due to oxidative stress, neuroinflammation, mitochondrial dysfunction, and protein aggregation. Phytochemicals possess

neuroprotective properties through antioxidant, anti-inflammatory, anti-apoptotic, and anti-amyloidogenic mechanisms. However, poor solubility, rapid metabolism, and limited transport across the blood–brain barrier restrict their clinical use.

Microemulsions provide an effective platform for delivering neuroprotective phytochemicals by enhancing solubility, protecting against degradation, and improving permeability. The surfactants used in microemulsions facilitate membrane transport and may enhance brain delivery, while sustained release maintains therapeutic concentrations in neural tissues. These advantages contribute to improved cognitive and motor outcomes and protection against neurodegenerative progression, highlighting the potential of microemulsion-based neuroprotective therapy.

Table 04: Phytochemical-Loaded Microemulsions for Neuroprotective Applications

Phytochemical	Type of Microemulsion	Route of Administration	Neurodegenerative Model	Key Findings	Study Type
Curcumin	Oil-in-water	Oral / Intranasal	Alzheimer's disease	Enhanced BBB penetration, improved cognition	Preclinical
Resveratrol	Oil-in-water	Oral	Parkinson's disease	Reduced oxidative stress, improved neuronal survival	Preclinical
Quercetin	Bicontinuous	Oral	Ischemic stroke	Reduced inflammation and apoptosis	Preclinical
Naringenin	Oil-in-water	Oral / Intranasal	Neuroinflammation model	Improved antioxidant and anti-inflammatory effects	Preclinical
EGCG	Oil-in-water	Oral	Huntington's disease model	Reduced protein aggregation and neuronal damage	Preclinical

Transdermal Delivery Applications

Transdermal drug delivery offers several advantages, including avoidance of first-pass metabolism, sustained drug release, and improved patient compliance. However, the stratum corneum presents a significant barrier, particularly for poorly soluble phytochemicals. Microemulsions enhance transdermal delivery by solubilizing lipophilic compounds, increasing skin contact through nanosized droplets, and disrupting stratum corneum lipid organization to enhance permeability.

Microemulsion-based transdermal systems protect phytochemicals from degradation and provide controlled release, maintaining therapeutic concentrations in dermal tissues over extended periods. These properties make them suitable for localized and systemic therapy, including anti-inflammatory, wound healing, cardioprotective, and neuroprotective applications.

Translational and Clinical Potential

Across diverse biomedical applications, phytochemical-loaded microemulsions demonstrate significant translational potential. They are composed of pharmaceutically acceptable excipients, exhibit excellent physical stability, and can be scaled up using conventional manufacturing processes. By enhancing bioavailability, reducing systemic toxicity, and improving patient compliance, microemulsion-based phytochemical delivery systems offer a versatile and promising approach for the development of safer and more effective therapies for chronic and complex diseases.

Table 05: Phytochemical-Loaded Microemulsions for Transdermal Delivery Applications

Phytochemical	Type of microemulsion	Route of Administration	Skin/ Transdermal model	Key findings	Study type
curcumin	O/W	Topical/Transdermal	Dermal inflammation	Improved skin penetration anti inflammation activity	preclinical
Resveratrol	O/W	Topical/Transdermal	UV induced oxidative stress	enhanced protection	preclinical
Quercetin	BI continuous	Topical	Skin inflammation	Reduced oxidative stress and inflammation	preclinical
naringenin	O/W	Topical/Transdermal	Inflammatory skin model	Reduced oxidative stress and inflammation	preclinical

MECHANISMS OF ENHANCED BIOAVAILABILITY

Anticancer Microemulsion Systems

Microemulsion-based drug delivery systems significantly enhance the bioavailability and therapeutic efficacy of anticancer phytochemicals by overcoming formulation-related and biological barriers. These systems improve systemic exposure, tumour accumulation, and overall therapeutic outcomes compared with conventional formulations.

1. Increased Surface Area and Enhanced Solubilization

Microemulsions spontaneously form nanosized droplets (10–100 nm), providing a markedly increased interfacial surface area. This nanoscale dimension enhances the solubilization of poorly water-soluble phytochemicals, increasing their apparent solubility and thermodynamic activity. Improved solubilization promotes efficient dissolution, leading to enhanced absorption, higher systemic availability, and improved tumour uptake.

2. Improved Membrane Permeability and Tumour Penetration

Surfactants and co-surfactants interact with cellular membranes, increasing membrane fluidity and permeability. These interactions facilitate both transcellular and paracellular transport of phytochemicals across epithelial barriers and tumour vasculature. Enhanced permeability supports improved oral absorption and deeper tumour tissue penetration, which is essential for effective anticancer therapy [18].

3. Protection from Chemical and Enzymatic Degradation

Many anticancer phytochemicals, particularly polyphenols and flavonoids, are chemically unstable and susceptible to enzymatic degradation. Encapsulation within the oil phase or surfactant interface of microemulsions protects these compounds from harsh physiological conditions, preserving chemical integrity, prolonging half-life, and maintaining therapeutic activity during systemic circulation.

4. Sustained and Controlled Release

The internal structure of microemulsions enables controlled and sustained release of encapsulated phytochemicals. Gradual drug release maintains therapeutic concentrations over extended periods, reduces dosing frequency, and ensures prolonged exposure of cancer cells to the active compound, thereby improving anticancer efficacy.

5. Enhanced Lymphatic Transport and Bypass of First-Pass Metabolism

Lipid-based microemulsions facilitate absorption via the intestinal lymphatic system, bypassing hepatic first-pass metabolism. This pathway enhances systemic availability and plasma concentrations of lipophilic phytochemicals, contributing to improved bioavailability and tumour targeting [19].

Anti-Inflammatory Microemulsion Systems

Microemulsion-based delivery systems improve the bioavailability and therapeutic effectiveness of anti-inflammatory phytochemicals by addressing limitations related to solubility, stability, permeability, and biological transport.

1. Increased Surface Area and Enhanced Solubilization

Nanosized droplets (10–100 nm) create a large interfacial surface area, improving solubilization and dissolution of poorly water-soluble phytochemicals. Enhanced solubility increases the fraction of drug available for absorption across biological membranes.

2. Improved Membrane Permeability

Surfactants and co-surfactants alter membrane lipid organization, increasing membrane fluidity and facilitating permeation across epithelial and endothelial barriers. In topical and transdermal applications, microemulsions disrupt stratum corneum lipids, enhancing drug diffusion into deeper tissues.

3. Protection from Chemical and Enzymatic Degradation

Labile anti-inflammatory phytochemicals such as curcumin and resveratrol are protected within the microemulsion oil phase or interfacial layer. This encapsulation shields them from oxidative, thermal, and enzymatic degradation, preserving stability and biological potency.

4. Sustained and Controlled Release

The nanostructured organization of microemulsions enables gradual drug release, maintaining therapeutic concentrations over extended periods. Sustained delivery is particularly beneficial in chronic inflammatory disorders, reducing dosing frequency and improving therapeutic consistency.

5. Enhanced Lymphatic Transport and Bypass of First-Pass Metabolism

Orally administered lipid-based microemulsions promote lymphatic uptake, bypass hepatic metabolism, and enhance systemic exposure of lipophilic anti-inflammatory phytochemicals, improving plasma levels and tissue distribution [20].

Wound Healing Microemulsion Systems

Microemulsion-based delivery systems enhance the stability, penetration, and therapeutic effectiveness of wound-healing phytochemicals, promoting sustained biological activity at the wound site.

1. Increased Surface Area and Enhanced Solubilization

Nanosized droplets (10–100 nm) provide extensive interfacial surface area, improving solubilization and thermodynamic activity of poorly water-soluble agents such as Asiatic side, chrysin, and rutin. Enhanced solubilization supports efficient penetration through epidermal layers.

2. Improved Membrane Permeability and Skin Penetration

Surfactants disrupt stratum corneum lipid bilayers, reducing barrier resistance and facilitating deeper penetration into dermal tissues. Effective skin permeation is essential for delivering antioxidants, anti-inflammatory agents, and collagen-stimulating compounds to damaged tissue.

3. Protection from Chemical and Enzymatic Degradation

Encapsulation of sensitive phytochemicals (e.g., aloin, thymol, carvacrol) protects them from oxidation, enzymatic degradation, and environmental stress. This stability ensures higher drug availability and sustained biological activity at the wound site.

4. Sustained and Controlled Release at the Wound Site

Microemulsions allow prolonged release of active compounds, preventing rapid loss due to wound exudate. Sustained drug levels support fibroblast proliferation, collagen synthesis, angiogenesis, and antimicrobial defence.

5. Moisture Retention and Enhanced Local Distribution

Microemulsions form semi-occlusive films that retain moisture at the wound surface, promoting cell migration, granulation tissue formation, and epithelialization. Uniform drug distribution ensures consistent therapeutic action across the wound area.

6. Facilitation of Lymphatic Uptake

The nano-scale and lipidic nature of microemulsions may facilitate lymphatic uptake through highly vascularized wound tissue, contributing to systemic anti-inflammatory and antioxidant effects alongside local wound repair.

Antimicrobial Microemulsion Systems

Microemulsion-based systems enhance the therapeutic performance of antimicrobial phytochemicals by improving solubility, stability, permeability, and sustained drug exposure.

Increased Surface Area and Solubilization

Nanosized droplets (10–100 nm) significantly increase interfacial surface area, enhancing dissolution and thermodynamic activity of lipophilic antimicrobial agents. Improved solubilization increases effective drug concentration at microbial targets.

Improved Membrane Permeability

Surfactants increase membrane fluidity and reduce resistance across microbial cell walls and biofilms, facilitating phytochemical penetration and improving antimicrobial efficacy.

Protection from Chemical and Enzymatic Degradation

Encapsulation within microemulsion droplets shields antimicrobial phytochemicals from oxidation, light, heat, and enzymatic degradation, preserving stability and prolonging activity at infection sites.

Sustained and Controlled Release

Gradual release maintains effective antimicrobial concentrations over extended periods, improving treatment of chronic or recurrent infections and enhancing patient compliance.

Potential Lymphatic Transport

Lipid-based microemulsions may promote lymphatic transport, bypassing first-pass metabolism and increasing systemic exposure of lipophilic antimicrobial agents [22].

Cardioprotective Microemulsion Systems

Microemulsion-based systems enhance the oral bioavailability and systemic effectiveness of cardioprotective phytochemicals that exhibit poor aqueous solubility, low permeability, and rapid metabolic degradation.

1. Increased Surface Area and Solubilization

Microemulsions form nanoscale droplets (<100 nm) that provide a very large interfacial surface area.This enhanced surface area improves dissolution and apparent solubility of lipophilic cardioprotectivephytochemicals.Increased thermodynamic activity creates a stronger concentration gradient, driving efficient absorption.

2. Improved Membrane Permeability

Surfactants and co-surfactants interact with intestinal and vascular membranes, increasing lipid fluidity.This interaction facilitates transcellular and paracellular transport of encapsulated phytochemicals.Improved permeability enhances systemic exposure and delivery to cardiovascular tissues.

3. Protection from Chemical and Enzymatic Degradation

Encapsulation within the microemulsion oil phase shields phytochemicals from oxidative and enzymatic degradation.This protection minimizes premature metabolism in gastrointestinal fluid and systemic circulation.As a result, drug stability and biological half-life are significantly prolonged.

4. Sustained and Controlled Release

The internal nanostructure of microemulsions allows gradual drug release over time. Controlled release prevents rapid plasma clearance and maintains steady therapeutic concentrations.This sustained exposure supports long-term cardioprotective effects with reduced dosing frequency.

5. Lymphatic Transport and Bypass of First-Pass Metabolism

Lipid-based microemulsions promote uptake into the intestinal lymphatic system. This pathway bypasses hepatic first-pass metabolism, enhancing systemic drug availability. Improved distribution to cardiovascular tissues contributes to enhanced therapeutic efficacy.

NEUROPROTECTIVE MICROEMULSION SYSTEMS

Microemulsion systems improve the bioavailability and brain delivery of neuroprotective phytochemicals that are limited by poor solubility and restricted blood–brain barrier penetration.

1. Increased Surface Area and Solubilization

Nanosized droplets significantly increase surface area for drug–membrane interaction. This enhances dissolution and apparent solubility of lipophilic neuroprotective compounds. Improved thermodynamic activity increases systemic absorption efficiency.

2. Improved Membrane Permeability

Surfactants interact with intestinal membranes and blood–brain barrier lipid domains. These interactions increase membrane fluidity and transiently reduce barrier resistance. As a result, phytochemical transport into the central nervous system is enhanced.

3. Protection from Chemical and Enzymatic Degradation

Encapsulation within microemulsions protects labile neuroprotective phytochemicals from degradation.The oil phase and surfactant interface shield compounds from enzymatic and oxidative attack.This protection prolongs circulation time and preserves therapeutic activity.

4. Sustained and Controlled Release

Microemulsions enable gradual release of neuroprotective agents into systemic circulation. Sustained release maintains stable plasma and brain tissue drug levels. This continuous exposure supports prolonged neuroprotection in chronic neurological disorders.

5. Potential Lymphatic Transport

Lipid-based microemulsions may stimulate lymphatic uptake of encapsulated phytochemicals. Lymphatic transport bypasses first-pass metabolism and enhances systemic exposure. Increased circulating drug levels improve the probability of brain delivery [23].

Transdermal Microemulsion Systems

Microemulsion-based transdermal systems improve skin permeation and bioavailability of poorly soluble phytochemicals by modulating the skin barrier and drug release behavior.

1. Increased Surface Area and Solubilization

Nanosized droplets increase contact between the drug and the skin surface. Enhanced solubilization improves thermodynamic activity at the application site. This drives greater drug diffusion into the skin layers.

2. Improved Skin Permeability

Surfactants and penetration enhancers disrupt stratum corneum lipid packing. This disruption reduces barrier resistance and increases membrane fluidity. Consequently, drug diffusion into deeper skin layers is enhanced.

3. Hydration and Lipid Fluidization

Microemulsions increase stratum corneum hydration through semi-occlusive effects. Hydration weakens lipid organization and enhances permeation pathways. Both hydrophilic and lipophilic drugs benefit from improved skin transport.

4. Protection from Degradation

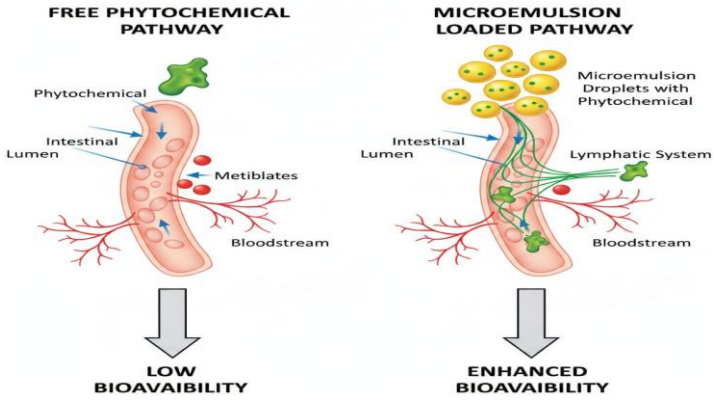
Encapsulation protects phytochemicals from chemical and enzymatic degradation at the skin surface. This protection preserves drug integrity during storage and application. Higher effective drug concentrations reach deeper tissues.

5. Controlled and Sustained Release

Microemulsions provide prolonged release of phytochemicals at the application site. Sustained release maintains therapeutic concentrations for extended periods. This enhances pharmacological efficacy and reduces application frequency.

Potential for Lymphatic Transport

Lipid-based microemulsions may facilitate uptake into dermal lymphatic vessels. Lymphatic transport contributes to improved systemic bioavailability. This mechanism complements local transdermal drug delivery [24].



Toxicity and Safety Considerations

Microemulsions are promising nanostructured carriers for phytochemical delivery due to their ability to enhance solubility, improve bioavailability, and protect labile compounds from degradation. These thermodynamically stable, optically clear systems consist of oil and water phases stabilized by surfactants and, in many cases, co-surfactants. Their small droplet size, high surface area, and spontaneous formation enable efficient drug delivery via topical, oral, transdermal, and parenteral routes.

Despite these advantages, the relatively high surfactant concentrations required for microemulsion formation and their interactions with biological membranes raise important safety and toxicity concerns. Therefore, a comprehensive understanding of toxicity mechanisms and mitigation strategies is essential for the successful clinical translation of phytochemical-loaded microemulsion systems.

Foundations of Microemulsion Toxicology

Composition-Driven Risks

Microemulsions require a delicate balance among oil, water, surfactant, and co-surfactant. Surfactant concentrations are typically much higher than in conventional emulsions, which may compromise biocompatibility. Excess surfactant can disrupt cellular membranes, leading to cytotoxicity and irritation.

Non-ionic surfactants such as polysorbates (Tweens) are commonly used due to their relatively low irritation potential. However, even these agents can cause adverse effects when used at high concentrations, highlighting the importance of formulation optimization [25].

Surfactants and Co-surfactants

Surfactant selection plays a critical role in determining both microemulsion stability and safety. Non-ionic surfactants generally exhibit reduced interaction with charged cellular membranes and lower toxicity. In contrast, ionic surfactants, although less frequently used, are associated with higher cytotoxicity and irritation.

Co-surfactants such as short-chain alcohols and glycols (e.g., propylene glycol) facilitate microemulsion formation but may increase irritant potential. Optimizing co-surfactant content can reduce overall surfactant requirements and mitigate toxicity.

Common Surfactants and Safety Profiles

- **Polysorbate 80 (Tween 80):** Non-ionic surfactant with low irritation; widely used in oral and parenteral formulations
- **Span series:** Often combined with Tweens; generally low toxicity depending on formulation
- **Propylene glycol:** Common co-surfactant; may cause mucosal irritation at high concentrations

Table 04: Common Surfactants and Safety Profiles in Microemulsion Systems

Surfactant type	Common Use in Microemulsions	Safety Considerations
Polysorbate 80 (Tween 80)	Non ionic surfactant	Low irritation; widely used in oral/parenteral forms
Span series	Often paired with Tween for balance	Generally low toxicity; formulation dependent
Propylene glycerol	Co surfactant	Possible mucosal irritation at high concentration

Cellular and Tissue Toxicity Mechanisms

Cellular Membrane Interaction

The primary mechanism of microemulsion toxicity involves surfactant interaction with lipid bilayers. Surfactants may insert into membranes, altering fluidity and integrity, which can lead to increased permeabilityor apoptosis.

Oxidative Stress and Inflammation

Microemulsion exposure may induce oxidative stress, resulting in inflammatory responses and the release of pro-inflammatory cytokines. Excessive oxidative stress can damage proteins, lipids, and nucleic acids.

Histological Changes

Animal studies have reported epithelial thinning and mild inflammatory infiltration following exposure to high surfactant concentrations. These findings emphasize the need for careful dose selection, particularly for systemic and mucosal applications.

Organ-Level and Systemic Toxicity

Liver and Kidney Effects

Microemulsion components may accumulate in detoxifying organs such as the liver and kidneys. Preclinical studies have reported elevated liver enzymes and altered renal markers at high doses or with prolonged exposure, indicating potential organ stress.

Immune System Modulation

Microemulsions may interact with the immune system, particularly through complement activation. Some surfactants can trigger complement activation-related pseudo-allergy (CARPA), leading to hypersensitivity reactions.

Route-Dependent Toxicity

Toxicity profiles vary with the route of administration. Topical and transdermal delivery is typically associated with localized irritation, whereas oral and parenteral routes pose a greater risk of systemic toxicity and require extensive safety evaluation.

TOXICITY IN PHYTOCHEMICAL DELIVERY SYSTEMS

Phytochemicals possess inherent biological activity, complicating safety assessments when combined with microemulsion excipients. Enhanced bioavailability may lead to higher intracellular concentrations, potentially intensifying both therapeutic and adverse effects. Synergistic interactions between surfactants and phytochemicals may further exacerbate cytotoxic responses if not properly controlled.

Strategies to Reduce Toxicity

Optimizing Surfactant Systems

Using mixed surfactant systems and optimizing co-surfactant levels can maintain microemulsion stability while reducing total surfactant load and toxicity.

Biocompatible and Green Surfactants

Biosurfactants and biodegradable surfactants represent emerging alternatives that may reduce irritation, improve biocompatibility, and lower environmental impact.

Surface Functionalization

Surface modification with biocompatible polymers, such as PEGylation, can reduce immune recognition and limit unintended membrane interactions.

Dose and Exposure Optimization

Comprehensive in vitro and in vivo dose–response studies are essential to define the therapeutic window and establish maximum safe exposure levels for both phytochemicals and excipients.

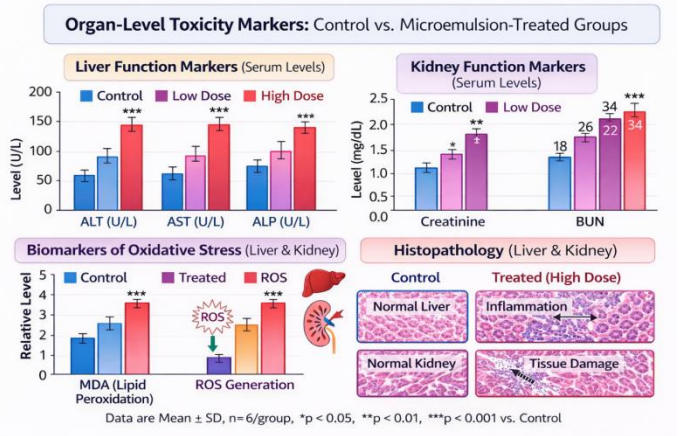


Figure 05: Organ-Level Toxicity Markers in Control vs. Microemulsion-Treated Groups

Regulatory and Clinical Safety Assessment

For clinical translation, microemulsion systems must comply with regulatory safety requirements, including evaluation of:

- Acute and chronic toxicity
- Genotoxicity and mutagenicity
- Carcinogenic potential
- Immunogenicity

These assessments must align with guidelines established by regulatory authorities such as the Food and Drug Administration and the European Medicines Agency to ensure the safety of both excipients and active phytochemical compounds [26].

Challenges and Future Perspectives

Microemulsion-based delivery systems have gained considerable attention for improving the solubility, stability, and bioavailability of phytochemical compounds such as curcumin, resveratrol, quercetin, and terpenoids. Their thermodynamically stable nanostructure, formulation simplicity, and compatibility with multiple administration routes make them attractive for biomedical and nutraceutical applications. Despite these advantages, several technical, regulatory, and translational challenges hinder their progression from laboratory research to clinical and commercial implementation. Addressing these challenges is essential for the future advancement of microemulsion platforms.

Challenges in Scale-Up and Manufacturing

Formulation Predictability and Reproducibility

Microemulsions are typically optimized at the laboratory scale using phase diagrams and precise surfactant ratios. Scaling up to industrial production requires consistent control of droplet size, polydispersity, and thermodynamic stability, which is difficult to maintain. Variations in mixing shear, temperature gradients, raw material batches, and equipment geometry can alter droplet characteristics, zeta potential, and internal structure, ultimately affecting drug release and performance.

Process Control and Manufacturing Technologies

Manufacturing methods such as micro fluidization, high-pressure homogenization, and spontaneous emulsification are widely used. However, these techniques do not always scale linearly. High shear forces and pressures effective at small volumes may cause formulation heterogeneity or degradation of sensitive phytochemicals at large scale.

Cost and Raw Material Availability

Pharmaceutical-grade surfactants and co-surfactants can be costly or limited in bulk availability, creating supply chain challenges. In addition, some co-surfactants require independent regulatory approval, further increasing production complexity and cost.

Stability Challenges

Physical and Phase Stability

Although microemulsions are thermodynamically stable, minor changes in formulation composition, temperature, or contamination can induce phase separation or transition into macroemulsions. Even slight deviations in oil–water–surfactant ratios may compromise system stability.

Chemical Stability of Phytochemicals

Many phytochemicals are sensitive to light, heat, and pH variations. While microemulsion encapsulation offers protection, excipients may still promote oxidation or hydrolysis, leading to degradation during storage or use.

Surfactant–Phytochemical Interactions

Certain surfactants can interact chemically or physically with encapsulated phytochemicals, potentially reducing therapeutic efficacy or causing unwanted transformations.

Regulatory Challenges

Lack of Standardized Guidelines

Unlike liposomes or polymeric nanoparticles, microemulsions lack dedicated regulatory frameworks for phytochemical delivery. Regulatory agencies such as the Food and Drug Administration and the European Medicines Agency provide general guidance for excipients and active ingredients but not microemulsion-specific criteria. This creates uncertainty regarding quality control parameters, bioequivalence requirements, stability testing, and clinical safety standards.

Safety and Toxicology Documentation

Microemulsions often contain surfactants at higher concentrations than conventional formulations. These excipients may require extensive toxicological evaluation, increasing development time and regulatory burden [27].

Personalized Phytomedicine and Targeted Delivery Challenges

Inter-Individual Variability

Personalized phytomedicine aims to tailor formulations based on genetic, metabolic, and microbiome differences among patients. Microemulsions must accommodate variability in gastrointestinal pH, transit time, absorption efficiency, and metabolic phenotypes. Currently, standardized personalization strategies for microemulsions remain limited.

Targeting Efficiency

Advanced microemulsions designed for targeted delivery face biological barriers such as opsonization, rapid clearance, and reduced targeting efficiency when translating from animal models to human systems [28].

Smart Microemulsions: Future Opportunities and Challenges

Smart microemulsions are designed to respond to physiological stimuli such as pH, temperature, enzymatic activity, or redox conditions, enabling controlled and site-specific release of phytochemicals. While promising, these systems introduce additional challenges.

Formulation Complexity

Incorporation of stimuli-responsive polymers, functional lipids, or sensing elements increases formulation complexity and may destabilize phase behaviour.

Safety and Biocompatibility

The addition of responsive components introduces new concerns related to toxicity, immunogenicity, and long-term biocompatibility, complicating regulatory approval.

Reproducibility and Scale-Up

Smart microemulsions are inherently more complex than conventional systems, making reproducibility and large-scale manufacturing more challenging [29].

Future Perspectives

Future research should focus on developing scalable manufacturing strategies, safer and biocompatible surfactants, standardized regulatory frameworks, and robust stability assessment methods. Integration of personalized medicine principles and smart-release technologies, supported by thorough safety and translational studies, will be critical for realizing the full therapeutic potential of microemulsion-based phytochemical delivery systems.

FUTURE PERSPECTIVES

Future research should focus on developing scalable manufacturing strategies, safer and biocompatible surfactants, standardized regulatory frameworks, and robust stability assessment methods. Integration of personalized medicine principles and smart-release technologies, supported by thorough safety and translational studies, will be critical for realizing the full therapeutic potential of microemulsion-based phytochemical delivery systems [30].

CONCLUSION

Phytochemical-loaded microemulsions offer an advanced and effective approach to overcoming the major limitations of phytochemicals, including poor aqueous solubility, low bioavailability, chemical instability, and rapid metabolism. By enhancing solubilization, absorption, stability, and controlled release, these systems significantly improve therapeutic efficacy across anticancer, anti-inflammatory, antimicrobial, wound healing, cardioprotective, and neuroprotective applications. Continued research focusing on safety, scalability, and clinical translation will further establish microemulsions as versatile platforms for phytochemical-based drug delivery.

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AUTHOR CONTRIBUTIONS

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