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# Targeted Delivery Strategies for Hydrophilic Phytochemicals

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## Featured Application

This review provides a knowledge base for designing efficient delivery systems for hydrophilic plant-derived compounds, offering practical guidance for pharmaceutical and cosmetic industries seeking to improve skin penetration, bioavailability, and formulation stability.

## Abstract

Hydrophilic phytochemicals, such as flavonoids and phenolic acids, possess important biological activities, including antioxidant, anti-inflammatory, and anticancer effects. However, their application is hindered by low membrane permeability, poor chemical stability, and limited skin penetration. This review provides a comprehensive analysis of advanced delivery strategies aimed at enhancing the solubility, bioavailability, and therapeutic efficacy of selected hydrophilic compounds. Specifically, it focuses on the encapsulation of flavonoids such as quercetin, luteolin, and apigenin, as well as phenolic acids including ferulic acid, caffeic acid, and chlorogenic acid. The review discusses various nanocarrier systems: liposomes, niosomes, exosomes, and polymeric nanoparticles (e.g., nanocapsules, nanospheres) and compares their structural characteristics, preparation methods, and functional benefits. These delivery systems improve the physicochemical stability of active compounds, enable controlled and targeted release, and enhance skin and cellular absorption. Despite certain challenges related to large-scale production and regulatory constraints, such approaches offer promising solutions for the pharmaceutical and cosmetic application of hydrophilic plant-derived compounds.

**Keywords:** hydrophilic phytochemicals; delivery systems; liposomes; niosomes; exosomes; polymeric nanoparticles; controlled release; bioavailability; skin penetration; antioxidant and anti-inflammatory potential



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# 1. Introduction

## 1.1. Background on Phytochemicals: Overview of the Importance and Therapeutic Potential of Plant-Derived Active Substances

Since ancient times, plants have played a vital role in human life. Traditionally, medicinal plants have been key ingredients in various cosmetic products and infusions, used for cosmeceutical purposes and even for addressing dermatological conditions. Nowadays, the list of plants, which appears in cosmetic formulations, continues to grow has still increasing. Plant extracts possess lots of properties including moisturizing, regenerating, anti-inflammatory as well as antioxidant and anti-aging activity, which are in great demand in cosmetics. Those functions are determined by the presence of valuable secondary metabolites, which are termed as phytochemicals [1–3].

Phytochemicals are plant-derived active substances, which mainly include alkaloids, terpenoids or polyphenolic compounds [4]. This review will focus on polyphenols, particularly flavonoids and phenolic acids along with the active molecules associated with them. Phytocompounds derived from the above-mentioned groups are popular ingredients in cosmetic formulations and act as important bioactive agents [5–8].

However, despite the benefits offered by those phytochemicals, issues arising from their hydrophilicity, stability and bioavailability remains challenging for designing cosmetic formulations [9,10].

## 1.2. The Overview on the Phytochemicals Penetartions Rates: Discuss Factors Affecting Skin Penetration

Skin is a large organ whose main role, aside from thermoregulation, is to protect the body from mechanical, biological, and chemical factors. Stratum corneum (SC), the outermost layer of the epidermis, acts as a barrier, which protects the skin from external factors including penetration of drugs or cosmetics. Active substances can penetrate the stratum corneum through several pathways. The most common is the transepidermal route, which includes two mechanisms: the intercellular route—used by the majority of compounds, and the transcellular route. Penetration can also occur through appendageal structures such as hair follicles and sweat glands. In the transepidermal pathway, compounds either pass directly through the corneocytes (transcellular) or move between them by crossing the intercellular lipid matrix—this intercellular route is the primary mode of penetration for most substances [11–19] (Figure 1).

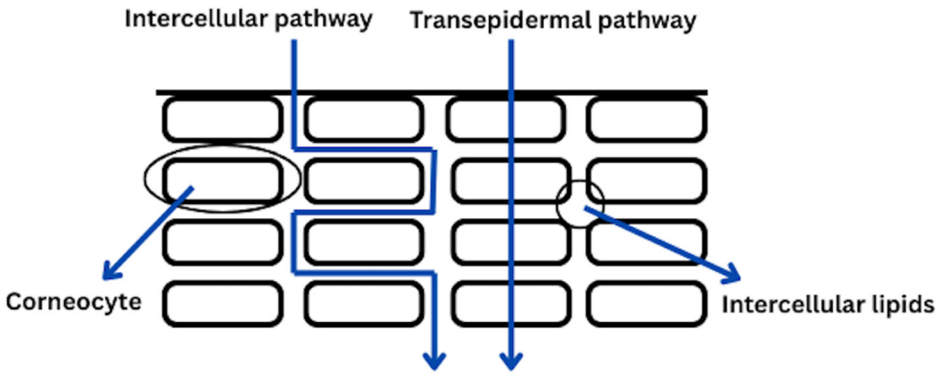


**Figure 1.** The main skin penetration routes of active substances.

The penetration rate of active substances is determined by their hydrophobic nature. The octanol/water partition coefficient *P* (log*P*) is an important factor, which has an impact on membrane permeability. Positive values for log*P* indicates more hydrophobic nature of

the compound. While hydrophilic compounds are characterized by negative values for log*P*, which determine its higher aqueous phase affinity following its low penetration [20,21].

The molecules successful penetration is determined by the suitable balance between lipophilicity and hydrophilicity and also appropriate molecular mass of the compounds, which should be less than 500 Da. In addition to physicochemical properties, the formulation characteristics is equally important for effective skin penetration. For instance, formulations with greater viscosity delay the absorption of active compounds, because of the reduced diffusion coefficient. The pH of the cosmetic base is also crucial because it determines whether the active molecule is dissociated. Undissociated molecules penetrate more effectively, because of its better lipid dissolution compared to dissociated molecules, which easily separate into ions. Moreover, the presence of skin penetration enhancers (e.g., alcohols, amides, glycols) in the cosmetic base also have an influence by reducing the skins barrier resistance [11,13–18]. Furthermore, skin permeation is also affected by physiological factors (e.g., age, skin condition and metabolism), as well as sufficient physicochemical characteristics of drug carrier (e.g., size, shape or surface charge), which must be satisfied to guarantee the effective penetration deep into the skin [19,20,22,23].

All the above-mentioned factors are extremely significant and relate to many active molecules. However, the primary focus reviewed here is on hydrophilic compounds and the additional factors, which affect its delivery efficiency.

### *1.3. Challenges of Hydrophilic Phytochemicals: Discuss Solubility, Stability, and Bioavailability Issues Associated with Hydrophilic Active Substances*

Considering the polar nature of hydrophilic phytochemicals, their effective penetration through the skin faces fundamental challenges. Since the stratum corneum extracellular lipid matrix predominantly contains lipids, e.g., cholesterol and ceramides, as well as free fatty acids, so it results on low solubility in nonpolar environments [19,24].

Hydrophilic phytochemicals are often chemically unstable under environmental stressors such as temperature, pH, oxygen, and light. These weaknesses result in poor skin absorption and limited bioavailability. For instance, polyphenols, being the most abundant plant-derived compounds, are unstable, because of the presence of hydroxyl groups (–OH) attached to benzene ring, which are highly reactive. Therefore, with an increase of hydroxyl groups the stability of polyphenols is lowered. Polyphenols also have a tendency to autooxidation, which provide peroxide and hydroperoxide formations. PH impacts polyphenols stability as well, high pH values decreases stability due to the chemical form changing [25]. For instance, anthocyanidins, which are sensitive to pH, are more stable in acidic conditions what manifest with its red color [26–29]. Furthermore, at high temperatures with alkaline conditions polyphenols undergo epimerization, leading to its instability [25].

The next challenge of hydrophilic phytochemicals resulting from its limited solubility and instability is low bioavailability. To improve their therapeutic potential, modern strategies increasingly utilize carriers. In recent years, different forms of topical administration have become available. For instance, nanostructured lipid carrier gel or nanogel are used to deliver quercetin and increase its bioavailability [30]. Lipid-derived carriers such as liposomes form the occlusive layer, which increase skin humidity and enhance the active molecules penetration [31,32].

This work aims to present a comprehensive review of selected lipid-based delivery systems as an effective tool to overcome the limitations of hydrophilic compounds.

## 2. Delivery Systems for Hydrophilic Phytochemicals

### 2.1. General Considerations

In recent years, especially organic vesicles e.g., liposomes, niosomes, exosomes or polymeric nanoparticles have been found to enable not only skin penetration through stratum corneum, but can also improve the biocompatibility, stability as well as prolongated action of the contained active ingredient [33,34].

The fundamental biological barriers related to hydrophilic compound delivery have been addressed in Section 1.2. Here we will focus specifically on the functional roles, advantages, and possible limitations of carrier technologies. As detailed in Section 1.2, hydrophilic phytochemicals face significant barriers to skin absorption due to their polar nature and low membrane permeability. Delivery systems based on nanotechnology, such as liposomes, niosomes, and polymeric nanoparticles (Figure 2), offer a viable solution by enhancing solubility, stabilizing active compounds, and facilitating their transport through the stratum corneum [35].

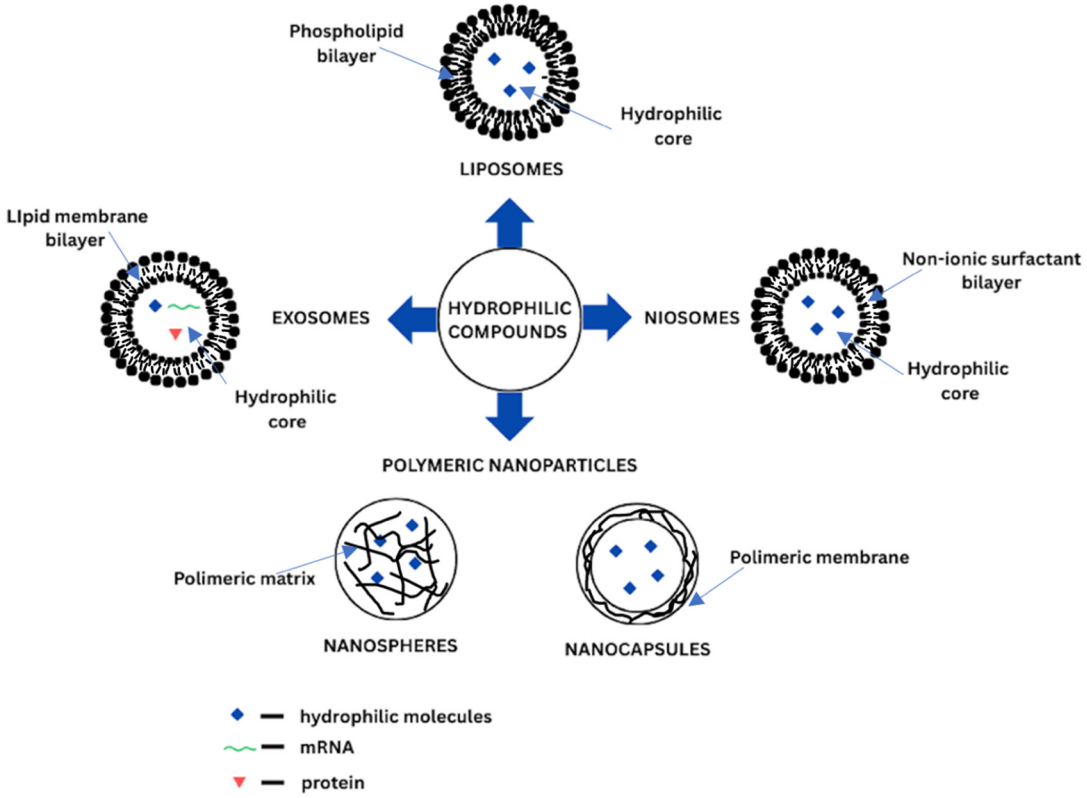


**Figure 2.** The structure of the selected carriers of hydrophilic compounds.

### 2.2. Liposomes

Liposomes (Figure 2) are the well-explored representatives of the carrier ensemble. They are defined as sphere-shaped vesicles, consisting of one or more phospholipid bilayers, which are self-formed in aqueous solution. Liposome's structure is biphasic composed of hydrophilic core and hydrophobic bilayer, enabling both hydrophilic and hydrophobic compounds to be delivered. Liposomes were first discovered in 1960s by the British scientist Alec Bangham. Since that time, they have started gaining popularity as a prospective delivery system. The Dior "Capture" was the first liposomal cosmetic product introduced to the market in 1986. Since that time, the list of liposomal products are increasing [36].

Based on the physical characteristics (e.g., structure, particle size, lamellarity), liposomes can be divided into different categories: small unilamellar vesicles (SUVs), large unilamellar vesicles (LUVs), giant unilamellar vesicles (GUVs), oligolamellar vesicles,

(OLVs), multilamellarvesicles (MLVs), and multivesicular vesicles (MVVs) [37] (Table 1). There is a wide list of liposome preparation methods, which includes, for instance, film hydration also known as "Bangham method", reverse phase evaporation or solvent injection (ethanol, diethyl ether). The application of the specific method is determined by the desired liposome characteristics [38,39]. All of techniques are presented in Table 1.

### 2.3. Niosomes

Niosomes (Figure 2) are self-assembled vesicles, which are formed of non-ionic surfactants (e.g., alkyl ethers, sorbitan fatty acid esters) and lipids such as cholesterol. Due to the amphiphilic character, niosomes could deliver both hydrophilic and hydrophobic drugs. The first niosome-based formulation was patented by L'Oreal (France) in 1970s. Then, in 1986, Lâncome (France) introduced to the market niosome formulation under the trade name "Niosôme" [40,41].

Compared to liposomes, niosomes are more chemically stable. The active substance entrapment efficiency of niosomes is also better compared to liposomes due to the fact that the dominant compounds of liposomes such as phospholipids are unstable and tend to degrade. The presence of cholesterol in niosomes results in enhanced vesicle stability as well as entrapment efficiency. As non-ionic surfactants, from which niosomes are composed, are not carrying a charge, they also offer better stability of system. Furthermore, to increase the stability of niosomes, the charged molecules such as dicetyl phosphate or stearyl amine could be provided, which by prevent the vesicles aggregation [41–44].

### 2.4. Exosomes

Exosomes (Figure 2) are defined as subgroup of nanosized spherical extracellular vesicles secreted by most cells. Exosomes are made of single lipid bilayer containing nucleic acids, proteins, lipids and lipid-related enzymes and an aqueous core, which enables delivery of hydrophilic drugs [45–49]. Exosomes are divided to natural (animal or plant-derived) and engineered, which are recognized as modified version of natural exosomes. Engineered exosomes are modified to enable advantageous drug delivery. They increase stability and bioavailability as well as reduce toxicity. In addition to the advantages of exosomes such as biocompatibility, biodegradability, or low toxicity, they also have some limitations (Table 1). For instance, exosomes cannot be stored long, for this reason protection techniques are required e.g., freezing or spray-drying [50,51].

### 2.5. Polymeric Nanoparticles

Polymeric nanoparticles (Figure 2) are defined as colloidal systems composed of polymers. They are divided into nanocapsules and nanospheres. Nanospheres consist of a solid core and polymeric matrix within which active molecules are encapsulated. In the case of nanocapsules, the active compound is entrapped in an inner liquid or solid core secured by polymeric membrane, which is composed of non-ionic surfactants, phospholipids and macromolecules. Active ingredients could be encapsulated or adsorbed on the polymers surface [35,52–56].

Polymeric nanoparticles hold scientific interest, because, similarly to liposomes or niosomes, they could deliver hydrophilic substances. Nanocapsules could have inner water or oil core, within which active ingredients could be solubilized this gives higher drug encapsulation compared to nanospheres. In nanospheres, the active molecule is entrapped in matrix of polymer (Figure 2) [54,57,58].

Table 1 provides short comparison of the selected carriers.

**Table 1.** Brief characteristics of the selected carriers for hydrophilic pthytochemicals.

| Group | Structure | Size | Preparation/Isolation Methods | Advantages | Limitations | References |
|---|---|---|---|---|---|---|
| Liposomes | Phospholipid bilayer (SUV, LUV, GUV) or several lipid bilayers (MLV, MVV), hydrophilic core | - SUV (20–200 nm)<br>- LUV (200 nm–1 μm)<br>- GUV (>1 μm)<br>- OLV (100 nm–1 μm)<br>- MLV (> 500 nm)<br>- MVV (>1 μm) | - film hydratation<br>- reverse phase evaporation<br>- solvent injection<br>- heating method<br>- microfluidic channel<br>- supercritical fluidic<br>- freeze-thawing<br>- freeze-drying<br>- detergent removal<br>- membrane extrusion<br>- sonication<br>- micro-emulsification<br>- dual asymmetric centrifuging | - biocompatible<br>- biodegradable<br>- high bioavailability<br>- low toxicity<br>- low immunogenicity<br>- both hydrophilic and hydrophobic compounds delivery<br>- controlled release of the of active compounds<br>- targeting delivery<br>- extension of drug half-life | - high cost of production<br>- low solubility<br>- possible instability (e.g., during storage)<br>- possible degradation via hydrolysis or oxidation<br>- possible encapsulated drug leakage<br>- special storage conditions are required | [32,59–76] |
| Niosomes | Non-ionic surfactant bilayer in conjunction with cholesterol | - SUV (10–100 nm)<br>- LUV (100–3000 nm)<br>- MLV (>10 μm) | - thin film hydratation<br>- reverse phase evaporation<br>- ether injection (solvent)<br>- emulsion method<br>- lipid injection<br>- bubble method<br>- microfluidisation method<br>- supercritical reverse phase evaporation<br>- micelle solution and enzyme<br>- trans membrane pH gradient drug uptake process<br>- formation from proniosomes<br>- sonication | - lower cost of production<br>- biocompatible<br>- biodegradable<br>- low toxicity<br>- low immunogenicity<br>- both hydrophilic and hydrophobic compounds delivery<br>- improved chemical stability<br>- structurally flexible<br>- controlled release of active compounds<br>- targeting delivery<br>- special storage conditions are not required | - low physical stability<br>- possible degradation via hydrolysis<br>- possible aggregation<br>- possible encapsulated drug leakage<br>- possible aggregation<br>- limited shelf-life | [41,43,76–79] |

**Table 1.** *Cont.*

| Group | Structure | Size | Preparation/Isolation Methods | Advantages | Limitations | References |
|---|---|---|---|---|---|---|
| Exosomes | Single lipid bilayer containing RNAs, proteins and lipids | −30–200 nm | - ultracentrifugation<br>- ultrafiltration<br>- size-exclusion chromatography<br>- polymer precipitation<br>- magnetic separation<br>- acoustic fluid separation<br>- immunological separation<br>- dielectrophoretic separation | - biocompatible<br>- biodegradable<br>- low toxicity<br>- low immunogenicity<br>- innate stability<br>- targeting delivery | - short-half life in circulation<br>- special storage conditions are required | [47,48,50,51,80–84] |
| Polymeric nanoparticles | Solid core with polymeric matrix<br><br>Inner liquid or solid core secured by polymeric shelf | - nanospheres (10–200 nm)<br><br>- nanocapsules (50–300 nm) | - dialysis<br>- emulsification diffusion<br>- interfacial polymerization<br>- nanoprecipitation<br>- phase inversion temperature<br>- salting out<br>- super critical fluid technology<br>- solvent evaporation | - biodegradable<br>- low toxicity<br>- high stability<br>- both hydrophilic and hydrophobic compounds delivery<br>- long shelf life<br>- both hydrophilic and hydrophobic compounds delivery<br>- controlled release of active compounds<br>- high loading capacity<br>- targeting delivery | - possible degradation<br>- possible monomer aggregation | [53,85–89] |

While the aforementioned delivery platforms offer a wide range of strategies for enhancing the dermal and systemic availability of hydrophilic compounds, their effectiveness ultimately depends on the molecular characteristics of the compounds themselves. Therefore, the following section presents a detailed analysis of selected polyphenols, focusing on their chemical structure, solubility, biological activity, and formulation-specific delivery challenges. This compound-level perspective provides essential context for understanding how delivery systems are matched to molecular needs.

## 3. Hydrophilic Phytochemicals

Hydrophilic phytochemicals are characterized by a high content of hydroxyl (–OH) and carboxyl (–COOH) groups, which increases their water solubility but simultaneously hinders their permeability across cell membranes and limits bioavailability [90–93]. Their molecular weight (500–4000 Da), polycyclic structures, and abundance of hydrogen bond donors further reduce passive diffusion and contribute to rapid excretion and metabolic degradation. Jacob et al. [94] highlighted that additional limitations in bioavailability result from their instability under environmental conditions—exposure to light, oxygen, pH changes, and elevated temperature can lead to photodegradation, hydrolysis, and oxidation [94]. Recent studies have shown that some phenolic substances (e.g., epicatechin, chlorogenic acid, isoquercetin) are only stable at low temperatures and degrade rapidly at 40 °C [92,94,95]. The excess of hydrogen bond donor groups (–OH and $–NH_2$) further impairs passive membrane diffusion, and their complex molecular structures (e.g., polycyclic features) promote swift elimination and metabolic breakdown [94]. They are also subjected to enzymatic degradation and interactions with microbiota and pH, necessitating the development of protective delivery systems [94,96]. In response, various strategies like advanced skin delivery systems are commonly applied [97].

Hydrophilic particles can undergo destabilization already at the stage of their extraction from plants raw materials. For instance, Khoddami et al. [98] emphasized the importance of polyphenol solubility, which depends on the number of hydroxyl groups, substituents, and degree of conjugation. The choice of solvents (ethanol, methanol, water) is crucial—high-polarity solvents improve extraction efficiency but may also cause degradation of thermolabile constituents [98,99]. As alternatives, hydrotropic solvents (e.g., sodium cumenesulfonate (NaCS), sodium *n*-butyl benzene sulfonate (NaNBBS)) offer high extraction efficiency, are eco-friendly, non-toxic, and reusable [100].

The application of auxiliary extraction techniques such as MAE (microwave-assisted extraction), UAE (ultrasound-assisted extraction), or EAE (enzyme-assisted extraction) increases extraction efficiency while limiting degradation of active compounds [98,99,101]. High hydrostatic pressure (HHPE) and pulsed electric field (PEF) improve cell membrane permeability, allowing cytoplasmic release without damaging compound structures [98].

Due to low membrane permeability (low value of log*P*) [102] and high polarity, efficient delivery of hydrophilic compounds requires the use of transport systems. The appropriate selection of surfactants, particle size, and viscosity enhances solubility in lipid environments and boosts bioavailability [103]. Hansen Solubility Parameters (HSP) are used to predict the compatibility of compounds (e.g., phenolic acids and flavonoids) with ionic liquids, emphasizing the need for supportive systems for their isolation and formulation [104].

A great advantage of hydrophilic phytochemicals is their strong biological activity. Their antioxidant and anti-inflammatory properties determine their ability to neutralize free radicals, chelate heavy metals, and modulate pro-inflammatory enzyme expression [91,103,105–107]. A correlation between phenolic content and antioxidant potential of the extracts has been confirmed [108,109]. Interestingly, thermal processing may even enhance the bioactivity of certain compounds [107]. Jacob et al. [94] stated that, the abundance

of hydrogen bond donor groups, typical for hydrophilic compounds, limits membrane permeability but supports receptor binding and neutralization of reactive oxygen species (ROS) [94].

Hydrophilic compounds represent a large and diverse group of plant metabolites. These substances are widely distributed in natural raw materials and play important roles in various biological processes. Below, we present examples of the most common classes of hydrophilic compounds found in botanical sources, highlighting their presence in natural extracts and their potential applications in cosmetic formulations.

### *3.1. Flavonoids*

Flavonoids constitute a vast class of plant-derived polyphenolic compounds characterized by a C6–C3–C6 skeleton, consisting of two aromatic rings linked by a three-carbon bridge forming a heterocyclic ring [110,111]. Their structure determines physicochemical properties such as solubility, polarity, biological activity, and bioavailability [7]. The hydrophilicity of flavonoids largely depends on the number and positioning of hydroxyl groups (–OH) as well as the presence of sugar moieties (glycosylation). The incorporation of glucose, rhamnose, or other sugars increases their water solubility and improves their pharmacokinetic properties, positively influencing absorption and distribution in the body [112–116]. Hydroxyl groups play a key role in forming hydrogen bonds with water molecules, and their location affects not only solubility but also the capacity to interact with biological receptors [110,111,117].

As mentioned above, flavonoids can occur as free aglycones or in glycosylated forms. Glycosides display higher solubility in aqueous environments, which enhances their biological availability [112,114,115]. In contrast, aglycones are less polar, which may favor their penetration through lipid membranes but simultaneously reduce their solubility in plasma. According to Journal of Immunology Research, highly hydrophilic flavonoids tend to localize near the surface of cellular membranes, where they form a hydrophilic protective layer. This localization aids in protecting membranes against oxidative stress and free radical-induced damage [116].

#### 3.1.1. Impact of Structural Modifications on Flavonoid Hydrophilicity and Bioavailability

Flavonoid hydrophilicity—and thus their bioavailability—depends not only on the native molecular structure but also on applied chemical and biotechnological modifications. Hydroxyl groups (–OH), glycosylation, and structural transformations that increase water solubility play key roles.

#### 3.1.2. Hydroxyl Groups, Glycosylation, and Polarity

Water solubility of flavonoids strongly depends on the number and placement of hydroxyl groups, the presence of glycosides, and structural modifications such as sulfonation, acetylation, or glycosylation [115,117–120]. As demonstrated by Heim et al. (2002), a higher number of hydroxyl groups significantly increases molecular polarity and hydrogen bonding potential, directly improving water solubility [119]. As described earlier in the context of quercetin, luteolin, and apigenin, glycosylation with sugar moieties like glucose or rhamnose enhances hydrophilicity, leading to greater water solubility and bioavailability [119]. For instance, quercetin-3-O-glucoside exhibits much higher solubility compared to its aglycone form, which directly influences its absorption and distribution in biological systems [119]. Similarly, luteolin-7-O-glucoside and glycosylated derivatives of apigenin demonstrate improved solubility and stability in aqueous environments, which enhances their biological effectiveness [119]. Despite its high number of hydroxyl groups, quercetin in its aglycone form has low water solubility (approximately 0.92 g/L at 25 °C) [115]. However, glycosylation or encapsulation in β-cyclodextrins increases its solubility and

stability, forming hydrophilic–lipophilic inclusion complexes that improve bioavailability and protect against degradation [115].

#### 3.1.3. Acetamide and Sulfate Modifications

Further chemical modifications, such as acetamide and sulfate substitutions, have been shown to enhance flavonoid hydrophilicity. Research by Isika (2022) demonstrated that replacing hydroxyl groups with acetamide moieties in flavonoids like quercetin and luteolin significantly improves their solubility and pharmacokinetic profile while retaining antioxidant properties [111]. This structural adjustment not only increases polarity but also enhances molecular stability.

Highly sulfated flavonoid derivatives, such as quercetin sulfate or (+)-catechin sulfate, exhibit extreme hydrophilicity due to their strong negative charge and elevated polarity [121]. These modifications, analyzed using capillary electrophoresis, provide enhanced solubility and biological stability in aqueous environments, offering potential for novel therapeutic applications [121].

#### 3.1.4. Cyclodextrin Complexation

The use of cyclodextrins, particularly β-cyclodextrin, facilitates the formation of inclusion complexes, where the hydrophobic segments of flavonoid molecules are encapsulated within the hydrophilic cavity of the cyclodextrin [113]. This strategy has been successfully applied to flavonoids like baicalin, kaempferol, and quercetin, substantially improving their water solubility and stability [113]. Encapsulation not only enhances solubility but also protects these compounds from environmental degradation, thereby improving their bioavailability.

#### 3.1.5. Membrane Localization and Hydrophilic Properties

The increased hydrophilicity of flavonoids influences their localization in biological membranes. According to Oteiza et al., more polar flavonoids tend to accumulate near the surface of cellular membranes, forming a hydrophilic layer that limits oxidative penetration and protects cellular structures from oxidative stress [116]. This is consistent with findings described for quercetin, which localizes within the lipid bilayer, enhancing its antioxidant and anti-inflammatory effects. The strategic positioning of hydrophilic flavonoids in membrane regions rich in polar phospholipids strengthens their interaction with membrane-bound receptors, amplifying their biological efficacy [113].

### *3.2. Quercetin*

#### 3.2.1. Structure and Solubility

Quercetin (Figure 3a) is a flavonol of a 3,3′,4′,5,7-pentahydroxyflavone structure, containing five hydroxyl groups, making it one of the most hydrophilic aglycones among flavonoids [111,114,119]. These groups facilitate numerous hydrogen bonds, influencing interactions with biological membranes and oxidative enzymes [7].

#### 3.2.2. Biological Activity

Despite its high polarity, the aglycone form of quercetin has low water solubility—approximately 0.92 g/L at 25 °C [115]. However, glycosylated derivatives such as quercetin-3-O-glucoside show significantly higher solubility and bioavailability [115]. Encapsulation of quercetin in β-cyclodextrins enhances its solubility and stability by forming hydrophilic–lipophilic inclusion complexes, thereby improving bioavailability and protecting the compound from environmental and physiological degradation [113,122]. Quercetin is a potent antioxidant; its activity derives from the number and position of hydroxyl groups that enable neutralization of hydroxyl and peroxyl radicals [115,119,122,123]. In addition to its

antioxidant properties, it inhibits inflammation-related enzymes such as COX and LOX (lipoxygenase), making it a promising agent for the prevention of metabolic and chronic inflammatory disorders [7,118,123]. Moreover, in vitro studies have shown that quercetin can suppress epidermal growth factor receptor (EGFR) activity in gastric cancer cells, indicating its potential as a targeted anticancer agent [124].

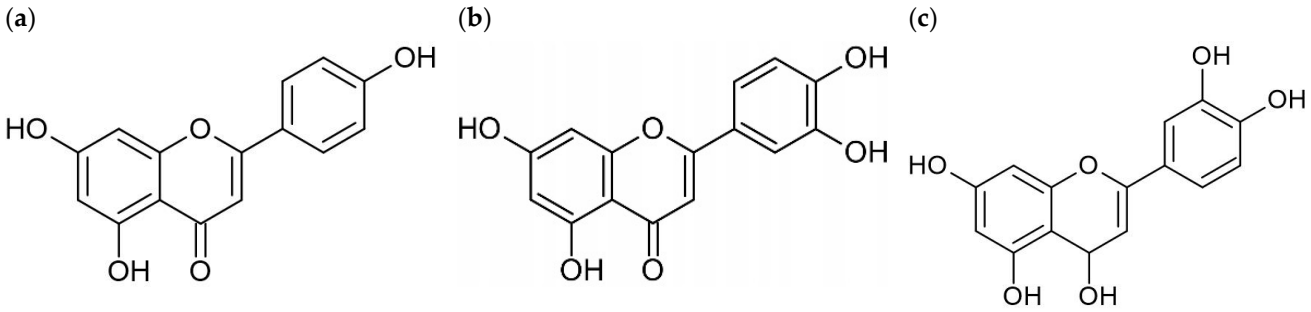


**Figure 3.** Chemical structure of high hydrophylic flavonoides; (**a**) Quercetin (**b**) Luteolin (**c**) Apigenin.

Quercetin acts as a potent antioxidant and anti-inflammatory agent, inhibits MMP activity, protects collagen, and improves skin elasticity and hydration. In vivo application of 1% quercetin after UV exposure increased glutathione levels and skin hydration, while reducing oxidative stress markers. It also inhibits tyrosinase activity, contributing to skin lightening and anti-pigmentation effects [125].

#### 3.2.3. Delivery Barriers and Carrier-Based Strategies

Applied in w/o microemulsions, it efficiently penetrates the stratum corneum and epidermis without causing irritation, protecting against UVB-induced photodamage [126]. For instance, quercetin-loaded phospholipid vesicles modified with edge activators, such as sodium cholate, increase dermal absorption by fluidizing the lipid bilayers of the stratum corneum.

### *3.3. Luteolin*

#### 3.3.1. Structural Properties and Biological Functions

Luteolin is a flavone with a 3′,4′,5,7-tetrahydroxyflavone structure (Figure 3b), containing four hydroxyl groups [119,123]. Although slightly less hydrophilic than quercetin, its polarity remains substantial, affecting its solubility and biological interactions. The highest solubility of luteolin is observed in polar protic solvents—especially mixtures of water with methanol or ethanol [99,127]. Luteolin exhibits broad biological activity, including antioxidant, anti-inflammatory, and anticancer effects [128,129]. As an aglycone, however, it suffers from limited bioavailability due to its moderate solubility in water and vulnerability to degradation. Glycosides like luteolin-7-O-glucoside exhibit significantly improved solubility and chemical stability, making them more effective formulations [115,117]. Despite the advantages of glycosylation, biotransformation of luteolin into its glycoside form remains inefficient, with a yield of approximately 8%, lower than that of other flavonoids [115]. According of Dias 2021, luteolin may inhibiting protein kinase activity and reducing expression of pro-inflammatory enzymes such as cyclooxygenase-2 (COX-2) [7,130]. Luteolin reduces the expression of pro-inflammatory cytokines (IL-6, IL-8, TNF-α) and the activity of COX-2 and iNOS, alleviating psoriatic skin [30]. In nanosuspensions and bilosomes, it accumulates more effectively in the skin, showing stronger anti-inflammatory and photoprotective activity [90]. Formulas containing Pluronic F127 and alginate improve its physicochemical stability and skin permeation [131]. Recent studies have demonstrated that luteolin exhibits anti-photoaging properties by inhibiting

the MAPK pathway in UVB-exposed skin cells, thereby mitigating oxidative stress and inflammation, which supports its dermatological application [132].

#### 3.3.2. Carrier-Based Delivery Strategies

Lipid-based delivery systems have shown promise in enhancing the solubility and bioavailability of luteolin. These carriers contribute to improved physicochemical stability, prolong the compound's residence time in the skin, and enable a more controlled release.

These advanced delivery systems represent a promising strategy for optimizing the clinical effectiveness of luteolin in dermatological and anti-inflammatory applications.

### *3.4. Apigenin*

#### 3.4.1. Structure and Solubility

Apigenin (4′,5,7-trihydroxyflavone) contains three hydroxyl groups (Figure 3c), making it less hydrophilic than quercetin or luteolin, yet still soluble in water–alcohol systems [112,119,123]. The hydrophilicity of apigenin can be enhanced by glycosylation and pH modulation. In acidic environments, it shows increased affinity for lipid membranes, facilitating its cellular penetration [116]. Glycosylation substantially improves the solubility of apigenin, with enzymatic methods using *Staphylococcus saprophyticus* strains proving effective [112]. This not only enhances the physicochemical properties of the compound but also its stability and bioavailability.

#### 3.4.2. Biological Activity

Apigenin demonstrates cytotoxic effects against cancer cells, primarily through the induction of apoptosis and inhibition of angiogenesis, as confirmed in studies on skin melanoma [111,114,118]. Its hydroxyl groups allow it to act as both an antioxidant and a metal ion chelator, protecting cells against oxidative stress [133]. Thanks to moderate hydrophilicity and a small number of functional groups, apigenin easily penetrates biological membranes, enabling intracellular action and interaction with key molecular pathways [116,129]. Apigenin improves skin barrier function by increasing filaggrin expression, lipid synthesis, and lamellar body formation, contributing to improved skin hydration and integrity [134]. It also exhibits significant anticancer effects by inhibiting mTOR, MAPK, PI3K/Akt, and Wnt/β-catenin pathways and inducing apoptosis [135]. Formulations with carriers such as PLGA and transfersomes significantly enhance its bioavailability and skin penetration [136].

In summary, although quercetin, luteolin, and apigenin differ structurally and vary in polarity and molecular weight, a consistent trend emerges in their delivery outcomes: encapsulation in lipid-based nanocarriers improves dermal targeting by enhancing compound stability, modulating release kinetics, and facilitating efficient skin penetration. Notably, each flavonoid responds differently depending on the carrier type, suggesting the importance of customized formulation strategies to optimize therapeutic performance.

### *3.5. Phenolic Acids*

According to Materska (2010), phenolic acids represent the most hydrophilic fraction of analyzed herbal extracts, surpassing other bioactive compound classes in solubility [137]. Their hydrophilicity is influenced not only by their intrinsic chemical structure but also by the application of carriers that enhance their solubility and bioavailability. The degree of hydrophilicity also depends on the chemical form—glycosides and esters can alter solubility and bioavailability [98]. Phenolic acids are among the most widely distributed natural phenolic compounds in plants. Their structure includes an aromatic ring—responsible for molecular stability and free radical neutralization—along with a hydroxyl group (–OH), which contributes to antioxidant activity, and a carboxyl group (–COOH), which im-

parts high polarity and acidic properties to the molecule [102,108,138]. Based on side chain length, phenolic acids are divided into two major subclasses: hydroxybenzoic acids derivatives (C6–C1), such as gallic, protocatechuic, vanillic, and syringic acids, and hydroxycinnamic acids derivatives (C6–C3), including caffeic, ferulic, p-coumaric, and sinapic acids [108,137,139].

The hydrophilicity of phenolic acids results from the presence of multiple hydroxyl and carboxyl groups that enable hydrogen bonding with water. As a result, these acids are readily soluble in water and polar organic solvents such as methanol, ethanol, and acetone [108,137,140]. Gallic acid, for instance, demonstrates high solubility (up to 11 g/L), while ferulic acid exhibits moderate yet significant solubility [108,137,140]. Due to their structural features, phenolic acids are primarily localized in aqueous compartments of the body (e.g., cytoplasm), where they effectively scavenge reactive oxygen species (ROS) [108,138,141].

According to Materska (2010) phenolic acids were found to represent the most hydrophilic fraction of analyzed herbal extracts, surpassing other bioactive compound classes in solubility [137]. The degree of hydrophilicity also depends on the chemical form—glycosides and esters can alter solubility and bioavailability [98].

In nature, phenolic acids exist in both free forms—easily extractable from cell sap—and bound forms such as glycosides (e.g., ferulic acid bound to sugars), esters (e.g., chlorogenic acid as an ester of caffeic and quinic acids), amides (with amino acids or polyamines), and as components of lignin and cell wall polysaccharides like arabinoxylans in cereals [98,108,137,139]. The chemical form plays a crucial role in solubility, absorption, and transport—compounds bound within the plant matrix require enzymatic or microbial hydrolysis for release [98,108]. Phenolic acids exhibit antioxidant activity—via hydrogen or electron donation to neutralize ROS—chelating activity (metal ion binding and Fenton reaction inhibition), anti-inflammatory effects (inhibition of COX and LOX enzymes), antimicrobial properties (antibacterial and antifungal), and anticancer effects (impacting cell cycle and apoptosis) [102,108,140].

#### 3.5.1. Ferulic Acid

Ferulic acid (4-hydroxy-3-methoxycinnamic acid, $C_{10}H_{10}O_4$) is a hydroxycinnamic phenolic acid containing hydroxyl (–OH), methoxy (–$OCH_3$), and carboxyl (–COOH) groups (Figure 4a). These groups confer good hydrophilicity and hydrogen bonding capability [108,142]. It naturally occurs mainly in cereal products, often in a bound form with cell wall polysaccharides such as arabinoxylans, which significantly limits its bioavailability [108,142–144]. Ferulic acid is well soluble in aqueous–alcoholic solutions especially in ethanol and methanol mixed with water (typically 40%, 70%, or 80% concentrations), but only moderately soluble in pure water [98,137]. Since it commonly exists in esterified form, its extraction often requires enzymatic or alkaline hydrolysis. Although other alcohols such as propanol and butanol can be used for extraction, they are less effective for phenolic compounds due to their lower polarity compared to ethanol and methanol. Propanol shows limited efficiency in solubilizing polar phenolic compounds, while butanol is mainly applied in later stages of serial extraction and not as a primary solvent. Mixtures of ethanol or methanol with water have been found to enhance the yield of phenolic extraction significantly, optimizing both solubility and extraction efficiency [98,137].

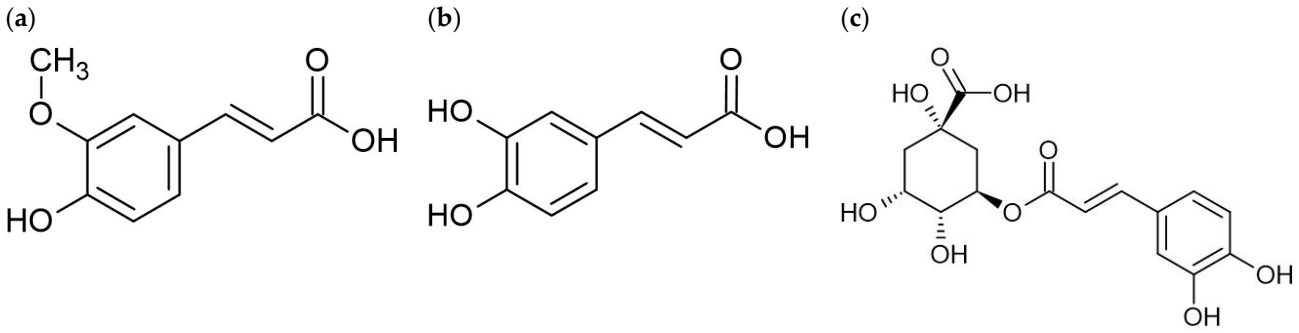


**Figure 4.** Chemical structure of high hydrophilic phenolic acids; (**a**) Ferulic acid (**b**) Caffeic acid (**c**) Chlorogenic acid.

#### 3.5.2. Biological Activity

Its bioavailability largely depends on chemical form and food matrix. In a study by Adama et al. (2002), ferulic acid bound to dietary fiber (e.g., in whole wheat flour) showed significantly lower bioavailability (<10%) compared to its free form, which can be absorbed at over 50% [142–144]. It circulates and is excreted primarily as conjugated metabolites, which may exhibit different biological activity from the parent compound [108,145]. Ferulic acid shows strong antioxidant, anti-inflammatory, antimicrobial, and neuroprotective properties. It scavenges free radicals, inhibits lipid peroxidation, modulates signaling pathways (e.g., Nrf2 (nuclear factor erythroid 2-related factor 2), NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells)), and protects DNA from oxidative damage. It improves skin elasticity, protects collagen and elastin, and stabilizes vitamin C in cosmetic formulations, enhancing its effectiveness [146]. Chemical modifications, such as amino acid esters, increase its solubility and bioavailability, improving its transdermal penetration [147]. It also acts anti-inflammatory, protects DNA from damage, and inhibits angiogenesis in skin cancer cells [135]. Its potential is applied in food, cosmetic, and pharmaceutical industries [108,145].

#### 3.5.3. Carrier-Based Delivery Strategies

To further optimize its bioavailability and skin penetration, ferulic acid has been effectively encapsulated in several carrier systems, including solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), liposomes, and nanoemulsions [135]. Liposomal formulations enhance its solubility and facilitate deeper penetration through the stratum corneum by mimicking the phospholipid layers of cell membranes, allowing ferulic acid to integrate seamlessly into the lipid matrix of the skin [148–150]. Nanoemulsions, characterized by their ultra-small droplet size, further improve the diffusion of ferulic acid through the skin barrier, enhancing its absorption into deeper layers [149,150]. Lipid-based carriers like SLN and NLC not only stabilize ferulic acid but also protect it from oxidative degradation and UV-induced damage, extending its therapeutic effects. These nanoparticles reorganize the lipid structure of the stratum corneum, reducing its barrier properties and facilitating improved transdermal delivery [148–150]. The biphasic release profile of SLN and NLC ensures both immediate and controlled release, enhancing the compound's retention in skin tissues and minimizing irritation [149]. Moreover, hydrogels have been explored as carriers for ferulic acid, providing sustained release and prolonged skin retention, which enhances its antioxidant and protective effects [149]. Although detailed studies on ferulic acid's individual transdermal mechanism are limited [148], its encapsulation in carriers clearly optimizes its permeation and stability. The incorporation into solid lipid nanoparticles, liposomes, nanoemulsions, and hydrogels not only enhances its solubility

but also improves its bioavailability and protective effects against oxidative stress, making it a valuable component in advanced dermatological formulations [135,148–150].

### 3.6. Caffeic Acid

#### 3.6.1. Structure and Solubility

Caffeic acid (3,4-dihydroxycinnamic acid, $C_9H_8O_4$) contains two hydroxyl groups and one carboxyl group (Figure 4b), providing it with high polarity and good solubility in water and aqueous–alcoholic solutions [102,108,137]. It is found in carrots, basil, oregano, cereals, and coffee [151,152]. After ingestion, caffeic acid is efficiently absorbed in the small intestine and subsequently metabolized in the liver (via glucuronidation, sulfation, and methylation), with bioavailability ranging from 5% to 20% depending on food source and chemical form [151,152].

#### 3.6.2. Biological Activity

Caffeic acid exhibits antioxidant, anti-inflammatory, and anticancer activities. It also shows synergy with other polyphenols, such as chlorogenic or ferulic acids, which may enhance its biological effects [108,109,145]. Caffeic acid has chemopreventive properties against skin cancer by inhibiting ERK1/2 kinases and reducing MAPK pathway signaling and pro-inflammatory factor expression [153]. It protects skin cell DNA from UVB-induced damage by activating DNA repair proteins of the NER pathway [136]. It also shows stability and high affinity for lipid emulsions used in topical formulations [154].

#### 3.6.3. Carrier-Based Delivery Strategies

Recent advancements in nanotechnology have significantly improved the bioavailability and transdermal delivery of caffeic acid through its encapsulation in various carrier systems, including ethosomes, hydrogels, nanoemulsions, microparticles, and liposomes [148–150,155,156]. Ethosomes—lipid-based vesicles enriched with ethanol—facilitate deep penetration of caffeic acid through the stratum corneum (SC) due to their flexible structure and enhanced lipid solubility. Ethanol increases the fluidity of the SC lipids, allowing ethosomes to effectively transport caffeic acid to deeper skin layers, maintaining its antioxidant properties for extended periods [155]. Another promising delivery system for caffeic acid involves hydrogels and nanoemulsions, which significantly improve its skin retention and penetration. Hydrogels enable controlled, sustained release of caffeic acid, ensuring long-lasting antioxidant protection [135]. Nanoemulsions, characterized by their ultrafine droplet size, enhance the diffusion of caffeic acid across the SC, increasing its solubility and enabling effective delivery to deeper epidermal layers [148]. Both carriers modify the lipid structure of the SC, reducing resistance to permeation and enhancing local bioavailability and stability [148,150]. Furthermore, microparticles (MPs) formulated in oil-in-water (O/W) emulsions have been investigated for their potential to target hair follicles and extend the residence time of caffeic acid in the skin [156]. MPs composed of chitosan encapsulate caffeic acid, facilitating its accumulation within hair follicles and enhancing its anti-inflammatory and antioxidant effects. This targeted delivery not only improves local bioavailability but also minimizes systemic exposure, reducing potential side effects [150]. Studies have demonstrated that MPs increase the fluidity of the SC lipids, creating microchannels that promote deeper penetration of caffeic acid and prolong its therapeutic action [156]. Additionally, liposomes have been employed to boost caffeic acid's transdermal absorption. Their phospholipid bilayer structure mimics cell membranes, enhancing the diffusion of caffeic acid across the skin barrier and providing localized antioxidant effects. Encapsulation in liposomes also protects caffeic acid from oxidative degradation, stabilizing the compound and allowing for controlled, sustained release in topical formulations [150]. Although structural analogies with ferulic acid sug-

gest that caffeic acid may benefit similarly from lipid-based carriers [149], direct studies are still limited. Current evidence clearly indicates that carrier-based delivery systems significantly enhance its bioavailability, stability, and therapeutic efficacy, making caffeic acid a promising candidate for advanced dermal and systemic applications.

### *3.7. Chlorogenic Acid*

#### 3.7.1. Structure and Solubility

Chlorogenic acid (CGA) is an ester of caffeic and quinic acids. It contains multiple hydroxyl and carboxyl groups (Figure 4c), which contribute to its high hydrophilicity. It is well soluble in water and 70% ethanol and remains stable under low pH conditions. It is found in coffee, carrots, olive oil, and whole grain products [98,137,151]. CGA is hydrolyzed in the intestine into caffeic and quinic acids, which are then absorbed and metabolized into conjugated forms. Its bioavailability is variable and influenced by fiber and lignin content in the plant matrix, as well as microbial enzyme activity [142,144]. Like its precursor caffeic acid, CGA exhibits potent antioxidant, anti-inflammatory, anticancerproperties (e.g., inhibition of digestive enzymes like α-glucosidase). Chlorogenic acid exhibits anti-inflammatory effects, increases skin hydration, and is highly soluble in water and ethanol, making it ideal for cosmetic applications.

#### 3.7.2. Biological Activity

Its strong antioxidant effect is due to multiple hydroxyl and carboxyl groups capable of neutralizing reactive oxygen species [146].

#### 3.7.3. Carrier-Based Delivery Strategies

Recent advancements in nanotechnology have significantly improved the bioavailability and transdermal delivery of chlorogenic acid through encapsulation in various carrier systems, including ethosomes, liposomes, nanophytovesicles (NPVs), and chlorogenic acid–hydrogenated soy phosphatidylcholine complex (CA–HSPC) [148,150,157] Ethosomes, which are lipid-based vesicles enriched with high concentrations of ethanol, effectively enhance the permeability of chlorogenic acid through the stratum corneum (SC). Ethanol increases the fluidity of the lipid bilayer, disrupting the barrier properties of the SC and allowing CGA to penetrate deeper into the epidermis. In vitro studies have demonstrated that ethosomal formulations not only improve the deposition of chlorogenic acid in the skin but also boost its antioxidant and therapeutic efficacy, especially in cosmetic and dermatological applications [148]. In addition to ethosomes, chlorogenic acid is also efficiently delivered through liposomes, which facilitate its solubility and transport across the lipid layers of the skin. Liposomal encapsulation enhances CGA's penetration through the stratum corneum by mimicking the phospholipid arrangement of cellular membranes, leading to deeper tissue absorption [148,150]. A particularly innovative system for CGA delivery is nanophytovesicles (NPVs), which are specialized phospholipid-based carriers designed to enhance lipid solubility and skin permeability. NPVs containing Phospholipon® 90H and LIPOID® S100 create microscopic channels within the SC, significantly increasing CGA's permeation through the lipid matrix. Phospholipon® 90H is specifically effective in enhancing stratum corneum penetration, while LIPOID® S100 facilitates deeper interactions with cellular membranes, allowing for improved bioavailability [146]. Additionally, NPVs boost lipid solubility more than 25-fold compared to the pure form of CGA, enhancing its stability and therapeutic impact. This carrier system also bypasses the hepatic first-pass effect, ensuring greater systemic availability of chlorogenic acid after transdermal application [157]. CGA encapsulated in Phospholipid Complex (CA–HSPC) has demonstrated increased stability, protection against oxidative degradation, and enhanced penetration through the stratum corneum. The HSPC (hydrogenated soy phosphatidylcholine) layer

acts as a protective barrier, prolonging the release of chlorogenic acid while simultaneously improving its therapeutic effects. This controlled-release mechanism not only reduces the frequency of application but also provides sustained antioxidant protection, particularly against UVA-induced photoaging [148]. The use of these carrier systems—ethosomes, liposomes, nanophytovesicles, and phospholipid complexes—substantially improves the skin penetration, stability, and bioavailability of chlorogenic acid. By optimizing its delivery, these technologies enhance CGA's potential for antioxidant, anti-inflammatory, and anti-aging effects in dermatological and cosmetic formulations.

Ferulic, caffeic, and chlorogenic acids, once ingested and absorbed, primarily circulate as conjugated metabolites—glucuronides and sulfates. These forms not only facilitate excretion but may also exert regulatory and protective functions depending on their biological activity and site of action [108,109,145].

The practical implications of these physicochemical characteristics and delivery mechanisms are further explored in the following section, which provides a comparative overview of their dermal and therapeutic applications.

## 4. Applications of Delivery Systems for Hydrophilic Phytochemicals

Building upon the structural properties and encapsulation strategies discussed in the previous section, this part of the review highlights practical applications of nanocarrier-based delivery systems for selected hydrophilic plant-derived compounds.

The table below (Table 2) presents a concise comparative overview of selected scientific publications focused on delivery systems for hydrophilic phytochemicals. The compounds summarized here, including apigenin, quercetin, luteolin, ferulic acid, chlorogenic acid, caffeic acid, curcumin, genistein, rutin, and others, are known for their antioxidant, anti-inflammatory or therapeutic properties. These phytochemicals have been encapsulated using diverse carrier systems to improve solubility, stability, skin penetration, and targeted bioavailability.

The analysis is organized according to key formulation and therapeutic aspects, including type of carrier, method of encapsulation, pharmacokinetic modifications, and targeted dermal effects. The table also expands the scope by including representative examples of compounds not discussed in detail earlier in the manuscript, thereby providing a broader view of the design and application of nanocarrier-based systems for plant-derived hydrophilic substances.

Overall, the summarized data underscores the pivotal role of nanocarriers in optimizing the dermal delivery of phytochemicals. The incorporation of lipid-based systems, polymeric matrices, and hybrid formulations enables enhanced skin permeation, greater compound stability, and effective site-specific action—underscoring their promise in transdermal therapeutic applications.

**Table 2.** Summary of delivery strategies for hydrophilic phytochemicals based on reviewed scientific data.

| Chemical Compound Encapsulated in the Carrier | Type of Carrier | Role of Carrier | Method of Encapsulation | Pharmacokinetics | Therapeutic Effect | References |
|---|---|---|---|---|---|---|
| Apigenin | Transfersomes, phytosomes, ethosomes, liposomes, hydrogels | Enhanced solubility and stability; improved skin penetration; controlled and prolonged release; protection from oxidative degradation | Lipid hydration, sonication, hydrogel encapsulation, phospholipid complexation | Prolonged release; improved retention in the stratum corneum; enhanced skin distribution | Anti-inflammatory and antioxidant effects; targeted delivery to inflamed skin areas | [148,158–163] |
| Quercetin | Liposomes, niosomes, nanoliposomes, phytosomes, polymeric micelles, nanocrystals, lipid nanoparticles (SLNs, PEVs), nanoemulsions, nanofibers, hydrogels | Enhanced solubility and stability; protection from enzymatic and oxidative degradation; improved penetration through stratum corneum | Lipid hydration, sonication, micro-/nanoemulsion, phospholipid complexation, polymer/lipid encapsulation | Slower elimination; prolonged and controlled release; improved metabolic and structural stability in physiological conditions | Increased transdermal bioavailability; targeted anti-inflammatory, antioxidant, and anticancer activity (e.g., EGFR (Epidermal Growth Factor Receptor) inhibition, deeper skin layer delivery) | [93,129,148,155, 159–161,163] |
| Luteolin | Niosomes, transfersomes, phytosomes, nanoemulsions, liposomes, SLNs, hydrogels | Improved physicochemical stability, enhanced skin penetration, anti-inflammatory and antioxidant support | Encapsulation in invasomes, transferso-mal/nanosystemic formulations, phospholipid complexation | Prolonged release, deeper diffusion, better skin distribution, improved structural retention | Increased transdermal bioavailability; targeted anti-inflammatory and antioxidant effects | [148,155,159–161,163] |
| Ferulic Acid | Phytosomes, SLNs, NLCs, nanoemulsions, liposomes, hydrogels | Enhanced stability, solubility, and skin penetration; protection from oxidative degradation; prolonged release | Lipid matrix encapsulation (SLN, NLC), phospholipid complexation, hydrogel and nanoemulsion integration | Slower release, improved structural integrity, protection in physiological conditions | Increased bioavailability via deeper skin penetration and resistance to metabolic degradation; targeted antioxidant and anticancer effects | [93,148,149,161] |

**Table 2.** *Cont.*

| Chemical Compound Encapsulated in the Carrier | Type of Carrier | Role of Carrier | Method of Encapsulation | Pharmacokinetics | Therapeutic Effect | References |
|---|---|---|---|---|---|---|
| Chlorogenic Acid | Phytosomes, liposomes, nanocapsules, nanoemulsions, hydrogels, NPVs (Phospholipon® 90H, LIPOID® S100), CA–HSPC complex | Improved solubility, stability, and skin penetration; protection from oxidation; enhanced SC retention | Lipid hydration, phospholipid complexation (HSPC, NPVs), hydrogel embedding | Prolonged release, enhanced SC retention, improved structural stability in physiological conditions | Increased transdermal bioavailability; targeted antioxidant action and UV protection in inflammatory sites | [148,150,157,160, 161] |
| Caffeic Acid | Ethosomes, liposomes, phytosomes, SLNs, hydrogels, polymeric/lipid nanoparticles, chitosan microparticles | Enhanced stability, solubility, and skin penetration; targeted release in skin and follicles; antioxidant protection | Lipid hydration, phospholipid complexation, hydrogel encapsulation, biodegradable nanoparticle formation, spray-drying (microparticles) | Slower or prolonged release, better distribution and penetration through stratum corneum and follicles | Improved bioavailability and retention; antioxidant action; potential for folliculitis treatment | [93,148,155,156, 160,161] |
| Curcumin | Transferosomes, nanosponges, liposomes, liposome-in-hydrogel | Enhanced penetration through SC, protection from oxidation, prolonged release, increased bioavailability | High-pressure technique, solvent diffusion, lipid hydration, chitosan hydrogel formation | Prolonged action, reduced degradation, improved structural stability | Higher transdermal bioavailability; targeted delivery to deep skin layers; applications in inflammation, endodontics, and periodontics | [155,164–166] |
| Genistein | Nanoemulsion, Liposomes, Polymeric Micelles | Enhanced skin permeability, protection from degradation, increased stability and bioavailability | Encapsulation in lipid and polymeric nanoparticles or micelles | Faster absorption, prolonged release, stability in physiological environment | Improved transdermal bioavailability; targeted antioxidant activity through the skin | [160,163] |

**Table 2.** *Cont.*

| Chemical Compound Encapsulated in the Carrier | Type of Carrier | Role of Carrier | Method of Encapsulation | Pharmacokinetics | Therapeutic Effect | References |
|---|---|---|---|---|---|---|
| Rutin | Nanoemulsion, Liposomes, Niosomes | Improved skin permeability, stability, solubility; protection from oxidation | Encapsulation in liposomes and niosomes using lipid hydration | Faster absorption, improved stability, prolonged action | Enhanced bioavailability; effective in anti-inflammatory therapy and skin delivery | [160,163] |
| Morusin | Niosome | Enhanced stability and skin penetration | Lipid-based encapsulation in niosomes | Increased dermal penetration and bioavailability | Targeted delivery through the skin | [163] |
| Capsaicin | Transferosome | Enhanced skin penetration, reduced systemic side effects | High-pressure encapsulation technique | Improved dermal absorption compared to conventional formulations | Targeted delivery to pain receptors and peripheral nerves | [164] |
| Vincristine sulfate | Transferosome | Site-specific delivery with minimized systemic toxicity | High-pressure encapsulation technique | Enhanced skin penetration | Targeted anticancer delivery with reduced effect on healthy tissue | [164] |
| Cannabidiol | Ethosome | Enhanced skin permeability and localized delivery | Ethosomal formulation | Increased accumulation in stratum corneum | Improved therapeutic targeting of cutaneous endocannabinoid system | [164] |
| Caffeine | Nanoemulsion | Improved solubility and enhanced penetration through the stratum corneum | Nanoemulsion with eucalyptus/oleic oil and Volpo-N10 emulsification system | Better diffusion through SC, increased solubility, enhanced skin retention | Effective delivery to deeper skin layers | [167,168] |
| Naproxen | Nanoemulsion | Improved solubility and deeper skin penetration | Nanoemulsion using Volpo-N10, ethanol, eucalyptus/oleic oil, and PBS (Phosphate-Buffered Saline) buffer | Increased solubility in the stratum corneum, enhanced diffusion | Enhanced transdermal bioavailability and targeted delivery to deeper skin layers | [167,168] |

**Table 2.** *Cont.*

| Chemical Compound Encapsulated in the Carrier | Type of Carrier | Role of Carrier | Method of Encapsulation | Pharmacokinetics | Therapeutic Effect | References |
|---|---|---|---|---|---|---|
| Kaempferol | Submicron Emulsion | Enhanced solubility and skin penetration | Submicron emulsion using PEG-400 (Polyethylene glycol) or eucalyptus oil | Improved penetration through the stratum corneum | Increased skin bioavailability with targeted action in the stratum corneum | [159] |
| Sulbutamol Sulfate | Ethosome | Enhanced skin penetration for systemic and localized delivery | Ethosomal formulation | Improved penetration through the stratum corneum | Targeted delivery to respiratory and cutaneous receptors | [164] |
| Ammonium Glycyrrhizinate | Ethosome | Anti-inflammatory action on the skin | In vitro percutaneous permeation through human skin | Improved availability in deeper skin layers | Improved therapeutic effectiveness | [164] |
| Cyclodextrins | Cyclodextrins | Stabilization against oxidation and improved bioavailability | Complexation with β-cyclodextrin | Stabilization against oxidation | Higher bioavailability with β-CD application | [164] |
| Econazole Nitrate | Polymeric Nanosponge | Improved skin penetration, therapeutic stabilization | Ultrasonic technique | Increased stability and prolonged action | Enhanced transdermal bioavailability | [165] |
| Resveratrol | PEGylated liposome | Enhanced stability, prolonged presence in tissues | PEGylation of liposomes | Prolonged action in tissues | Enhanced bioavailability and protection from degradation | [155] |
| Calcein | pH-sensitive Liposome | Enhanced penetration through the SC depending on pH | Lipid layer technique and freeze-thaw cycles | Faster penetration at pH 5.0 | Targeted delivery to the stratum corneum at pH 5.0 | [169] |
| NBD-PE (N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl) phos-phatidylethanolamine) | pH-sensitive Liposome | Facilitated skin penetration in acidic conditions | Lipid layer technique and freeze-thaw cycles | Increased penetration at pH 5.0 | Targeted delivery to the stratum corneum at pH 5.0 | [169] |

**Table 2.** *Cont.*

| Chemical Compound Encapsulated in the Carrier | Type of Carrier | Role of Carrier | Method of Encapsulation | Pharmacokinetics | Therapeutic Effect | References |
|---|---|---|---|---|---|---|
| Ascorbyl Palmitate (AsP) | Ethosome | Anti-inflammatory action, assessed by in vitro skin permeation | Ethosomal formulation | Improved availability in deeper skin layers | Enhanced therapeutic effectiveness, targeted dermal action | [170] |
| Sodium Fluorescein (NaFI) | Limonene-containing Liposome | Enhanced skin penetration due to limonene, modification of stratum corneum | Thin-layer lipid hydration technique, sonication, addition of limonene | Increased fluidization of the lipid membrane, improved penetration | Improved transdermal bioavailability | [171] |
| Carboxyfluorescein (CF) | Liposome | Enhanced skin penetration through liposomal carriers | Rotational evaporation technique, formation of thin lipid layer, hydration | Improved distribution to the stratum corneum and deeper skin layers | Improved transdermal bioavailability | [172] |
| Tetracaine | Liposome | Local skin anesthesia | Thin lipid layer hydration, sonication method | Faster penetration through the stratum corneum | Improved bioavailability in the stratum corneum | [172] |
| Betamethasone dipropionate | Liposome | Improved effectiveness in eczema treatment | Hydration and sonication technique | Improved penetration and retention in deeper skin layers | Higher bioavailability and therapeutic effectiveness | [172] |
| Hesperidin | Lipid-Polymer Hybrid Nanoparticles (LPHNPs), Microemulsion-based ointment | Enhanced skin penetration, controlled release, protection from degradation | Encapsulation in lipid-polymer hybrid nanoparticles; eucalyptus oil-based water emulsion | Initial burst followed by prolonged release; improved diffusion through the skin | Improved bioavailability in deeper skin layers, with targeted action and enhanced stability | [159,172] |
| Hesperetin | Microemulsion, Topical Film | Improved bioavailability, enhanced skin penetration | Microemulsion with eucalyptus oil, film matrix | Faster penetration through the stratum corneum | Enhanced transdermal bioavailability | [159] |

**Table 2.** *Cont.*

| Chemical Compound Encapsulated in the Carrier | Type of Carrier | Role of Carrier | Method of Encapsulation | Pharmacokinetics | Therapeutic Effect | References |
|---|---|---|---|---|---|---|
| Naringenin | Ubmicron Emulsion, Gel, Elastic Liposome | Enhanced stability, improved bioavailability, better skin penetration | Encapsulation in submicron emulsion and elastic liposomes | Increased skin diffusion, controlled release | Targeted antioxidant and anti-inflammatory action | [159] |
| Catechins | Nanotransfersomes, Grape Seed Extract Cream, Multilamellar phosphatidylcholine liposomes, Ethanol-enriched liposomes | Improved skin absorption and penetration, protection from degradation | Nanotransfersomes with hyaluronic acid, grape seed extract cream; multilamellar and ethanol-based liposomes | Longer retention in the skin, increased penetration, slower release | Higher bioavailability through the stratum corneum; targeted antioxidant and protective action in skin layers | [159] |
| Myricetin | Lipid Nanoparticles, Liposomes | Protection from degradation, increased stability | Multilamellar liposomes, lipid nanoparticles | Improved stability, prolonged action | Enhanced bioavailability in skin layers, targeted anti-inflammatory action | [160] |
| Imperatorin | Lipid-Polymer Hybrid Nanoparticles (LPHNPs) | Prolonged action and controlled release | Encapsulation in lipid-polymer hybrid nanoparticles | Initial burst followed by sustained release | Enhanced skin penetration | [173] |
| Norfloxacillin | Lipid-Polymer Hybrid Nanoparticles (LPHNPs) | Prolonged action and controlled release | Encapsulation in lipid-polymer hybrid nanoparticles | Initial burst release and prolonged release | Enhanced skin penetration | [174] |
| Indomethacin | Polymeric Nanoparticles | Enhanced penetration, controlled release | Encapsulation in polymeric nanocapsules and nanospheres | Diffusion-based release (Higuchi model) | Increased bioavailability via deeper skin layers | [174] |
| Amphotericin B | Polycaprolactone (PCL) Nanoparticles | Skin penetration and controlled release | Encapsulation in PCL polymeric nanoparticles | pH-dependent release (faster at pH 7.4) | Enhanced delivery to deeper skin layers | [174] |

## 5. Summary

Advanced drug delivery systems such as liposomes, niosomes, exosomes, and polymeric nanoparticles offer a promising approach for improving the overall performance of hydrophilic compounds. They enhance its stability, bioavailability and considering its amphiphilic character, they also constitute an effective strategy for the phytochemicals transport through the stratum corneum allowing the increasing of hydrophilic molecules absorption.

While the majority of available research is descriptive and in vitro-based, a critical comparative evaluation reveals distinct advantages and limitations among the nanocarrier types. Liposomes and ethosomes are supported by the most consistent in vivo evidence for skin applications, demonstrating improved drug retention in the epidermis and superior permeation profiles compared to conventional topical formulations [175–177]. Ethosomes, for instance, have been shown to deliver active substances more efficiently through the stratum corneum due to their high ethanol content, which fluidizes skin lipids [178]. In contrast, solid lipid nanoparticles (SLNs) offer greater stability and control over release profiles but may face limitations in drug loading capacity and skin permeation depth [179].

Despite these advances, clinical translation remains limited. Main barriers to adoption include: (1) high production and scaling costs, particularly for complex nanocarriers like polymeric micelles or lipid-polymer hybrids; (2) regulatory uncertainty concerning safety and long-term stability; and (3) lack of standardization in preparation methods, which affects reproducibility [180,181].

Further comparative studies, particularly clinical trials, are essential to substantiate the therapeutic superiority of individual delivery platforms and to determine the most viable candidates for clinical translation in dermatological care.

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