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Original Article

Phenolic Compounds and Skin Permeability: An In Silico Investigation

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Abstract

Background: The skin is the largest organ of the body and provides the main barrier between the internal and external environment. Assessment of skin permeability is of critical importance for understanding and predicting in vivo efficacy and bioavailability of bioactive phenolic compounds.

Objectives: This study investigated the relationship between skin permeability and phenolic compounds using in silico methods.

Methods: Screening of skin permeability was performed on 475 randomly selected phenolic compounds. Molecules were expressed in SMILE format downloaded from Phenol-Explorer Database (version 3.6, 2016). Then, their skin permeability was determined by the linear model of the quantitative structure-activity relationship (QSAR). The obtained results were investigated for normal distribution and correlation with pharmacological properties.

Results: Our investigation showed that ferulate hydroxycinnamic acid derivatives were the most important phenolic subclass with a permeability of -1.65 cm/s. The relationship between permeability and lipophilicity, water solubility, synthetic accessibility, and bioavailability was evaluated. The statistical analysis revealed that the highest skin permeability was associated with three parameters: the topological polar surface area (TPSA), molecular weight, and lipophilicity (iLog P).

Conclusion: The cutaneous permeability depended on several chemical parameters of the molecule used. The classification of phenolic compounds according to their structures proved a wide variability in this permeability.

Keywords: Phenolic compounds, In silico, Skin, Cosmetic, Permutation

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Background

The skin is the largest organ of the body and provides the main barrier between the internal and external environment. It consists of three separate and diverse layers, each one with a distinct cellular composition, characteristic, and function: epidermis, dermis, and hypodermis. The stratum corneum represents the outermost layer of the epidermis in contact with the external environment and is composed of large flat polyhedral cells, the corneocytes, which have lost their organelles and are said to be dead but remain biochemically active (1). First and foremost, it keeps water inside the body. Similarly, the stratum corneum is also a barrier against UV radiation due to keratins and proteins that compose it. This skin layer limits the entry of applied substances and regulates water loss through its stratum corneum (2). The barrier function of the skin is not absolute, and its permeability is linked to the physicochemical properties of the molecules in contact (3). The absorbed molecules are distributed in the organism after a passive transfer, eliminated, or stored. Hence, the importance of studying the permeability of active substances introduced into cosmetic preparations for cutaneous use (4). The in vitro diffusion tests through the skin are expensive and delicate. Today, this test has become more accessible by in silico methods (5,6). This permeability is deduced by calculating the skin permeability coefficient (Log Kp). This prediction is based on the linear model by Potts and Guy (7).

The ability of phenolic compounds as plant-derived natural agents to act as photoprotectors, antioxidants, and antimicrobial substances is of interest for cosmetic and therapeutic purposes. Due to their natural origin and weak toxicity, phenolic compounds are interesting agents for innovative pharmaceutical treatments for skin disorders or the development of new cosmetic products (8). The bioavailability of phenolic compounds depends on their subclass and physicochemical properties, including the degree of polymerization, glycosylation, or molecular properties, their polarity and their interaction with nutrients, the proteins and carbohydrates in their cells, as

well as the other components of the formulation in which they are introduced (9,10). The common classification of phenolic compounds distinguishes flavonoids and non-flavonoids. The chemical structure of flavonoids is based on two aromatic rings connected by a bridge consisting of three carbons (C6-C3-C6). Flavonoids are divided into six main subclasses, namely flavonols, flavones, flavanones, flavan-3-ols, isoflavones, and anthocyanidins. In the physiological state, flavonoids occur usually in association with sugar as glycosides. The subclasses of non-flavonoids are phenolic acids (hydroxybenzoates (C6-C1), hydroxycinnamates (C6-C3)), lignans (C6-C3), and stilbenes (C6-C2-C6) (11). Two other subclasses of non-flavonoids are tannins and lignins (10). These compounds occur mainly as complicated biopolymers; hence, they lack a defined primary carbon base, and the chemical structure is unique to a particular polyphenol (12,13).

In our study, screening was carried out on 25 classes of phenolic compounds (Table 1), and the results of multivariate analysis showed that certain classes of phenolic compounds are more correlated with this coefficient. Ferulate hydroxycinnamic acid derivatives were the most crucial phenolic subclass. Afterwards, we studied the statistical interaction of this coefficient with the pharmacological properties, lipophilicity, water solubility, synthetic accessibility, and bioavailability.

Table 1. Class and Subclass of Phenolic Compounds Studied for their Skin Permeability

Class	Subclass
Flavonoids	Anthocyanins
	Dihydrochalcones
	Flavanols
	Flavanones
	Flavones
	Flavonols
	Isoflavonoids
Phenolic acids	Hydroxybenzoic acids
	Hydroxyphenylacetic acids
	Hydroxyphenylpropanoic acids
Stilbenes	Stilbenes
Lignans	Lignans
Other polyphenols	Hydroxycinnamaldehydes
	Alkylmethoxyphenols
	Hydroxycoumarins
	Hydroxyphenylpropenes
	Methoxyphenols
	Naphthoquinones
	Hydroxybenzaldehyde
	Phenolic terpenes
	Tyrosols
	Ferulate hydroxycinnamic acids
	Curcuminoids
	Furanocoumarins
	Other polyphenols

Materials and Methods

Data Collection

The screening of skin permeability was performed on 475 randomly selected phenolic compounds. Molecules were expressed in SMILE format, downloaded from Phenol-Explorer Database version 3.6, 2016, a comprehensive online database on polyphenol contents in foods (14-16). These molecules were classified into 5 chemical classes and 25 subclasses according to their structures (Table 1).

Skin Permeability

The linear model of quantitative structure-activity relationship (QSAR) was used to predict the permeability coefficient (Kp) according to Potts and Guy (7). The model was expressed by the following formula:

$$log\ Kp\ (cm/s) = 0.71 log\ K_{OW} - 0.0061\ MW - 6.3$$

Where Kp (cm/s) = skin permeability; K_{OW} = octanol-water partition coefficient; MW = molecular weight.

Pharmacological Properties

The analysis of the pharmacological properties was carried out according to Daina et al (17). The topological polar surface area (TPSA) of phenolic compounds was defined as the surface sum over all polar atoms, primarily oxygen, including their attached hydrogen atoms. The lipophilicity was expressed as a consensus Log Po/w, it is defined as the decimal logarithm of the ratio of the molar concentrations of the neutral form in n-octanol and water (18). The aqueous solubility was calculated according to Delaney (19). Bioavailability score is formulated as the likelihood that a compound will have > 10% bioavailability in rats or measurable Caco-2 permeability (20). Synthetic accessibility value is a score based on the fragmental analysis of the structures of more than 13 million compounds. The score was normalized between 1 (easy synthesis) and 10 (complicated synthesis) (21).

Statistical Analysis

The statistical analysis was performed using Orange data mining software version 9.0 (Massachusetts, USA), and Metascape network analysis was performed using Cytoscape version 3.9.1 (U.S. National Institute of General Medical Sciences) (22). Pharmacological properties were evaluated online using SwissADME tool (http://www.swissadme.ch/index.php) (17,23).

Results

Skin Permeability Distribution

The normal distribution of various phenolic compounds according to their chemical class and subclass is illustrated in Figures 1A and 1B. The distribution was expressed as the mean (μ) and the standard deviation (σ). According

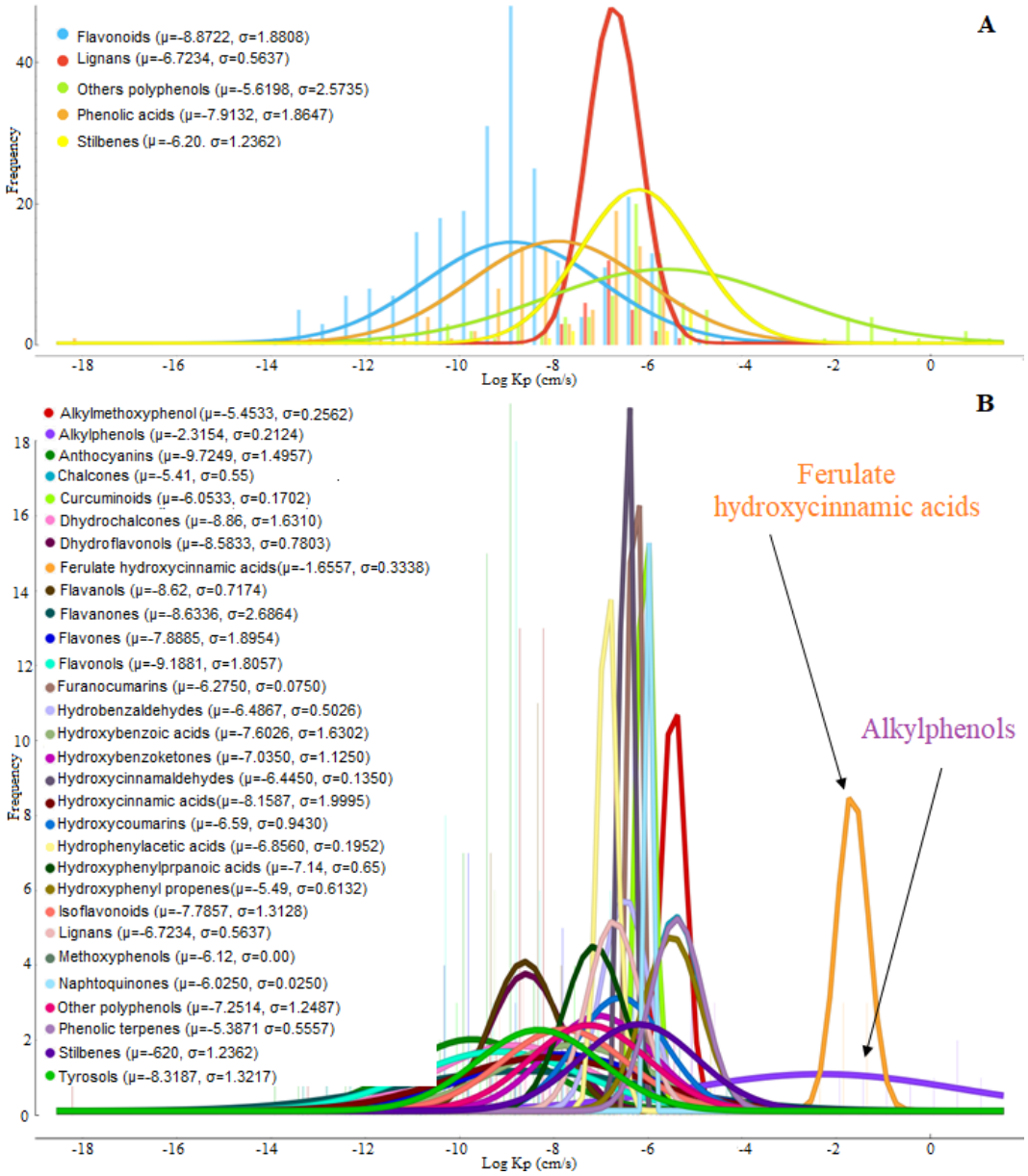

Figure 1. Bell Plot of Skin Permeability Distribution of Phenolic Class (A) and Subclass (B)

to Figure 1A, the lowest skin permeability values were associated with flavonoids with μ and σ equal to -8.872 and 1.880, respectively. Phenolic acids (μ=-7.913), lignans (μ=-7.913), and stilbenes (μ=-6.20) followed flavonoids. The normal distribution of phenolic subclass showed that ferulate hydroxycinnamic acid derivatives have the highest skin permeability (with a log Kp of -1.65 cm/s), followed by alkylphenols (with a log Kp of -2.31 cm/s). The lowest values were recorded for anthocyanins with a log Kp of -9.793 cm/s (Figure 1B). The studied ferulate hydroxycinnamic acids derivates were 24-methylcholestanol ferulate, 24-methylcholesterol ferulate, 24-methyllathosterol ferulate, stigmastanol ferulate, sitosterol ferulate, schottenol ferulate, and 24-methylenecholestanol ferulate.

Linear Projection of Polyphenol Class and Subclass According to Pharmacological Properties

The linear projection of polyphenol class and subclass is illustrated in Figure 2A-B. For phenolic classification (Figure 2A), the class of flavonoids was associated with three parameters: the TPSA, the molecular weight, and skin permeability. Lignans, phenolic acids, and stilbenes were characterized by a random distribution. The higher skin permeability was associated with other phenolic classes, which leads us to study the subclasses of phenolic compounds. According to Figure 2B, it can be observed that the phenolic compounds classified under "others" in Figure 2A were better classified. It can also be seen that the classification gave a random distribution for most of the subclasses except for the alkylphenols and ferulates. In fact, these two classes were characterized by synthetic

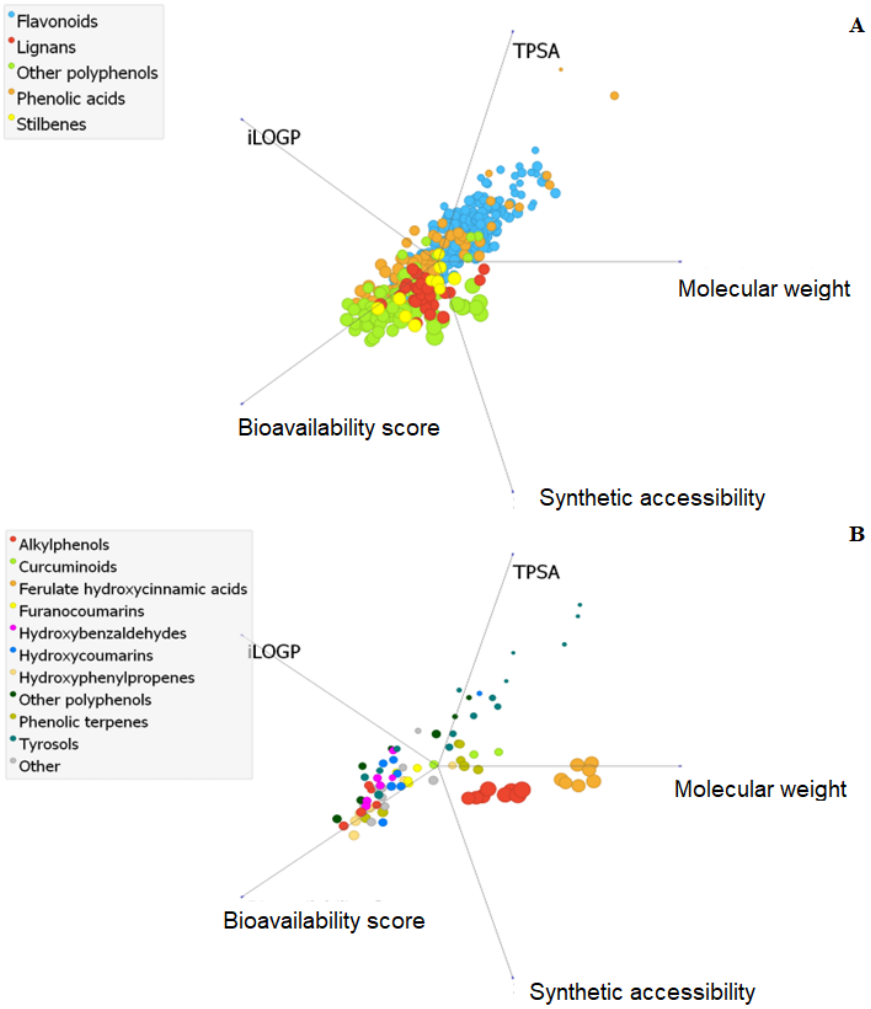

Figure 2. Linear Projection of Polyphenol Class (A) and Subclass (B) According to Pharmacological Properties. Differences in sizes was associated with skin permeability

accessibility and molecular mass.

Correlation Analysis of Polyphenol Pharmacological Properties and Skin Permeability

In Figure 3, seven hexagons are represented. These hexagons represent the nodes of the network. The red and blue lines represent negative and positive correlations, respectively. The line thickness means the correlation size at a P value ≤ 0.05. These hexagons represent the nodes of the Metascape correlation network. The skin permeability was negatively correlated with TPSA, water solubility (ESOL Log S), molecular weight, and synthetic accessibility. The Pearson correlation coefficients of log Kp were -0.866 for TPSA, -0.638 for molecular weight, -0.510 for ESOL Log S, and 0.529 for iLOGP.

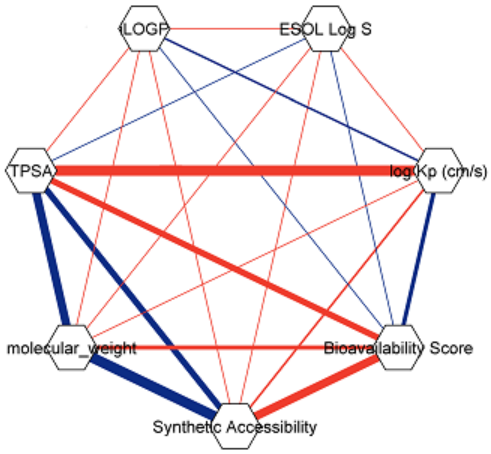

Figure 3. Metascape Correlation Network of Pharmacological Properties and Skin Permeability of Polyphenols. TPSA: topological polar surface area, iLog P: lipophilicity, ESOL Log S: water solubility, "log Kp": skin permeability

Discussion

Skin permeability is widely recognized as an essential parameter to be considered for the delivery of active substances. Many different in silico approaches have been used to identify the correlation between the structure of the permeants and their permeability, reproduce the skin behavior, and predict the ability of specific chemicals to permeate this barrier.

The skin permeability is deduced by calculating the skin permeability coefficient (log Kp). The relationship between

skin permeability and log partition coefficient (log Kp) has been extensively studied in recent years (6,24). Log Kp is a measure of the ability of a substance to partition or distribute between different phases, such as the skin and the surrounding environment. Log Kp values can be used as a predictor of the skin permeability of a substance, with higher log Kp values indicating a greater ability to penetrate the skin (25). Recent research has focused on developing in silico models to predict the skin permeability based on log Kp values, as well as investigating the impact of other factors such as chemical properties and solubility on skin permeability (26). Furthermore, another study has been conducted on specific classes of compounds as phenolic compounds to understand the skin permeability in relation to log Kp (27). Overall, research in the past decade has established log Kp as an important predictor of skin permeability; however, it is not the only factor and other properties should be taken into account (27).

Phenolic compounds are a class of naturally occurring compounds that have been found to have a wide range of beneficial effects on the skin owing to their antioxidant and anti-inflammatory properties (28-30). One of the main benefits of phenolic compounds for the skin is their ability to protect against UV damage and prevent photoaging (31). Additionally, phenolic compounds have been shown to improve the barrier function of the skin and reduce transepidermal water loss. In addition, phenolic compounds can help to boost collagen production, which is important for maintaining skin elasticity and firmness. They also create a more youthful and healthy-looking skin by improving skin texture, tone, and hydration (32).

Flavonoids, phenolic acids, stilbenes, and lignans are all types of phytochemicals found in plants. They have some similarities in terms of the chemical structure and biological activity; however, there are also some notable differences between them (33). Phenolic acids are a group of compounds that contain a phenolic group, which is an aromatic ring with one or more hydroxyl groups (33). Stilbenes are a class of compounds that have a stilbene skeleton including compounds such as resveratrol, which is found in grapes and red wine, and pterostilbene, which is found in blueberries (33). Lignans are a group of compounds that are found in plants, particularly in the seeds of flax and sesame. They have a complex structure that includes a phenylpropanoid and a neolignan unit (33). In our work, the research on the effect of the chemical class of phenolic compounds has shown that the classes studied, including flavonoids, phenolic acids, stilbenes, lignans, and so on, differ in their responses to cutaneous permeability. Flavonoids were characterized by the lowest skin permeability. The normal distribution of phenolic subclass showed that the ferulate hydroxycinnamic acids derivates had the highest skin permeability (with a log kp of -1.65 cm/s), followed by alkyphenols (with a log kp of -2.31 cm/s). The lowest values were recorded with anthocyanins, a log Kp of -9.793 cm/s.

Ferulate is a hydroxycinnamic acid derivative. It is characterized by the presence of a ferulic acid moiety, which is an ester of ferulic acid and a carbohydrate or a sugar alcohol (33). In our stutdy, ferulic acid was characterized by a low skin permeabilty (-6.4 cm/s). Ferulate is considered to have low skin permeability by Zhang et al (34). However, Hartati et al (35) showed that ferulate could have the potential to act as a skin permeation enhancer, which means that it can help other molecules to penetrate the skin more easily. It is also known to have a free radical scavenging activity, which makes it an interesting molecule for the cosmetic industry (35). In our case, ferulic acid was associated with phytosterols, which are non-polar molecules, meaning that they do not have a positive or negative charge and are not attracted to polar substances such as water (36). They are hydrophobic, meaning that they do not dissolve in water and tend to repel it. Due to their non-polarity, phytosterols are mostly found in the lipid portion of the cell membrane and are not found in the aqueous portion of the cell (36).

The second subclass that has high skin permeability was alkylphenols, which is a group of compounds that contain both a phenolic group and an alkyl group. The phenolic group is an aromatic ring with one or more hydroxyl groups, while the alkyl group is a hydrocarbon chain that can vary in length and saturation. Some examples of alkylphenols include 5-pentacosylresorcinol (1.16 cm/s) and 5-pentacosenylresorcinol (0.86 cm/s). Alkylphenols, also called alkylresorcinols, belong to the family of phenolic lipids and are usually found in numerous biological species. In the particular case of higher plants, alkylresorcinols have been found in various counterparts with chains of 13-27 carbon atoms containing several saturations (37,38). Synthetic alkylphenols, such as nonylphenol and octylphenol, have been shown to have a wide range of potential environmental and health effects (39). Some studies have shown that some alkylphenols can mimic estrogenic hormones in the human body and can disrupt the endocrine system, leading to potential developmental and reproductive effects (40). In addition, alkylphenols can also be toxic to aquatic organisms and can lead to the feminization of fish populations (41).

In Orange data mining software, a linear projection graph is a visualization technique used to represent high-dimensional data in a lower-dimensional space. It is commonly used in data mining and machine learning to reduce the complexity of data and make data easier to interpret. The graph is created by projecting the data onto a linear subspace, typically using a technique such as principal component analysis (PCA) or multi-dimensional scaling (MDS). The resulting graph can be used to identify patterns, clusters, or outliers in the data and gain a better understanding of the underlying structure of the data (23,24). According to the linear projection (Figure 2) and the Metascape correlation network (Figure 3) of polyphenol class and subclass according to pharmacological properties, it was revealed that the highest skin permeability was associated with

three parameters: the molecular weight, lipophilicity (iLog P), and the TPSA. TPSA is a molecular descriptor used to describe the polar surface area of a molecule. It is based on the concept of topological analysis of molecular surface and is related to the ability of a molecule to interact with polar environments, such as the polar regions of cell membranes (42). There are studies that have suggested a correlation between TPSA and skin permeability. Nakao et al (43) found that TPSA was a good predictor of skin permeation for a diverse group of compounds, including lipophilic and hydrophilic compounds. Phenolic compounds with a polar surface area greater than 140 angstroms squared ($Å^2$) tend to be poor at permeating cell membranes (44). To penetrate the blood-brain barrier and act on receptors in the central nervous system, a TPSA of less than 90 $Å^2$ is usually required for molecules (45).

Bioavailability corresponds to the speed and extent of the passage of the active principle (drug or metabolite) into the general circulation, thus reaching the site of action (46). The bioavailability of active ingredients in dermal preparations is a key factor (47). In our work, it was revealed that phenolic compounds with high skin permeability were not associated with high bioavailability scores. Hydroxyphenylacetic, hydroxybenzoic, and hydroxycinnamic acids were characterized by the best bioavailability score (0.85). On the contrary, ferulate hydroxycinnamic acid derivatives were characterized by a very low bioavailability score (0.11), independent of their molecular weights (48). On the other hand, skin permeability was positively correlated with lipophilicity (iLog P) and bioavailability score. Since the passage of substances through the skin barrier is done according to a passive diffusion mechanism, only molecules that are small (molecular mass less than 1000 g/mol) and without electrical charge, not ionized, penetrate (49). Tian et al (50) showed that skin penetration of the drug showed a significant correlation with physicochemical parameters (log $K_{O/W}$, molecular weight, polar surface, and polarizability). Pranitha and Lakshmi (51) concluded that the TPSA was the main significant factor for the study of ex-vivo transdermal flux variability of six drugs.

Prediction of skin permeability is an important factor in medicine because it determines how easily drugs and other compounds can penetrate the skin and reach the underlying tissues and organs. The skin is a barrier that protects the body from harmful external agents; however, it has to allow the passage of certain molecules to perform their functions (52). In dermatology, understanding skin permeability is important for the development of topical treatments for skin conditions, such as eczema, psoriasis, and acne (52). The ability of a drug or cosmetic product to penetrate the skin and reach the site of action can affect its efficacy and safety (53). In transdermal drug delivery, the ability of a drug to penetrate the skin and reach the bloodstream can be used to deliver drugs to the body in a controlled and sustained manner, avoiding the first-pass metabolism and the need for injection (54). This can be useful for the treatment of chronic conditions such as pain and hypertension, as well as hormone replacement therapy (54). Additionally, the skin permeability can be a concern in cosmetics and personal care products, as some compounds may be harmful if they penetrate the skin and reach the bloodstream. Therefore, it is important to understand the skin permeability to ensure the safety of the products (55).

There are several limitations to predicting skin permeability. In vitro methods, such as Franz diffusion cells and artificial membranes, are commonly used to predict skin permeability while they may not accurately reflect the in vivo situation. The skin has a complex structure and physiology, and the artificial membranes used in in vitro methods may not fully mimic the barrier properties of the skin (56). For the in silico studies, there is a lack of data on the permeability of many compounds through the skin. This can make it difficult to predict the permeability of new compounds or to compare the permeability of different compounds (57). Likewise, there is significant interindividual variability in skin permeability, and this can make it difficult to predict the permeability of a compound in a specific individual. Factors such as age, gender, genetics, and skin condition can all affect skin permeability. Besides, the pH and temperature of the skin can affect the permeability of a compound. The pH of the skin can vary depending on the location, and the temperature can vary depending on the time of day and the individual's body temperature (58).

Conclusion

In conclusion, our study showed that the cutaneous permeability depended on several chemical parameters of the molecule used. The classification of phenolic compounds according to their structures proved a wide variability in this permeability. Chemical classes with relatively low molecular weights were better rated for penetrating the skin. The normal distribution of phenolic subclass showed that ferulate derivative had the highest skin permeability. The lowest permeability values were associated with flavonoids. The statistical analysis showed that the TPSA was the main significant factor in the study.

Authors' Contribution

Conceptualization: Majdi Hammami, Emna Chaabani, Walid Yeddes.
Data curation: Majdi Hammami.
Formal analysis: Emna Chaabani, Walid Yeddes, Wissem Aidi
Investigation: Majdi Hammami, Emna Chaabani, Walid Yeddes, Wissem Aidi Wannes, Soumaya Bourgou.
Methodology: Emna Chaabani.
Resources: Emna Chaabani, Walid Yeddes, Wissem Aidi Wannes, Soumaya Bourgou.
Visualization: Emna Chaabani, Walid Yeddes.
Wannes, Soumaya Bourgou.
Writing–original draft: Majdi Hammami.

Competing Interests

None to be declared.

Ethical Approval

Not applicable.

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