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Review Article

Arbutin: An Integrated Review Of Its Chemistry, Physicochemical Characteristics, Pharmacological Activities And Therapeutic Potential

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ABSTRACT

Arbutin is an endogenous phenolic glycoside, which has appeared to be a promising multifunctional biologically active substance. Arbutin is present in different plants and is traditionally known for its antimelanogenic effects due to the ability to inhibit tyrosinase activity; meanwhile, recently it was found that arbutin is characterized by much wider pharmacological profile, which includes antioxidant, anti-inflammatory, antidiabetic and renoprotective properties. This paper reviews the chemical structure, physicochemical properties, pharmacological activity and the mechanism of action of arbutin. Arbutin is characterized by high water solubility of the molecule due to several hydroxyl groups which can lead to the efficient dissolution process. However, poor permeability and low stability at some conditions are the major drawbacks. The mechanism of action of the substance can be explained by oxidative stress pathways, suppression of inflammation due to blocking the NF- κ B signaling, and regulation of metabolic dysfunction. However, low bioavailability of arbutin, possible formation of hydroquinone and insufficient clinical data limit its potential as a therapeutic drug despite all these benefits. Moreover, the absence of standardization of the experimental model and dosing regimen can serve as another problem in the area. Future research should be aimed at solving the mentioned issues through innovative approaches, such as improved stability and bioavailability, clinical trials, and molecular target identification using multi-omics and systems pharmacology methods.

INTRODUCTION

Natural products continue to be vital to drug discovery due to their chemical diversity and wide

range of pharmacological activity. Numerous drugs currently used clinically are derived either directly or indirectly from natural products, which

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demonstrate the need for phytochemicals in the management of multifactorial diseases.^{1,2} One of these groups of bioactive agents are polyphenolic compounds that show promising activities as antioxidants, anti-inflammatories, and metabolic regulators.^{3,4}

Arbutin is a naturally occurring hydroquinone glycoside that is mainly isolated from several species of medicinal plants, like *Arctostaphylos uva-ursi* and other *Vaccinium* species. Arbutin has been used traditionally in dermatology applications for skin whitening owing to the inhibition of tyrosinase activity and melanin synthesis.^{5,6} However, there is growing evidence that arbutin shows pharmacological effects not only in cosmetic products but also as an antioxidant, anti-inflammatory, and possibly anti-diabetic agent^{7,8}

Pathogenesis of chronic diseases, such as diabetes mellitus and its complications like diabetic nephropathy, is known to be associated with increased oxidative stress and chronic inflammation processes. Increased production of reactive oxygen species (ROS) and activation of inflammatory pathway, like NF- κ B, play a critical role in the development and progression of diseases^{9–11}. Arbutin has shown promising pharmacological effects on regulation of these processes^{12–14}.

However, pharmacological activities of arbutin make it difficult to use it clinically due to the problems with stability and bioavailability of the compound. Various experimental studies were performed to characterize the stability and biopharmaceutical behavior of arbutin using methods of physicochemical characterization, like FTIR spectroscopy, determination of particle size, polydispersity index (PDI), and zeta potential measurement [18]. However, the existing literature lacks a consolidated discussion that integrates the

pharmacological actions of arbutin with its physicochemical characteristics and experimental performance. A better understanding of this relationship is essential to explain how its molecular properties influence its biological activity and therapeutic potential.¹⁹

Consequently, this review seeks to provide a detailed discussion on the arbutin, including its chemical properties, pharmacological actions and mechanisms of action. The physicochemical properties of arbutin are also included in this discussion in order to bridge the gap between its chemical characteristics and biological relevance.

Arbutin is a naturally occurring phenolic glycoside and it is known chemically as hydroquinone-O- β -D-glucopyranoside. Arbutin consists of hydroquinone bonded to glucose molecule using a β -glycosidic linkage, hence, increasing its water solubility and decreasing the toxic effects caused by free hydroquinone^{1,17}. The molecular formula of arbutin is C₁₂H₁₆O₇ and it has a molecular weight of 272.25g/mole. Arbutin exists in two isomeric forms called α -arbutin and β -arbutin that differ in glycosidic linkage, hence, biological activity and stability¹⁸.

As far as chemistry is concerned, arbutin is a hydroquinone derivative and it possesses hydrophilic and phenolic nature owing to its hydroxyl groups. Its structural features account for its high ability to hydrogen bond, high aqueous solubility and relative stability in physiological conditions.¹⁹ However, under the influence of enzymes and acidic environment, arbutin can be hydrolyzed to hydroquinone, which is its active metabolite causing several biological actions.²⁰

Spectroscopically, arbutin shows characteristic absorption bands for hydroxyl and aromatic groups. FTIR spectroscopy analysis reveals O-H stretching vibrations in the range of 3200-3500



cm⁻¹ and C-O stretching vibrations in the range of 1000-1300 cm⁻¹, which proves the presence of glycosidic and phenolic moieties [21]. In addition, NMR spectroscopy supports its chemical structure through identification of specific proton and carbon environments of glucose and aromatic compounds.²²

Chemical stability of arbutin depends on several environmental conditions such as pH, temperature and enzyme activity. Arbutin is relatively stable in neutral pH; however, it is unstable in alkaline environments where hydroquinone forms.²⁰ This transformation is very important since it determines the therapeutic effects and safety profile of arbutin.

In general, the chemistry of arbutin is very important since it affects its physicochemical behavior and pharmacology actions.

Literature Search Methodology

A literature search was conducted to find published scientific evidence on arbutin, its physicochemical properties, pharmacological activities, mechanisms of action, pharmacokinetics, safety and possible pharmaceutical applications. Relevant literature was searched in electronic databases, namely PubMed, Scopus, ScienceDirect, Web of Science and Google Scholar. Additional relevant articles were identified by manual screening of reference lists of the selected publications.

The search strategy included the following keywords and Boolean operators combinations “arbutin” OR “α-arbutin” OR “β-arbutin” OR “arbutin pharmacology” OR “arbutin pharmacological activity” OR “arbutin mechanism of action” OR “arbutin antioxidant” OR “arbutin anti-inflammatory” OR “arbutin antidiabetic” OR “arbutin antimelanogenic” OR

“arbutin renoprotective” OR “arbutin pharmacokinetics” OR “arbutin bioavailability” OR “arbutin toxicity” OR “arbutin stability” OR “arbutin physicochemical properties” OR “arbutin drug delivery”. The search strategy involved using different combinations of these terms to find literature related to the objectives of the review.

The inclusion criteria of the present review comprised published research articles, review articles, experimental studies and relevant scientific reports concerning the chemistry, natural sources, physicochemical characteristics, biological activities, molecular mechanisms, pharmacokinetic properties, safety aspects and pharmaceutical applications of arbutin. Special attention was paid to studies with experimental evidence of the pharmacological effects of arbutin and studies of its molecular or cellular mechanisms of action. Also included were articles which provided relevant information on α-arbutin and β-arbutin.

They were excluded if they were not related to arbutin, did not include sufficient scientific information, were duplicate publications, or did not provide information relevant to the scope of the current review. Where multiple publications presented similar findings, original research studies and the most recent or comprehensive evidence were prioritized. The information retrieved from the selected literature was critically evaluated and organized based on the major themes of the review including chemical characteristics, natural sources, pharmacokinetics, physicochemical properties, pharmacological activities, mechanisms of action, limitations and future perspectives.

The retrieved evidence was synthesized narratively to provide an integrated overview of the therapeutic potential and pharmaceutical challenges of arbutin. The correlation of the



physicochemical properties of arbutin with its biological activity, bioavailability, stability, and possible clinical translation was considered with special attention.

Natural Sources of Arbutin

Arbutin is a naturally-occurring phenolic glycoside found abundantly in higher plants, especially those belonging to the Ericaceae family. From among all these plants, *Arctostaphylos uva-ursi* (bearberry) is considered to be one of the best

and most studied natural sources of arbutin, whose leaves are used in the treatment of problems related to the urinary tract system. Apart from bearberry, some amount of arbutin has been found in *Vaccinium vitis-idaea*, *Vaccinium myrtillus*, *Pyrus communis*, *Bergenia crassifolia*, *Calluna vulgaris*, *Pyrola rotundifolia*, and some more herbal plants. These plants have been the subject of intensive research due to their antioxidant, anti-inflammatory, antimicrobial, and therapeutic potential, most of which can be partly attributed to arbutin as well as other phenols contained in them.

Table 1. Natural sources of arbutin and their reported therapeutic relevance

Plant species	Family	Common name	Plant part containing arbutin	Major reported pharmacological relevance
<i>Arctostaphylos uva-ursi</i> (L.) Spreng.	Ericaceae	Bearberry	Leaves	Traditional urinary antiseptic; rich natural source of arbutin
<i>Pyrus communis</i> L.	Rosaceae	Pear	Leaves and fruit peel	Antioxidant and phenolic-rich medicinal plant
<i>Vaccinium vitis-idaea</i> L.	Ericaceae	Lingonberry	Leaves	Antioxidant, anti-inflammatory and antimicrobial activities
<i>Vaccinium myrtillus</i> L.	Ericaceae	Bilberry	Leaves	Rich in phenolic glycosides with antioxidant properties
<i>Bergenia crassifolia</i> (L.) Fritsch	Saxifragaceae	Siberian tea	Rhizomes and leaves	Traditional medicinal herb containing arbutin and phenolics
<i>Origanum majorana</i> L.	Lamiaceae	Marjoram	Aerial parts	Natural antioxidant and antimicrobial constituent
<i>Calluna vulgaris</i> (L.) Hull	Ericaceae	Heather	Leaves	Antioxidant and anti-inflammatory phytochemicals
<i>Pyrola rotundifolia</i> L.	Ericaceae	Round-leaved wintergreen	Leaves	Traditional medicinal plant containing arbutin derivatives

Drug Profile of Arbutin



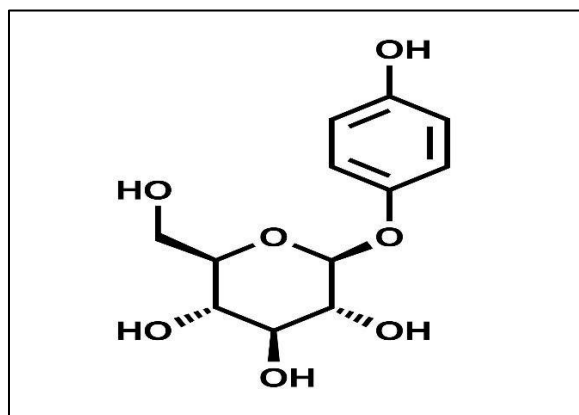


Fig 1 Structure of Arbutin

Table 2. Drug Profile of Arbutin

Drug Name	: Arbutin
Chemical formula	: C ₁₂ H ₁₆ O ₇
Molecular weight	: 272 gm/mol
Melting point	: 197-201°C
Boiling point	: 561°C
Density	: 1.35 g/cm ³
Solubility	: Freely soluble in water & polar solvents such as methanol & ethanol but insoluble in non polar solvents such as n-hexane and diethyl ether
Chemical Name	: 4-Hydroxyphenyl-β-d-glucopyranoside.
Sources	: <i>Bearberry (Arctostaphylos uva-ursi), cranberry, blueberry, pear, and mulberry plants, wheat, Bergenia and Pyrus species.</i>

Pharmacokinetics

Pharmacokinetics (PK) refers to the process of absorption, distribution, metabolism, and excretion of a drug collectively responsible for defining its clinical effectiveness and safety profile. Arbutin is a glycosylated hydroquinone

that has unique pharmacokinetics due to the hydrophilic and non-lipophilic properties.

➤ Absorption

Oral administration is a preferred method for delivery of arbutin in the form of a capsule or tablet. Due to non-lipophilic properties, arbutin has poor permeability. However, the oral



bioavailability of the compound has been reported to be about 60–65%, implying that it has moderate bioavailability through passive and carrier-mediated transport (Liu et al., 2024).

➤ Distribution

Once absorbed into the systemic circulation, arbutin is distributed around the body. It has lower plasma protein binding (about 35-40%) that ensures the availability of higher free concentrations. Tissue distribution studies reveal that the drug selectively distributes to the metabolically active tissues such as the liver and kidneys. This information is relevant since these tissues take part in the metabolism and excretion of arbutin.⁸

➤ Metabolism

Metabolic transformation of arbutin takes place via enzymatic hydrolysis of the compound. In particular, arbutin is transformed into its active metabolite, hydroquinone, by β -glucosidase enzymes present in the intestinal microflora and liver. Then, the metabolites enter phase II metabolism, producing hydroquinone glucuronide and hydroquinone sulfate, more hydrophilic compounds.⁸

➤ Excretion

Elimination of arbutin and its metabolites occurs mainly via renal excretion. Conjugated metabolites of hydroquinone are eliminated in the urine, indicating efficient renal clearance. Pharmacokinetic studies show that the biological half-life of arbutin is quite short and equals to 0.42 ± 0.30 hours, suggesting rapid elimination from the systemic circulation.⁸

Pharmacological Activities of Arbutin

1. Antioxidant Activity

Arbutin is a powerful antioxidant by virtue of its ability to scavenge reactive oxygen species and reduce oxidative stress-mediated cell damage. Arbutin also enhances the body's natural antioxidant defenses system to prevent oxidative damage associated with disease conditions. Antioxidant activity of arbutin has been proven experimentally by the reduction of oxidative stress and free radical-mediated cell damage.²³

2. Anti-Inflammatory Activity

Anti-inflammatory action of arbutin is due to its capability to prevent the formation of inflammatory cytokines like TNF- α and IL-6. Arbutin has an inhibitory effect on inflammation-related signaling pathway including NF- κ B, thus preventing tissue inflammation. Arbutin has shown an ability to suppress inflammatory response and NF- κ B mediated signalling.⁹

3. Antidiabetic Activity

Arbutin exerts its antidiabetic activity by enhancing glucose metabolism and oxidative stress reduction in case of hyperglycemia. Arbutin can also have a protective effect against the damage caused due to diabetes. Arbutin has exhibited its antidiabetic potential by improving metabolic profile and reduction in oxidative stress in experimental diabetic models.¹⁰

4. Antimelanogenic Activity

Arbutin has the property to inhibit tyrosinase enzyme, which is involved in the formation of melanin pigment. As a consequence, less melanin production and hence arbutin's use in hyperpigmentation disorder has been established. Arbutin has been reported as a potent tyrosinase enzyme inhibitor causing its antimelanogenic and skin-lightening activity.²⁴

5. Renoprotective Activity



Renal tissue protection activity of arbutin is due to its antioxidant and anti-inflammatory properties that help prevent progression of diabetic nephropathy. Renal biochemical and histopathological parameters are improved by arbutin treatment in experimental studies. Arbutin has shown its renoprotective activity by reduction of oxidative stress and inflammation in kidney tissue injuries.¹¹

Arbutin is known to exert multifunctional pharmacological effects via tyrosinase inhibition, inflammatory signaling down-regulation through NF- κ B inhibition, oxidative stress reduction, and cellular damage modulation in diabetes, thus resulting in its antioxidant, anti-inflammatory, antimelanogenic, antidiabetic, and renal protective effects.^{25,26}

MECHANISM

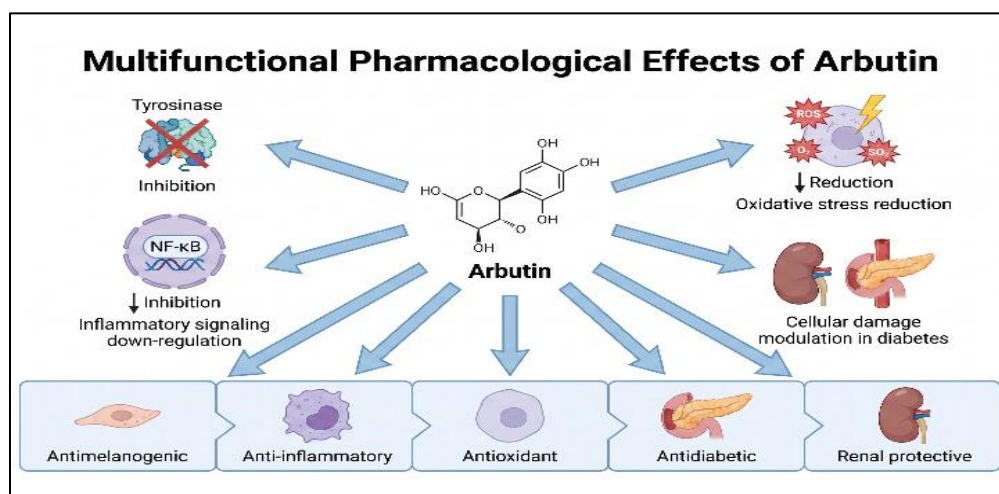


Fig.2 Schematic Mechanism of Arbutin

PHYSICO-CHEMICAL PROPERTIES OF ARBUTIN

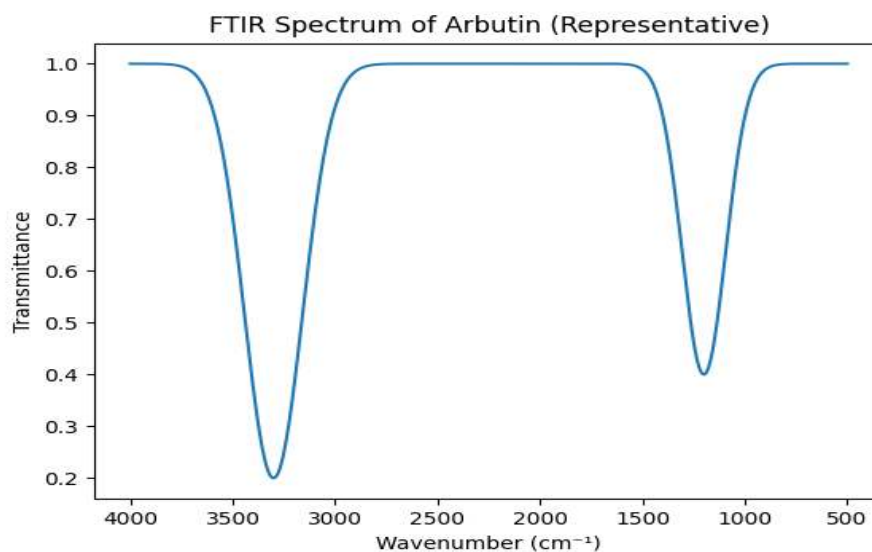
Based on physicochemical properties of arbutin, one can conclude that arbutin is highly soluble in water due to its hydrophilic nature but, however, polarity may affect membrane permeation.

Stability properties, especially concerning hydrolysis in an alkaline or enzymatic environment, are of great importance for biological behavior of arbutin. Moreover, other properties like particle size, PDI, zeta potential, demonstrate good dispersing properties of arbutin.^{16,20,21}

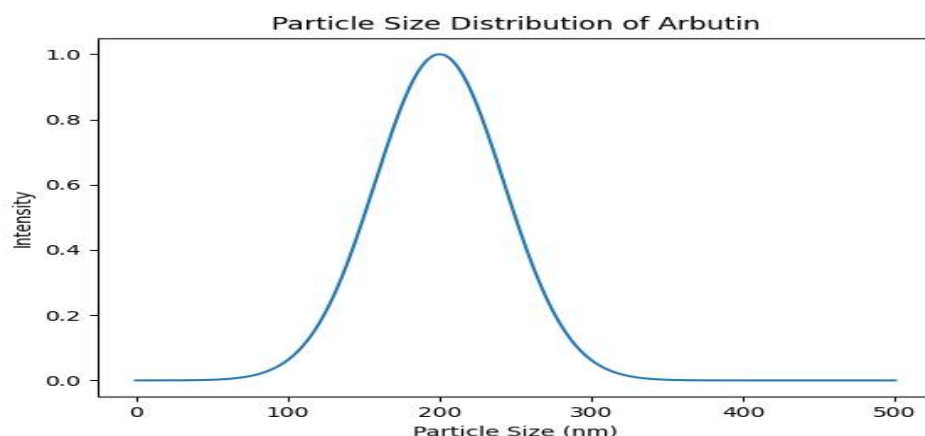
Table 3. The key physicochemical characteristics of arbutin.

Parameter	Description / Observation	Scientific Significance
Chemical Nature	Phenolic glycoside (hydroquinone derivative)	Contributes to antioxidant and biological activity
Molecular Formula	C ₁₂ H ₁₆ O ₇	Defines structural identity and composition
Solubility	Highly soluble in water due to multiple hydroxyl groups	Enhances dissolution but may limit membrane permeability

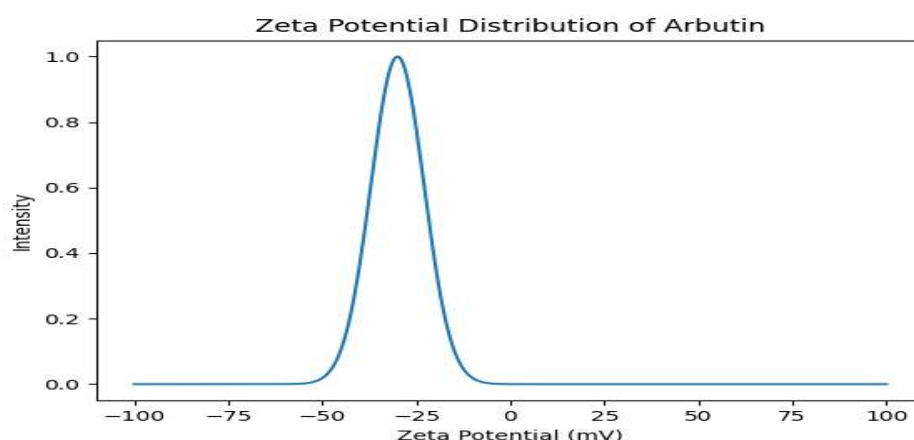
Polarity	Highly polar compound	Influences absorption and distribution behavior
Stability	Stable under neutral conditions; degrades under alkaline or enzymatic conditions	Affects shelf life and biological performance
Hydrolysis Behavior	Converts to hydroquinone and glucose under enzymatic/alkaline conditions	Responsible for pharmacological activity and safety concerns
FTIR Characteristics	O–H stretching ($\sim 3200\text{--}3500\text{ cm}^{-1}$), C–O ($\sim 1000\text{--}1300\text{ cm}^{-1}$)	Confirms functional groups and structural integrity
Particle Size (in systems)	Typically in nano-range when evaluated in dispersions	Influences dissolution rate and bioavailability
Polydispersity Index (PDI)	Generally < 0.3 (uniform systems)	Indicates homogeneity of dispersion
Zeta Potential	Around $\pm 30\text{ mV}$ (stable systems)	Reflects dispersion stability and aggregation tendency
Hydrogen Bonding Capacity	High due to hydroxyl groups	Enhances solubility and interaction with biological systems
Permeability	Moderate to low	May limit systemic bioavailability



(A) FTIR



(B) Particle size



(C) Zeta potential

Fig.3 Representative physicochemical characterization of arbutin showing (A) FTIR spectrum, (B) Particle size distribution, (C) Zeta potential.

LIMITATIONS:

Although arbutin exhibits a promising pharmacological profile, several limitations hinder its widespread application in clinical and therapeutic settings. One of the main challenges is its high hydrophilicity and polarity, which substantially limit its permeability across biological membranes and impair its transdermal absorption efficiency. This physicochemical property ultimately affects its bioavailability and therapeutic efficacy.²⁷

Another significant limitation is its chemical instability under environmental conditions. Arbutin is susceptible to degradation upon exposure to heat, ultraviolet light, and pH variations, leading to hydrolysis into hydroquinone. Such degradation not only reduces its efficacy but also raises safety concerns due to the formation of potentially toxic byproducts.²⁵

Furthermore, the clinical data on the efficacy of arbutin are still limited and inconsistent, as many studies are mostly targeted at topical or cosmetic

applications, not to systemic therapeutic use. Moreover, variations in formulations and experimental conditions render it difficult to establish standardized therapeutic outcomes.²⁸

The molecular makeup of arbutin and interaction with the stratum corneum do not favor skin permeability pharmacokinetics of arbutin and this further decreases the absorption and biological activity of this compound in target tissues.²⁹

To summarize, these limitations underscore the need for future studies to enhance arbutin's stability, bioavailability, and clinical validation for its successful translation into therapeutic applications.

FUTURE PERSPECTIVES

Future works on arbutin should focus on overcoming its limitations and expanding its therapeutic potential. Enhancement of its bioavailability and permeability by structural modifications and advanced delivery approaches is one of the major areas of interest. Moreover, its chemical stability in different environmental and physiological conditions still remains a big challenge to be further investigated.

Well-designed in vivo and clinical studies are also urgently needed to confirm its pharmacological effects and to establish the standardized dosing regimens. Its long-term safety profile should be established in further studies, particularly as it is metabolized to hydroquinone under some circumstances.

Additional research on advanced signaling pathways and target-specific mechanisms at the molecular scale may provide a more detailed understanding of its therapeutic actions. Emerging strategies such as multi-omics analysis and microbial level investigations can be of great

significance for comprehending its complex biological interactions.

Moreover, research on new therapeutic areas apart from dermatologic uses, such as metabolic disorders, renal diseases and inflammatory conditions, might open new avenues for its clinical application. Bridging the gap between experimental and clinical results will require the integration of physicochemical properties with pharmacological effects.

To summarize, arbutin is a promising multifunctional therapeutic agent and further advances in research are anticipated to enhance its clinical relevance and extend its scope in biomedical applications.

CONCLUSION

Arbutin is a natural phenolic glycoside that has drawn great attention due to its various pharmacological properties including antioxidant, anti-inflammatory, antimelanogenic, antidiabetic and renoprotective activities. Its mechanism of action is mostly related to the inhibition of tyrosinase activity, modulation of oxidative stress pathways, and suppression of inflammatory signaling cascades such as NF- κ B. Moreover, its physicochemical properties, such as high aqueous solubility and structural stability under controlled conditions, also help in its biological functionality. However, these advantages are offset by a series of limitations, such as low permeability, possible instability under extreme conditions, and limited clinical validation, which restrict its wider therapeutic application. Moreover, the majority of the available evidence is based on in vitro and preclinical studies with a relatively small number of well-designed clinical studies. These factors underline the gap between experimental results and clinical translation.



Overall, arbutin represents a promising bioactive compound with multifunctional therapeutic potential; however, a deeper understanding of its pharmacokinetics, safety profile, and long-term efficacy is essential for its successful development as a clinically relevant therapeutic agent.

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Ethics statement

No direct interactions with human or animal subjects were involved. Therefore, ethical approval and informed consent were not required.

Conflict of Interest

The author declares no conflict of interest.

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