Icariin: Multi-target natural products for the multi-stage prevention and treatment of breast cancer (Review)

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Received November 6, 2025; Accepted April 23, 2026

DOI: 10.3892/mco.2026.2954

Abstract. The present review examines the intricate relationship between icariin and breast cancer (BC), encompassing foundational theoretical concepts, epidemiological data, diagnostic methodologies, therapeutic approaches, ongoing debates and prospective future developments. The foundational theoretical concepts address the mechanisms through which icariin influences BC pathogenesis, as well as its pharmacokinetic and pharmacodynamic properties and historical context. The epidemiological section analyzes the global incidence and prevalence of BC, alongside its underlying pathophysiology. Diagnostic methodologies are discussed with a focus on imaging technologies, biomarkers, and the innovative role of icariin in advancing diagnostic techniques. Therapeutic approaches investigate icariin's potential as a chemo-preventive agent, its synergistic interactions with conventional therapies and the outcomes of clinical trials. The section on controversies explores discussions surrounding icariin's efficacy, safety and the associated regulatory and ethical considerations. Future directions emphasize emerging trends, the potential for personalized medicine, and future prospects in BC treatment. The present review aims to offer a comprehensive understanding of icariin's role in BC research and therapeutic applications.

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Key words: icariin, breast cancer, natural products, multi-target therapy, chemoprevention

Contents

1. Introduction

In 2022, an estimated 2.3 million new breast cancer (BC) cases and 666,000 BC-related deaths occurred globally, accounting for 23.8 and 15.4% of all cancer cases and deaths in women, respectively. The forecasted BC disability-adjusted life years increased from 238.6 (223.2-254.2) per 100,000 in 2022 to 239.5 (186.9-300.6) per 100,000 in 2050 (1). Over recent decades, there has been a marked increase in the incidence of BC across Asia. In China, this rise is characterized by an earlier onset age compared with Western nations, with incidence peaking at ~50 years of age. This trend has been substantiated by numerous studies. For example, the article 'BC Screening in Asian Countries: Epidemiology, Screening Practices, Outcomes, Challenges and Future Directions' reports that the incidence of BC among Asian women peaks between the ages of 40 and 50, roughly a decade earlier than in Western countries (2). Furthermore, the 2021 Global Burden of Disease Study has revealed that between 1990 and 2021, there was a general increase in the age-standardized incidence rate, disability-adjusted life year rate, and mortality rate of BC among Asian women, with the highest incidence observed in the 50-54 age group (3).

2. Historical perspectives on icariin research

Herba Epimedii, the source of icariin, whose structure is illustrated in Fig. 1, possesses a longstanding history of utilization within traditional Chinese medicine. For millennia, it has been incorporated into various traditional Chinese formulations,

particularly for addressing sexual dysfunction and osteoporosis (4). In recent decades, the advent of modern scientific research has facilitated a more comprehensive exploration of the pharmacological properties of icariin.

Pharmacokinetics of icariin. The pharmacokinetics of icariin have been investigated across various animal models and human subjects. Following the oral administration of *Epimedii* herba extract, which contains icariin, to rats, several primary pharmacokinetic parameters were assessed. Specifically, the maximum concentration (Cmax) of icariin was 0.45-4.11 μg/ml, with a time to reach Cmax of 0.21-0.26 h. The elimination half-lives were determined as follows: t1/2α of 0.06-0.12 h; t1/2β of 2.02-3.48 h. The area under the concentration-time curve from zero to infinity (AUC-∞) was 0.50-2.58 μgh/ml, with a clearance rate of 19.53-44.72 l/kg/h, and a mean residence time of 2.25-3.77 h (5). In comparative studies of icariin and icariside II in rats, it was noted that 91.2% of icariin was converted to icariside II following oral administration, whereas only 0.4% conversion occurred following intravenous administration. Following oral administration, the Cmax and AUC0-t values for icariside II were found to be 3.8 and 13.0-fold greater, respectively, than those of icariin. Conversely, following intravenous administration, the Cmax and AUC0-t values for icariside II were 12.1-4.2% of those observed for icariin, respectively (6).

Icaritin was found to exhibit *in vitro* half-maximal inhibitory concentrations (IC_{50}) in the micromolar range (1-10 μM, equivalent to ~0.4-4 μg/ml), which markedly exceed its pharmacokinetically achievable systemic exposure levels *in vivo*. In preclinical studies, the maximum plasma concentration (C_{max}) following oral administration in animal models was 0.45-4.11 μg/ml, well below the lower bound of its *in vitro* IC_{50} values. In human clinical studies, the parent compound is either undetectable or present only at trace levels in systemic circulation, indicating negligible systemic bioavailability (7,8). Consequently, the *in vitro* antitumor potency of icaritin cannot be translated into systemic therapeutic effects under standard oral dosing regimens. Its observed biological activity *in vivo* is therefore more plausibly attributable to active metabolites, site-specific tissue accumulation [for example, in liver or tumor microenvironments (TME)], or advanced delivery strategies, including nanocarrier-based formulations, that enhance local exposure and bypass first-pass metabolism.

The icariin soft capsule (trade name: Aclaridin), containing icariin as its principal component, received approval from the China National Medical Products Administration (NMPA) in June 2022 (https://www.nmpa.gov.cn/; index number: FGWJ-2022-10076) for the first-line treatment of unresectable hepatocellular carcinoma.

Pharmacodynamics of icariin. In the realm of pharmacodynamics, icariin has demonstrated a range of effects. Research involving estrogen-deficient and other osteoporosis animal models has revealed that *Epimedium* prenylflavonoids, including icariin, confer positive effects on bone health by targeting estrogen signaling and various bone morphogenesis pathways within mesenchymal stem cells (MSCs), osteoblast and osteoclast lineages (9). Furthermore, icariin facilitates the osteogenic differentiation of bone MSCs, as evidenced by increased alkaline phosphatase activity and the upregulation of genes such as collagen type I, osteocalcin and osteopontin (10).

3. BC risk and underlying pathobiological mechanisms

Risk factors and genetic predispositions. Numerous risk factors are associated with BC, with reproductive factors being significant. Women who experience early menarche (before the age of 12), late menopause (after the age of 55), or who have never borne children or had their first child at a later age (after the age of 30) face an elevated risk of developing BC. These reproductive factors are linked to prolonged exposure of breast tissue to estrogen (11).

Molecular and cellular mechanisms in BC. BC is a heterogeneous disease characterized by intricate molecular and cellular mechanisms. At the molecular level, a variety of genetic and epigenetic alterations contribute to its onset and progression. Mutations in genes such as BC gene 1 (BRCA1) and BRCA2 are well-established genetic predispositions for BC, as they can impair DNA repair mechanisms, resulting in genomic instability and an elevated risk of cancer development (12).

Icaritin and BC: Mechanistic insights into signaling pathway modulation and cellular responses. The dysregulation of signaling pathways is critically involved in BC pathogenesis. At the cellular level, the plasticity of cancer cells is a critical determinant in oncogenesis. Icariin has certain correlations with BC at the pathway and cellular levels (Table I). Furthermore, cancer stem cells have been identified within breast tumors. These cells possess the capacity for self-renewal and differentiation into diverse cell lineages, thereby contributing to tumor initiation, recurrence and therapeutic resistance (13).

4. Icariin and BC: Basic theoretical foundations

Our research integrates data from molecules, cells, and animals to elucidate the multidimensional mechanisms behind astragalin's anti-BC effects. Critical issues are addressed, such as drug resistance and material quality differences in clinical applications, thereby enhancing the study's practicality.

Concurrently, research on the anticancer effects of icariin has been advancing. Both *in vitro* and *in vivo* studies have demonstrated that icariin and its derivatives exhibit anticancer activity across a broad spectrum of cancer cell types, including BC cells. These compounds exert their effects through various mechanisms, including the induction of apoptosis, modulation of the cell cycle, inhibition of angiogenesis and metastasis, and immunomodulation.

Mechanisms of icariin in BC pathogenesis. Icariin has been demonstrated to exert anticancer effects through multiple mechanisms in BC. Within the context of osteoclast-related processes, it inhibits the differentiation of pre-osteoclast cells into osteoclasts and suppresses the expression of various genes involved in osteoclast formation and bone resorption. The aberrant activation of the NF-κB pathway has been widely implicated in tumor progression across multiple malignancies, functioning as a central regulator of proliferation, survival

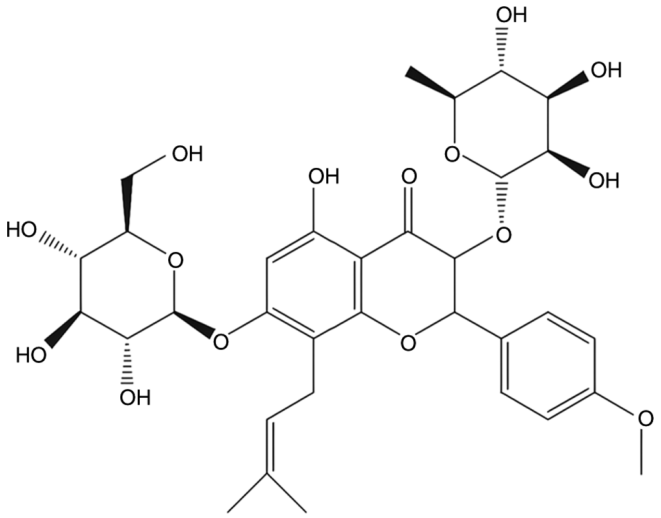

Figure 1. Chemical structure of icariin.

and metastasis (17). Icariin impedes the osteoclastogenesis induced by BC cell lines such as MCF7 and MDA-MB-231 by inhibiting NF-κB activation. Specifically, icariin inhibits receptor activator of NF-κB ligand (RANKL)-stimulated TNF receptor-associated factor 6 (TRAF-6) expression, subsequently suppressing the phosphorylation of ERK, without affecting the activation of p38, c-Jun N-terminal kinase and AKT (23) (Fig. 2).

Regarding cell cycle regulation and apoptosis, icariin exhibits significant effects. In the tamoxifen-resistant BC cell line MCF-7/tamoxifen (TAM), it not only inhibits cell proliferation but also overcomes tamoxifen resistance. Icariin significantly induces cell cycle arrest at the G0/G1 phase and promotes apoptosis, while also suppressing autophagy. At the molecular level, it decreases the expression levels of cyclin-dependent kinase 2 (CDK2), CDK4, cyclin D1, Bcl-2, microtubule-associated protein 1 light chain 3, type I (LC3-I), LC3-II, autophagy-related protein 5 and beclin-1, and increases the expression levels of caspase-3, poly(ADP-ribose) polymerase (PARP) and p62 (Fig. 3) (20).

Effects of icariin on the immune system and stem cells. Icariin suppresses tumor growth and decreases programmed death-ligand 1 expression in murine BC models. It enhances intratumoral infiltration of platelet glycoprotein iiib-positive $(CD41)^+$ and cluster of differentiation 8 $(CD8)^+$ T lymphocytes while reducing the accumulation of myeloid-derived suppressor cells (18). In BC stem cells, icariin primarily targets signaling pathways governing stemness maintenance: It inhibits epithelial-mesenchymal transition (EMT) and stem cell-like phenotypes through the long non-coding RNA nuclear paraspeckle assembly transcript 1 (NEAT1)/TGF-β/Smad family member 2 (SMAD2) axis, and regulates expression of core stemness-associated genes, including aldehyde dehydrogenase 1 (ALDH1), homeobox protein nanog (NANOG) and sry-box transcription factor 2 (SOX2), through microRNAs (miRs) such as miR-148a (21,22). Collectively, these mechanistic insights support icariin's potential to attenuate tumor stemness, thereby limiting recurrence and metastatic progression; however, rigorous preclinical validation and translational studies remain essential prior to clinical evaluation.

Mechanistic basis of icariin-mediated suppression of triple-negative BC (TNBC). In TNBC tissues, the expression of dynamin-related protein 1 (DRP1), a central regulator of mitochondrial fission, is significantly increased. Icariin reduces DRP1 protein levels in a concentration-dependent manner and induces mitochondrial elongation and network consolidation (24). In MDA-MB-231 and MDA-MB-468 cell lines, icariin suppresses the TGF-β1/SMAD2 signaling axis and downregulates canonical EMT effectors, including N-cadherin, vimentin and matrix metalloproteinase-9, thereby inhibiting EMT progression and the associated metastatic potential (25).

Mechanisms of icaritin in BC pathogenesis. Icaritin, a derivative of icariin, has been demonstrated to significantly inhibit the proliferation of MDA-MB-453 and MCF7 BC cell lines. At concentrations of 2-3 μM, icaritin induces cell cycle arrest at the G2/M phase, while concentrations of 4-5 μM lead to apoptotic cell death (26). Furthermore, research on the effects of icariin on bone metabolism has laid the groundwork for its potential application in the prevention and treatment of BC-related bone metastasis. Icariin has been shown to enhance bone formation by promoting the osteogenic differentiation of bone marrow stromal cells and inhibiting osteoclastogenic differentiation, thereby potentially reducing the risk of bone-related complications in BC patients (27).

In TNBC cells, icariin selectively inhibits cell proliferation and induces apoptosis in a concentration- and time-dependent manner. This apoptotic effect is mediated through a mitochondria-dependent pathway, as evidenced by the increased Bax/Bcl-2 ratio and the induction of reactive oxygen species (ROS). In addition, icariin disrupts the activation of the NF-κB/EMT pathway, as indicated by the upregulation of sirtuin 6, which subsequently inhibits the migration and invasion of BC cells (19).

Icariin demonstrates an anti-BC activity in preclinical models, including the estrogen receptor-positive MCF-7 and TNBC MDA-MB-231 cell lines. These findings offer mechanistic insights and a foundational rationale for further investigation. Nevertheless, successful clinical translation hinges on resolving three key translational barriers. In the present study, investigation was centered on the core proposition of translating *in vitro* experimental findings into clinical therapies for human BC and carried out a systematic and critical discourse. An in-depth analysis of the three key challenges impeding the success of such translation was conducted, with the aim of elucidating the current research bottlenecks and providing guidance for future breakthroughs.

(i). Limited physiological relevance of monolayer cell cultures: Conventional two-dimensional (2D) cell line models, despite their experimental utility, fail to recapitulate the structural heterogeneity, dynamic stromal interactions, and metabolic gradients characteristic of human breast tumors. Furthermore, extensive *in vitro* passaging induces genetic and epigenetic drift, diminishing representativeness. Critically, interpatient variability, including differences in menopausal

Table I. Effects of Icariin on key signaling pathways and cellular mechanisms in BC.

First author/s, year	Pathway/ Cellular Mechanism	Role in BC	Effect of icariin	Correlation/Implication	(Refs.)
Sharaky *et al*, 2025	PI3K/AKT/mTOR pathway	Inhibition of this pathway induces cell cycle arrest and apoptosis in BC cells.	Icariin inhibits the phosphorylation of PI3K/AKT/mTOR pathway components.	Suggests potential to suppress tumor growth and survival signaling.	(14)
Noyan and Dedeoğlu, 2025	MAPK/ERK pathway	Activation promotes enhanced cell proliferation and resistance to apoptosis.	Icariin induces apoptosis and counteracts estrogen-induced proliferation via modulation of the ERK/MAPK pathway.	Indicates a possible role in reversing pro-survival signaling in estrogen-responsive BC.	(15)
Wang *et al*, 2025	EMT	Dysregulation of EMT transcription factors enhances migration, invasion and metastasis.	Icariin downregulates EMT-related proteins, impeding the transition process.	Implies a mechanism for reducing BC metastatic potential.	(16)
Li *et al*, 2024	Osteoclastogenesis and NF-κB	Promotion of osteolytic bone metastasis via RANKL-mediated signaling.	Suppression: Inhibits NF-κB activation; downregulates TRAF-6; suppresses ERK phosphorylation (independent of p38/JNK/AKT).	Attenuates Bone Resorption: Inhibits BC cell-induced osteoclast differentiation and bone loss.	(17)
Ran and Yu, 2024	Cell Cycle Control	Dysregulation of CDK-Cyclin complexes driving uncontrolled proliferation.	Arrest: Icariin: G0/G1 phase arrest. Icaritin: G2/M phase arrest (2-3 μM).	Anti-Proliferative: Overcomes tamoxifen resistance; downregulates CDK2, CDK4, and Cyclin D1.	(18)
Song *et al*, 2020	Apoptosis and mitochondrial pathway	Evasion of apoptosis via imbalance of Bcl-2 family proteins.	Induction: Upregulates Cleaved Caspase-3/PARP; downregulates Bcl-2; increases Bax/Bcl-2 ratio and ROS generation.	Pro-Apoptotic: Triggers mitochondrial-dependent intrinsic apoptosis.	(19)
Cheng *et al*, 2019	Autophagy flux	Cytoprotective autophagy sustaining survival of resistant phenotypes.	Inhibition: Downregulates LC3-I/II, Beclin-1, and ATG5; upregulates p62/SQSTM1.	Sensitization: Disrupts survival homeostasis, potentially enhancing cytotoxic effects.	(20)
Ran and Yu, 2024	Tumor immune microenvironment	Immune evasion mediated by PD-L1 and immunosuppressive MDSCs.	Modulation: Downregulates PD-L1; enhances $CD8^+$ T-cell infiltration; reduces MDSC accumulation.	Immuno-restoration: Shifts the microenvironment from immunosuppressive to immunocompetent.	(18)
Song *et al*, 2024; Song *et al*, 2023	Cancer stemness and EMT	Maintenance of stemness and metastatic potential via EMT transcription factors.	Suppression: Inhibits lncRNA NEAT1/TGF-β/Smad2 axis; modulates miR-148a; downregulates N-cadherin, Vimentin, MMP-9.	Anti-Metastatic: Reduces stem cell markers (ALDH1, NANOG, SOX2); inhibits invasion and recurrence.	(21,22)

Summarized from preclinical *in vitro* and *in vivo* studies. BC, breast cancer; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; EMT, epithelial-mesenchymal transition, epithelial-mesenchymal transition; MDSC, myeloid-derived suppressor cell; RANKL, receptor activator of nuclear factor κB ligand.

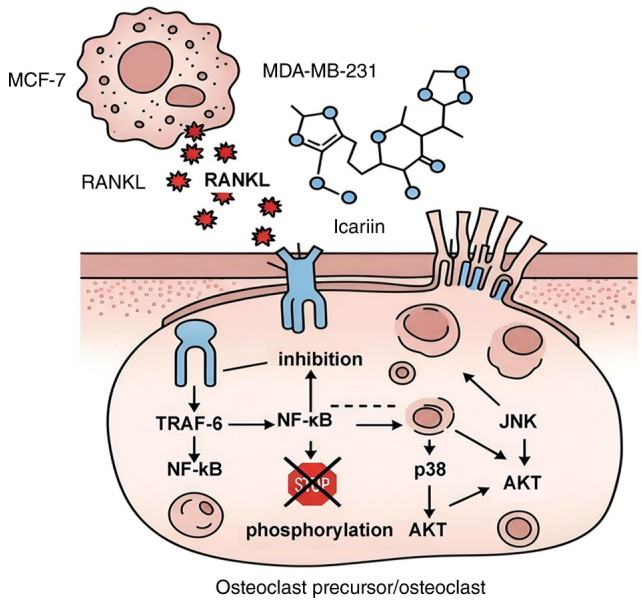

Figure 2. Icariin suppresses breast cancer cell-induced osteoclastogenesis by inhibiting the RANKL/TRAF-6/ERK/NF-κB signaling axis. RANKL, receptor activator of nuclear factor κB ligand; TRAF-6, TNF receptor-associated factor 6; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; AKT, protein kinase B.

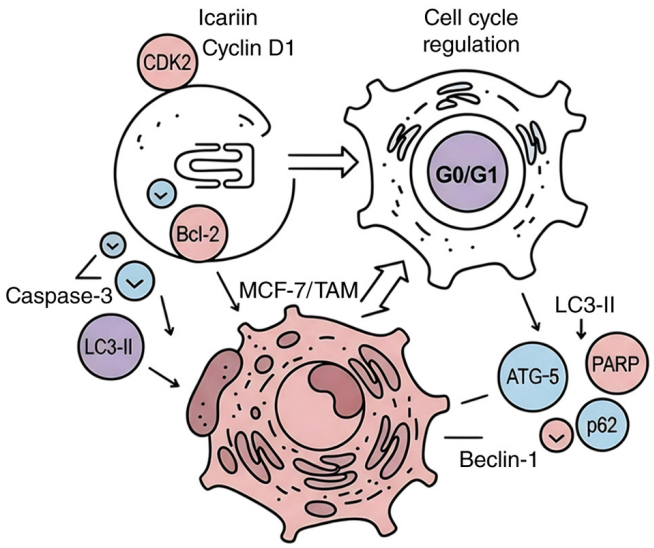

Figure 3. Icariin overcomes tamoxifen resistance in MCF-7 breast cancer cells by inducing G0/G1 arrest, apoptosis and autophagic suppression through the modulation of CDK2, Bcl-2, caspase-3, LC3-II and p62. TAM, tamoxifen; CDK2, cyclin-dependent kinase 2; LC3-II, microtubule-associated protein 1 light chain 3, type II; p62, sequestosome-1; PARP, Poly(ADP-ribose) polymerase; ATG5, autophagy-related protein 5.

status, germline genetics, intratumoral clonal architecture and prior systemic therapy, further undermines the generalizability of *in vitro* efficacy data to diverse clinical populations.

(ii). Pharmacokinetic infeasibility of *in vitro* effective concentrations: The icariin concentrations required for anti-proliferative effects *in vitro* (for example, IC_{50} ≈528 μg/ml, or ~1.0 mmol/l in MCF-7 cells) vastly exceed achievable systemic exposures in humans. Preclinical pharmacokinetic studies indicate peak plasma concentrations of icariin following oral administration rarely exceed low nanomolar ranges, several orders of magnitude below *in vitro* thresholds. Such a profound exposure gap raises fundamental questions about therapeutic feasibility, necessitating strategies to enhance bioavailability or identify more potent analogues.

(iii). Inconsistency in material quality and analytical characterization: Icariin content varies significantly across *Epimedium* species (for example, *E. brevicornum* vs. *E. sagittatum*), cultivation regions, harvest seasons and extraction protocols. Furthermore, commercially available icariin reference standards and botanical preparations frequently lack comprehensive certification of identity, assay purity (>98% by high-performance liquid chromatography), residual solvent levels, and degradation profile under standardized storage conditions. This variability compromises experimental reproducibility, dose-response interpretation, and regulatory acceptability in clinical development.

5. Role of icariin in diagnostic innovations

While icariin is primarily investigated for its therapeutic potential in BC, it may also have implications for diagnostic advancements. Studies on the pharmacokinetics of icariin and its metabolites could inform the development of novel diagnostic methods. For example, the precise quantification of icariin and its metabolites in biological samples could serve as a biomarker-like approach. If distinct alterations in the levels of icariin or its metabolites are observed in BC patients compared with healthy individuals, this could be developed into a diagnostic tool.

In addition, the mechanisms through which icariin influences BC cells may offer valuable insights for the advancement of diagnostic innovations. Given that icariin has the capacity to modulate various signaling pathways within BC cells, a comprehensive understanding of these effects could potentially facilitate the development of diagnostic tests targeting these specific pathways. For example, if the impact of icariin on the NF-κB pathway in BC cells is thoroughly characterized, it may be feasible to create a diagnostic assay that assesses the activation status of this pathway in breast tissue samples, thereby aiding the early detection or prognosis of BC. Nonetheless, further research is required to thoroughly explore and validate these prospective diagnostic applications of icariin.

6. Therapeutic strategies involving icariin

Icariin as a chemo-preventive agent in BC. Icariin has demonstrated potential as a chemo-preventive agent against BC. *In vitro* studies have shown its capability to inhibit the proliferation of BC cells through multiple mechanisms.

For instance, a study investigating the tamoxifen-resistant BC cell line MCF-7/TAM demonstrated that icariin treatment inhibited cellular proliferation, induced cell cycle arrest at the G0/G1 phase and promoted apoptosis. In addition, icariin suppressed autophagy, a process frequently linked to drug resistance in cancer cells. This effect was achieved through the downregulation of proteins such as CDK2, CDK4, cyclin D1, and Bcl-2, alongside the upregulation of caspase-3, PARP and p62. These molecular alterations suggested that icariin may enhance the efficacy of tamoxifen, potentially serving as an adjuvant in cancer chemotherapy.

In TNBC cells, icariin selectively inhibits proliferation and induces apoptosis through a mitochondria-mediated pathway, as evidenced by an increased Bax/Bcl-2 ratio and the induction of ROS. Furthermore, icariin disrupts the activation of the NF-κB/EMT pathway, resulting in the inhibition of cancer cell migration and invasion.

The observed effects indicated that icariin may have the potential to impede the progression of TNBC. Furthermore, icariin has been demonstrated to influence the EMT and stem-cell-like characteristics in BC cells. By modulating the lncRNA NEAT1/TGF-β/SMAD2 signaling pathway, icariin inhibits the proliferation, EMT and stem-cell-like properties of MDA-MB-231 cells, which may contribute to its chemo-preventive properties (21).

Synergistic effects of icariin with conventional therapies. The integration of icariin with conventional therapies has shown promise in increasing the efficacy of BC treatment. In other malignancies, such as acute promyelocytic leukemia (APL), icariin has been shown to enhance the *in vitro* antitumor efficacy of arsenic trioxide (ATO). Icariin inhibits proliferation and induces apoptosis in APL cells, effects that are amplified when combined with ATO. This combination therapy may represent a novel therapeutic strategy for APL patients, and similar synergistic effects warrant exploration in BC treatment (28).

Clinical trials and outcomes of icariin-based treatments. Clinical trials investigating icariin-based treatments for BC remain relatively scarce. Nonetheless, preclinical studies have yielded insights into its potential efficacy. Icariin has demonstrated promising outcomes in studies targeting other diseases. For instance, in a 24-month randomized, double-blind, placebo-controlled clinical trial, icariin proved effective in preventing post-menopausal osteoporosis, exhibiting relatively low side effects. This finding suggested that icariin may possess a favorable safety profile, which is crucial for its prospective application in BC treatment.

In addition, an open-label pilot study examining icariin for co-morbid bipolar and alcohol use disorder reported that icariin was well-tolerated and resulted in a significant reduction in depressive symptoms and alcohol consumption. Although the present study does not directly pertain to BC, it further corroborates the safety profile of icariin (29).

That most clinical trials cited for icariin's safety and efficacy actually pertain to osteoporosis or bipolar disorder, not BC, and that much of the anticancer evidence is based on specific cell lines. In the context of BC treatment, there is a pressing need for additional clinical trials to rigorously assess the efficacy of icariin-based therapies. These trials should comprehensively explore various dimensions, including optimal dosing regimens, potential synergies with other pharmacological agents, and the long-term effects of such treatments. For instance, elucidating the appropriate dosage of icariin when used in conjunction with chemotherapy or targeted therapies could enhance therapeutic outcomes while mitigating adverse effects. Furthermore, it is crucial to investigate the impact of icariin on the quality of life of patients with BC, as this remains a significant consideration for future clinical investigations.

7. Controversies and challenges in icariin research

Debates on the efficacy of icariin in BC. The efficacy of icariin in BC treatment is currently a subject of ongoing debate. Some studies have demonstrated notable anticancer properties of icariin in BC cell lines. Specifically, icariin has been shown to inhibit the proliferation of BC cells, induce apoptosis, and suppress metastatic activity.

Nevertheless, other studies may have yielded less definitive results. The variability in experimental models, the cell lines employed and the treatment conditions may contribute to these discrepancies. Different BC cell lines may exhibit varying responses to icariin due to their intrinsic genetic and molecular differences. Some cell lines may be more susceptible to the effects of icariin, whereas others may demonstrate resistance. Furthermore, the dose-response relationship of icariin in BC treatment remains inadequately defined. Identifying the optimal dose that maximizes efficacy while minimizing toxicity continues to pose a challenge. Currently, there is limited evidence for the use of diosgenin in the treatment of BC in clinical practice. Additional research, particularly well-designed preclinical and clinical studies, is required to elucidate the true efficacy of icariin in BC treatment.

Safety and toxicity concerns of icariin. The safety and toxicity of icariin are critical considerations. Some studies have suggested that icariin possesses a relatively favorable safety profile. In an open-label pilot study of icariin for co-morbid bipolar and alcohol use disorder, icariin was well-tolerated, with no participants withdrawing due to side effects. In a 24-month randomized, double-blind, placebo-controlled clinical trial investigating the efficacy of icariin for postmenopausal osteoporosis, the compound demonstrated effectiveness with relatively low incidence of side effects.

Nevertheless, as with any pharmacological agent, potential safety and toxicity concerns must be considered. *In vitro* studies utilizing certain cell lines may not accurately represent *in vivo* conditions. For instance, although icariin may not exhibit significant cytotoxicity in specific cell lines at particular concentrations, its long-term effects on normal tissues and organs remain inadequately understood. Furthermore, there is a paucity of comprehensive investigations into the potential interactions between icariin and other medications commonly administered to patients with BC. Such interactions could potentially influence the efficacy and safety profiles of both icariin and the concomitant drugs. Consequently, there is a pressing need for more extensive preclinical and clinical safety studies to thoroughly assess the safety and toxicity of icariin in the context of BC treatment.

Regulatory and ethical considerations in icariin research. In the study of icariin, regulatory and ethical considerations are of paramount importance. From a regulatory standpoint, ensuring the quality control of icariin-containing products is essential. Given that icariin is frequently derived from natural sources, maintaining consistent quality with respect to purity, potency and stability presents significant challenges. It is imperative to establish standardized extraction and manufacturing processes to ensure the reproducibility of research findings and the safety and efficacy of icariin-based treatments.

Ethically, in the context of clinical trials investigating icariin for BC, obtaining informed consent from patients is of the utmost importance. Patients must be thoroughly informed about the potential benefits, risks and uncertainties associated with icariin-based treatments. Furthermore, the selection of study participants should be conducted in a fair and unbiased manner, without discrimination based on race, gender or socioeconomic status. In addition, the use of animal models in icariin research must adhere to ethical guidelines. It is imperative to address ethical considerations such as minimizing animal suffering, ensuring adequate housing and care, and providing a robust justification for the use of animals in research.

8. Future directions and innovations

Emerging trends in icariin and BC research. A notable emerging trend in the study of icariin and BC is its potential synergistic application with immunotherapy. Given the promising outcomes of immunotherapy in BC treatment, the integration of icariin with immune checkpoint inhibitors or other immunotherapeutic agents may enhance the antitumor immune response. For instance, icaritin, a derivative of icariin, has demonstrated an ability to increase tumor immunogenicity and increase the antitumor immune response when used in conjunction with intratumoral injection of CpG in a murine melanoma model. Investigating similar strategies in BC could potentially improve the efficacy of immunotherapy (30).

Integrated single-cell and spatial transcriptomic analyses elucidate the dynamic remodeling of the BC TME, revealing mechanistic links between metabolic reprogramming and immune cell adaptation (31). Metabolic reprogramming profoundly influences tumor-immune interactions (32). A notable trend in current research is the investigation of icariin's impact on the TME, which is pivotal in the development, progression and treatment response of BC. Icariin has the potential to modulate the TME by influencing processes such as angiogenesis, immune cell infiltration and the composition of the extracellular matrix. Elucidating these effects may facilitate the creation of novel therapeutic strategies that integrate icariin-based treatments with approaches targeting the TME.

In addition, the application of advanced technologies, particularly nanotechnology, for the delivery of icariin represents an emerging field of study. Nanoparticle-based delivery systems have the capability to enhance the solubility, bioavailability and specificity of icariin. For instance, innovative multifunctional nanoparticles, which are designed to target folic acid, biotin and CD44 receptors and are pH-sensitive, have been developed using icariin and curcumin. These 'nano-actiniaes' have demonstrated increased cytotoxicity and tumor-targeting efficacy in BC therapy.

Potential of icariin in personalized medicine. Icariin exhibits potential as a component of personalized medicine for BC, attributable to its diverse mechanisms of action that may be adapted to specific BC subtypes. In estrogen receptor-positive BC, for instance, icariin may engage distinct pathways compared with its action in TNBC. Elucidating these subtype-specific effects could facilitate the development of personalized therapeutic strategies.

In addition, icariin's capacity to modulate signaling pathways, such as the mechanistic target of rapamycin phosphoinositide 3-kinase (PI3K)/protein kinase b (AKT)/mechanistic target of rapamycin (mTOR) and NF-κB pathways, presents opportunities for its integration into personalized medicine. By assessing the activation status of these pathways in individual patients, icariin could be strategically combined with other pharmacological agents targeting the same or related pathways to optimize treatment outcomes. For example, in patients exhibiting hyperactivation of the PI3K/AKT/mTOR pathway in BC, the concurrent administration of icariin and a PI3K inhibitor may synergistically enhance the suppression of cancer cell proliferation and survival.

Furthermore, the pharmacokinetics of icariin warrant consideration in the context of personalized medicine. Given that the metabolism and distribution of icariin exhibit interindividual variability, elucidating these differences is crucial for determining the optimal dosage and treatment regimen tailored to each patient. Such an approach could enhance the efficacy and safety of icariin-based therapies for patients with BC.

Future prospects for icariin in BC treatment. Although the future potential of icariin in BC treatment appears promising, it requires further investigation. A comprehensive understanding of its mechanisms of action could facilitate the development of icariin as a more targeted and effective therapeutic agent. For instance, if its role in modulating the TME and cancer cell plasticity is fully understood, icariin could be strategically combined with other pharmacological agents to disrupt the tumor-promoting microenvironment and inhibit metastasis.

Future research directions for icariin in BC therapy fall into three priority domains: i) Mechanistic investigation, leveraging patient-derived organoids and patient-derived xenograft models to delineate subtype-specific sensitivity and resistance mechanisms across molecular subtypes of BC; ii) pharmaceutical optimization, developing advanced delivery strategies, including nanocarrier-based formulations and prodrug derivatives, to improve oral bioavailability and tumor-targeting efficiency; and iii) clinical translation, designing and executing early-phase clinical trials to rigorously assess safety, tolerability and preliminary efficacy of icaritin as an adjuvant or combination agent. Notwithstanding these promising avenues, significant translational challenge, including pharmacokinetic limitations, biomarker-defined patient selection and regulatory pathway definition, remain to be addressed.

Acknowledgements

Not applicable.

Funding

The present study was supported by a scientific research project of Notification of the Guiding Projects for Medical and Health Care in Xiamen City in 2020 (grant no. 3502Z20209122).

Availability of data and materials

Not applicable.

Authors' contributions

YW, YYC, LY and XMC collected related literature and drafted the manuscript. TFW, QHP and HYX participated in the design of the review and draft of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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