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Hesperetin as a Potential Drug Candidate for the Treatment of Pancreatic Cancer

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Abstract

Pancreatic cancer remains one of the most lethal malignancies worldwide, characterized by late diagnosis, rapid progression, and poor responsiveness to existing therapeutic modalities. The search for novel, safe, and effective anticancer agents has drawn considerable attention to bioactive natural compounds, particularly flavonoids. Hesperetin, a flavanone derived from citrus fruits, has demonstrated promising anticancer properties in various in vitro and in vivo studies. This mini-review highlights the pharmacological potential of Hesperetin against pancreatic cancer, focusing on its physicochemical and pharmacokinetic profiles, biological activities, and underlying mechanisms of action. Hesperetin exerts anti-proliferative, pro-apoptotic, anti-angiogenic, and anti-metastatic effects through modulation of key oncogenic pathways, including PI3K/Akt/mTOR and NF-κBsignaling. However, its clinical applicability is limited by poor water solubility, low bioavailability, and rapid metabolic degradation. Advanced nanocarrier-based formulations have been proposed to overcome these limitations and enhance therapeutic efficacy. This review also discusses current challenges and outlines future research directions necessary for the clinical development of Hesperetin as a potential therapeutic or adjuvant agent in pancreatic cancer treatment.

Keywords: Hesperetin, Pancreatic cancer, Flavonoids, Anticancer activity, Nanoparticle drug delivery, Natural compounds

1. Introduction

Pancreatic cancer represents one of the most aggressive and lethal malignancies worldwide, ranking as the seventh leading cause of cancer-related mortality. Its prognosis remains exceedingly poor, with a five-year survival rate of less than 10%, primarily due to late diagnosis, early metastatic dissemination, and intrinsic resistance to conventional therapies.[1] The current therapeutic modalities, including surgical resection, systemic chemotherapy (e.g., gemcitabine, FOLFIRINOX), and radiation therapy, offer only limited clinical benefit, particularly in advanced or unresectable stages of the disease. Furthermore, these treatments are often associated with considerable systemic toxicity and marginal improvements in overall survival.[2]

The pathophysiology of pancreatic cancer is complex, involving multiple genetic and epigenetic alterations, deregulation of signaling pathways such as KRAS, PI3K/Akt, NF-κB, and the presence of a dense desmoplastic stroma that impedes drug penetration and fosters immune evasion. These challenges underscore the urgent need for the development of safer, more effective, and targeted therapeutic strategies capable of overcoming these biological barriers.[3]

In recent years, bioactive phytochemicals have garnered increasing interest as potential therapeutic agents for cancer treatment. Among these, flavonoids—polyphenolic compounds widely distributed in fruits, vegetables, and medicinal plants—have emerged as promising candidates due to their broad-spectrum pharmacological activities, including anti-inflammatory, antioxidant, and anticancer effects. Their relatively low toxicity and ability to modulate multiple molecular targets make them attractive alternatives or adjuncts to conventional chemotherapeutics.[4]

Hesperetin, a naturally occurring flavanone derived primarily from citrus fruits such as oranges and lemons, has shown considerable potential as an anticancer agent. It is the aglycone form of hesperidin and is known for its favorable bioactivity profile. Preclinical studies have demonstrated that Hesperetin exerts potent anti-proliferative, pro-apoptotic, and anti-metastatic effects in various cancer models, including pancreatic cancer. These effects are mediated through the modulation of key signaling cascades, suppression of inflammatory mediators, and induction of oxidative stress within tumor cells.[5,6]

Given these attributes, Hesperetin is being increasingly explored as a potential candidate for the treatment of pancreatic cancer. However, despite encouraging laboratory findings, further research is required to overcome pharmacokinetic limitations and to validate its therapeutic efficacy in clinical settings. [7]

2. Physicochemical Profile of Hesperetin

Hesperetin (chemical name: 3′,5,7-trihydroxy-4′-methoxyflavanone) is a naturally occurring flavanone and the aglycone form of hesperidin, a predominant flavonoid glycoside found in citrus fruits. It belongs to the flavonoid subclass of polyphenolic compounds and possesses a typical flavanone backbone structure comprising two aromatic rings (A and B) connected by a three-carbon bridge forming a heterocyclic ring (C-ring). The physicochemical properties of Hesperetin are crucial in determining its solubility, stability, permeability, metabolism, and overall pharmacokinetic and pharmacodynamic behavior, all of which are integral to its effectiveness as a therapeutic agent.[8,9]

2.1 Molecular Structure and Chemical Properties

Hesperetin has the molecular formula $C_{16}H_{14}O_6$, with a molecular weight of 302.28 g/mol. Its chemical structure is characterized by the presence of three hydroxyl groups at positions C-5, C-7, and C-3′, and one methoxy group at position C-4′ of the flavanone skeleton. This configuration is responsible for its antioxidant properties and ability to participate in hydrogen bonding, which significantly influences its solubility and interaction with biological membranes.[10,11]

The compound exists as a yellow crystalline solid and has a melting point of approximately 226–228°C, indicating relatively good thermal stability under physiological conditions. Its structure allows for

tautomeric equilibrium and resonance stabilization, which contributes to its chemical reactivity, particularly in the presence of reactive oxygen and nitrogen species. [12]

2.2 Solubility and Lipophilicity

One of the most significant challenges associated with Hesperetin's therapeutic application is its poor aqueous solubility, which directly affects its oral bioavailability. At physiological pH, Hesperetin exhibits a solubility of approximately 1.5–2.0 µg/mL, classifying it as a Biopharmaceutics Classification System (BCS) Class II compound—characterized by high permeability but low solubility. [13] Its poor solubility is attributed to its hydrophobic aromatic rings and limited ionizable functional groups, making it relatively insoluble in water but soluble in organic solvents such as ethanol, methanol, dimethyl sulfoxide (DMSO), and acetone. [14]

The lipophilicity of Hesperetin is quantified by its partition coefficient (log P), which typically ranges from 2.2 to 2.8, depending on the measurement conditions. This moderate lipophilicity facilitates membrane permeability, enabling Hesperetin to passively diffuse across biological membranes such as the gastrointestinal tract and cellular bilayers. However, excessive lipophilicity may also promote nonspecific tissue binding and rapid metabolism, which could limit its systemic bioavailability. [15]

2.3 pKa and Ionization Behavior

The ionization behavior of Hesperetin is governed by the presence of phenolic hydroxyl groups, which can undergo deprotonation depending on the pH of the surrounding environment. The pKa values of Hesperetin are reported to be around 7.55, 9.47, and 10.34, corresponding to the hydroxyl groups at positions 3′, 5, and 7, respectively. At physiological pH (~7.4), Hesperetin predominantly exists in its neutral or partially ionized form, which allows for reasonable membrane permeability while maintaining some solubility in aqueous media. [16]

Understanding the pKa profile is essential for predicting Hesperetin's absorption, distribution, and interaction with drug transporters or metabolic enzymes. For instance, ionization affects its binding to serum proteins, partitioning into cells, and formulation strategies such as salt formation or encapsulation into nanoparticles.[17]

2.4 Crystallinity and Polymorphism

The crystalline nature of Hesperetin also influences its dissolution rate and, consequently, its bioavailability. Hesperetin typically exists in a crystalline polymorph, which is less soluble than its amorphous counterpart. Studies utilizing techniques such as X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), and Fourier-transform infrared spectroscopy (FTIR) have confirmed its crystalline character with a distinct melting point and enthalpy of fusion.[18]

To overcome the limitations posed by its crystallinity, formulation strategies often aim to convert Hesperetin into amorphous solid dispersions or nano-crystalline forms. These transformations enhance dissolution rates by increasing surface area and reducing lattice energy, thereby improving solubility and absorption in vivo.[19]

2.5 Stability and Degradation

The chemical stability of Hesperetin is influenced by environmental factors such as temperature, pH, light, and oxygen. It is relatively stable under neutral and mildly acidic conditions but undergoes oxidative degradation upon prolonged exposure to air and light. The hydroxyl groups in its structure are prone to oxidation, especially in alkaline environments, leading to the formation of quinones and other degradation products that may compromise biological activity. [20]

Moreover, Hesperetin can be enzymatically conjugated to form glucuronides and sulfates, which may be more water-soluble but less pharmacologically active. These biotransformations, mainly occurring in the liver and intestinal mucosa, significantly affect Hesperetin's half-life and systemic exposure. Therefore, maintaining chemical and metabolic stability is crucial for its therapeutic application.[21]

2.6 Permeability and Absorption

Despite its poor solubility, Hesperetin demonstrates high passive permeability across intestinal epithelial cells, as evidenced by in vitro studies using Caco-2 and MDCK cell models. This high permeability is attributed to its lipophilic nature and small molecular size, which facilitate transcellular diffusion.[22]

In vivo absorption studies suggest that Hesperetin is rapidly absorbed in the gastrointestinal tract, with peak plasma concentrations typically achieved within 1–3 hours post-oral administration. However, first-pass metabolism significantly reduces the bioactive concentration reaching systemic circulation, necessitating strategies to bypass or inhibit this effect.[23]

2.7 Pharmacokinetics and Biotransformation

Following oral administration, Hesperetin undergoes extensive phase II metabolism, primarily glucuronidation and sulfation, catalyzed by uridine 5′-diphospho-glucuronosyltransferases (UGTs) and sulfotransferases (SULTs). The major metabolites detected in plasma and urine include Hesperetin-7-O-glucuronide and Hesperetin-3′-O-glucuronide, which possess diminished biological activity compared to the parent compound.[24]

The plasma half-life of Hesperetin varies between 2 to 4 hours, and it exhibits moderate plasma protein binding (~50–70%). Its elimination occurs predominantly via renal and biliary excretion in conjugated forms. These pharmacokinetic properties underscore the need for delivery systems that can prolong circulation time, enhance tissue targeting, and protect against premature metabolism.[25]

2.8 Implications for Drug Delivery and Formulation

Due to its suboptimal solubility and rapid metabolism, Hesperetin's clinical translation as a therapeutic agent is limited in its native form. As a result, various formulation approaches have been explored to improve its physicochemical and pharmacokinetic properties. These include:

- Nanoformulations such as liposomes, solid lipid nanoparticles (SLNs), and polymeric nanoparticles to enhance solubility and protect against degradation.[26]
- Cyclodextrin complexes to improve aqueous solubility through inclusion complex formation.
- Prodrug strategies aimed at modifying its functional groups to improve membrane permeability or metabolic stability.

- Solid dispersions and micelles to enhance dissolution rates and oral absorption.[27]

These strategies aim to maximize the therapeutic potential of Hesperetin while addressing its inherent physicochemical limitations.

3. Pharmacological Profile of Hesperetin

Hesperetin, a naturally occurring flavanone, represents the aglycone derivative of hesperidin—a major citrus flavonoid abundant in fruits such as oranges, lemons, and tangerines. Upon ingestion of hesperidin-rich foods, enzymatic hydrolysis by intestinal microflora leads to the liberation of Hesperetin, which is subsequently absorbed through the gastrointestinal tract. This compound has garnered significant interest due to its favorable pharmacological properties and potential application in the prevention and treatment of a variety of diseases, including cancer, cardiovascular disorders, and inflammatory conditions.[28,29]

3.1 Absorption, Bioavailability, and Metabolic Fate

Following oral administration, Hesperetin demonstrates rapid but moderate absorption across the gastrointestinal epithelium. Its lipophilic nature facilitates passive diffusion through the intestinal membranes, although its aqueous solubility is limited, which can pose a constraint on its overall absorption efficiency. Despite this, in vivo pharmacokinetic studies in animal models and humans have confirmed that Hesperetin achieves measurable plasma concentrations within 1–3 hours post-administration, indicating relatively good intestinal permeability.[30,31]

The oral bioavailability of Hesperetin is reported to be moderate, typically ranging between 15% and 30%, depending on the formulation and experimental conditions. This limited systemic availability is primarily attributed to extensive first-pass metabolism, wherein Hesperetin undergoes rapid phase II conjugation reactions in the intestinal wall and liver. The primary metabolic pathways include glucuronidation and sulfation, yielding conjugated metabolites such as Hesperetin-7-O-glucuronide and Hesperetin-3′-O-glucuronide, which circulate in the plasma as the predominant forms. While these metabolites exhibit enhanced water solubility and renal excretion, they are generally less biologically active compared to the parent aglycone.[32,33]

3.2 Antioxidant Activity

One of the hallmark pharmacological attributes of Hesperetin is its potent antioxidant capacity. The presence of hydroxyl groups on its aromatic rings allows Hesperetin to act as an effective free radical scavenger, neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS) that contribute to oxidative stress and cellular damage. In vitro studies have demonstrated Hesperetin's ability to inhibit lipid peroxidation, reduce hydrogen peroxide levels, and restore endogenous antioxidant enzyme activities such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx).[34]

This antioxidant property is particularly relevant in the context of carcinogenesis, as oxidative stress plays a pivotal role in DNA damage, genomic instability, and activation of oncogenic pathways. By mitigating oxidative insults, Hesperetin may exert a chemopreventive effect and attenuate the progression of malignant cells.[35]

3.3 Anti-Inflammatory Effects

Hesperetin exhibits significant anti-inflammatory activity, which is central to its pharmacological profile, especially in chronic diseases like cancer where inflammation contributes to tumor initiation, promotion, and metastasis. It has been shown to downregulate the expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) in various cell and animal models. Moreover, Hesperetin suppresses the activation of key transcription factors such as nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1), both of which regulate the transcription of multiple genes involved in inflammatory responses.[36,37]

Additionally, Hesperetin inhibits the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS)—enzymes that are often overexpressed in inflammatory and cancerous tissues. By reducing the levels of prostaglandins and nitric oxide, Hesperetin contributes to the resolution of inflammation and inhibition of the tumor-supportive microenvironment.[38]

3.4 Modulation of Cell Signaling Pathways

A critical aspect of Hesperetin's pharmacological action lies in its ability to modulate a wide range of intracellular signaling pathways implicated in tumorigenesis, proliferation, apoptosis, and metastasis. Several studies have documented the inhibition of the PI3K/Akt/mTOR pathway by Hesperetin, resulting in the suppression of cell growth and promotion of apoptotic cell death in cancer cells, including pancreatic carcinoma models.[39]

In addition to targeting the Akt pathway, Hesperetin also interferes with MAPK/ERK signaling, thereby reducing the phosphorylation of ERK1/2 and downstream effectors involved in cell survival and proliferation. Hesperetin's impact on Wnt/β-catenin, Notch, and STAT3 signaling further underscores its multi-targeted mechanism of action.[40]

The compound has also been shown to enhance the expression of pro-apoptotic proteins such as Bax and caspase-3 while downregulating anti-apoptotic regulators like Bcl-2 and survivin, thereby promoting programmed cell death. These effects are often accompanied by cell cycle arrest at the G0/G1 or G2/M phases, depending on the cancer type and experimental context.[41]

3.5 Anticancer and Anti-Metastatic Properties

Beyond its cytostatic and pro-apoptotic effects, Hesperetin has demonstrated substantial anti-metastatic potential in preclinical cancer models. It inhibits epithelial-mesenchymal transition (EMT), a critical process in cancer metastasis, by downregulating markers such as vimentin, N-cadherin, and Snail, and upregulating E-cadherin. Hesperetin also suppresses matrix metalloproteinases (MMP-2 and MMP-9), which are enzymes involved in the degradation of the extracellular matrix and tumorinvasion.[42,43]

In the context of pancreatic cancer, Hesperetin has shown the ability to inhibit cell proliferation, impair glucose metabolism, and enhance the sensitivity of cancer cells to chemotherapeutic agents. Some studies suggest that Hesperetin can act synergistically with agents like gemcitabine, enhancing their cytotoxic effects while potentially mitigating toxicity.[44]

3.6 Neuroprotective, Cardioprotective, and Antidiabetic Effects

In addition to its anticancer properties, Hesperetin exerts beneficial effects on other physiological systems. Its neuroprotective activity has been demonstrated through attenuation of oxidative stress and inflammation in neuronal cells, making it a candidate for neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease.[45]

Hesperetin's cardioprotective effects are attributed to its ability to improve endothelial function, reduce low-density lipoprotein (LDL) oxidation, and lower blood pressure through vasodilatory mechanisms. It also modulates lipid metabolism and glucose homeostasis, thereby exhibiting antidiabetic effects. These systemic benefits are of particular interest in oncology, where co-morbid conditions may influence treatment outcomes and quality of life.[46]

4. Mechanisms of Anticancer Action

Hesperetin demonstrates significant anticancer activity against pancreatic cancer through a multifaceted mechanism involving the modulation of key molecular pathways associated with tumor cell survival, proliferation, and metastasis.

4.1 Induction of Apoptosis:

Hesperetin promotes apoptosis predominantly via the intrinsic (mitochondrial) pathway. It facilitates the upregulation of pro-apoptotic proteins such as Bax and simultaneously downregulates anti-apoptotic proteins like Bcl-2, thereby shifting the Bax/Bcl-2 ratio in favor of cell death. This alteration leads to mitochondrial outer membrane permeabilization and subsequent activation of downstream effector caspases, particularly caspase-3, which orchestrates the execution phase of apoptosis in pancreatic cancer cells.[47]

4.2 Cell Cycle Arrest:

Another critical mechanism by which Hesperetin exerts its antiproliferative effect is through cell cycle modulation. It has been shown to induce arrest at both the G1 and G2/M phases of the cell cycle. This is achieved through the regulation of cell cycle-related proteins such as cyclins and cyclin-dependent kinases (CDKs), thereby halting DNA replication and mitosis, which suppresses tumor cell proliferation.[48]

4.3 Inhibition of PI3K/Akt/mTOR and NF-κB Pathways:

The PI3K/Akt/mTOR and NF-κBsignaling cascades are frequently hyperactivated in pancreatic cancer and are associated with tumor progression, survival, and chemoresistance. Hesperetin has been reported to inhibit the phosphorylation of Akt and mTOR, thereby attenuating downstream survival signals and enhancing apoptotic sensitivity. Furthermore, Hesperetin suppresses the nuclear translocation and transcriptional activity of NF-κB, leading to reduced expression of its target genes involved in inflammation, proliferation, and anti-apoptosis.[49,50]

4.4 Anti-Angiogenic and Anti-Metastatic Activities:

Hesperetin exhibits anti-angiogenic effects by downregulating the expression of vascular endothelial growth factor (VEGF), a key pro-angiogenic factor involved in neovascularization of tumors. In addition, Hesperetin inhibits the activity of matrix metalloproteinases (MMP-2 and MMP-9), which are responsible for the degradation of extracellular matrix components, a prerequisite for tumor invasion and metastasis. By interfering with these processes, Hesperetin not only impairs the tumor's ability to spread but also disrupts the formation of a supportive vascular network.[51]

Collectively, these mechanisms highlight Hesperetin's potential as a promising multi-targeted agent for the treatment of pancreatic cancer.

5. Challenges and Future Directions

Despite the compelling preclinical evidence supporting Hesperetin's anticancer potential, especially against pancreatic malignancies, several limitations hinder its successful clinical translation. These challenges predominantly relate to its physicochemical properties, pharmacokinetics, and the lack of comprehensive clinical evaluations.

5.1 Physicochemical and Pharmacokinetic Limitations:

Hesperetin suffers from inherently poor aqueous solubility, which severely restricts its dissolution in biological fluids and thereby limits its oral bioavailability. Upon oral administration, only a small fraction of the administered dose is absorbed into systemic circulation, diminishing its therapeutic effectiveness. In addition, Hesperetin is subject to rapid first-pass metabolism in the liver and intestines, where it undergoes conjugation reactions such as glucuronidation and sulfation. These metabolic transformations result in rapid systemic clearance, further reducing the concentration of the active compound available at the tumor site.[52]

5.2 Formulation-Based Challenges and Nano-Delivery Strategies:

To overcome these pharmacokinetic hurdles, recent research has focused on advanced drug delivery systems, particularly nanotechnology-based approaches. Nanoformulations such as polymeric nanoparticles, lipid-based carriers (e.g., liposomes and solid lipid nanoparticles), and polymeric micelles have shown promise in enhancing the aqueous solubility, chemical stability, and bioavailability of Hesperetin. These nanocarriers also facilitate passive and active tumor targeting, enabling preferential accumulation in tumor tissues via the enhanced permeability and retention (EPR) effect and through surface modification with targeting ligands. Moreover, encapsulation within nanosystems can protect Hesperetin from premature degradation and metabolism, thereby prolonging its circulatory half-life and increasing therapeutic efficacy.[53]

5.3 Toxicological and Pharmacological Data Gaps:

While Hesperetin has demonstrated a favorable safety profile in vitro and in animal models, comprehensive toxicological evaluations are still lacking. Detailed investigations are required to assess organ-specific toxicity, immunogenicity, genotoxicity, and potential long-term adverse effects. Such data are critical for establishing the maximum tolerated dose (MTD) and no-observed-adverse-effect level (NOAEL), both of which are essential prerequisites for advancing to human trials.

5.4 Need for Pharmacokinetic Optimization:

Further research is needed to optimize Hesperetin's absorption, distribution, metabolism, and excretion (ADME) characteristics. This includes improving oral bioavailability through prodrug approaches or structural analog design, as well as exploring alternative routes of administration, such as intravenous or intraperitoneal delivery. Pharmacokinetic modeling and simulation studies could be employed to predict systemic exposure, dosing regimens, and therapeutic windows.

5.5 Transition to Clinical Trials:

To date, there are no well-documented clinical trials investigating Hesperetin specifically for pancreatic cancer. This represents a significant bottleneck in its translational journey. Future directions must include

rigorously designed clinical trials to evaluate Hesperetin's safety, tolerability, pharmacokinetics, and therapeutic efficacy in humans. These trials should be supported by robust biomarker analysis and pharmacodynamic endpoints to elucidate the molecular targets and mechanism of action in clinical settings. Additionally, combining Hesperetin with standard chemotherapeutic agents or targeted therapies may offer synergistic effects and should be explored to enhance treatment outcomes.

6. Conclusion

Hesperetin, a naturally occurring flavanone primarily found in citrus fruits, has emerged as a promising candidate in the field of anticancer drug development, particularly for the treatment of pancreatic cancer. Extensive preclinical studies have demonstrated its ability to exert potent anticancer effects through multiple mechanisms, including the modulation of critical oncogenic signaling pathways, induction of programmed cell death, inhibition of cell proliferation, suppression of angiogenesis, and prevention of metastasis. These multi-targeted actions are particularly advantageous in the context of pancreatic cancer, a malignancy characterized by aggressive progression, high metastatic potential, and resistance to conventional therapies.

One of Hesperetin's key therapeutic strengths lies in its ability to interfere with dysregulated molecular pathways commonly associated with pancreatic tumorigenesis, such as the PI3K/Akt/mTOR and NF-κB cascades. Moreover, its pro-apoptotic effects mediated via the mitochondrial pathway and its capacity to induce cell cycle arrest highlight its role in directly impairing tumor cell viability. Such a broad spectrum of biological activities underscores Hesperetin's potential utility not only as a standalone therapeutic agent but also as an adjuvant to enhance the efficacy and reduce the toxicity of existing chemotherapeutic regimens.

Despite these encouraging findings, the clinical translation of Hesperetin remains limited by several pharmacological barriers, including poor aqueous solubility, low oral bioavailability, and rapid systemic clearance. These limitations have prompted the exploration of advanced drug delivery systems—particularly nanotechnology-based formulations—to improve its pharmacokinetic and pharmacodynamic profiles. The application of nanoparticles, liposomes, and polymeric micelles has shown considerable promise in enhancing Hesperetin's stability, bioavailability, and tumor-targeting efficiency, thereby revitalizing its potential for clinical use.

Looking forward, the successful development of Hesperetin as a viable anticancer therapeutic will depend on addressing these formulation challenges through innovative delivery approaches. In parallel, comprehensive in vivo toxicological assessments and well-structured pharmacokinetic studies are essential to establish its safety and efficacy profiles. Most critically, translational research efforts must culminate in the design and execution of robust clinical trials to validate its therapeutic potential in human subjects, particularly those suffering from pancreatic cancer.

In conclusion, Hesperetin represents a compelling natural compound with considerable promise in the treatment of pancreatic cancer. With the integration of formulation science, molecular oncology, and clinical pharmacology, Hesperetin could ultimately contribute to the development of more effective, targeted, and less toxic treatment strategies for this devastating disease.

DECLARATION OF COMPETING INTEREST

The authors confirm that there are no known competing financial interests or personal relationships that could have influenced the findings presented in this paper.

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REFERENCES

1. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: global trends, etiology and risk factors. World journal of oncology. 2019 Feb 26;10(1):10.
2. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, Choné L, Francois E, Artru P, Biagi JJ, Lecomte T. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. New England Journal of Medicine. 2018 Dec 20;379(25):2395-406.
3. Mustafa M, Abbas K, Alam M, Habib S, Hasan GM, Islam S, Shamsi A, Hassan I. Investigating underlying molecular mechanisms, signaling pathways, emerging therapeutic approaches in pancreatic cancer. Frontiers in Oncology. 2024 Jul 17;14:1427802.
4. Batra P, Sharma AK. Anti-cancer potential of flavonoids: recent trends and future perspectives. 3 Biotech. 2013 Dec;3:439-59.
5. Sohel M, Sultana H, Sultana T, Al Amin M, Aktar S, Ali MC, Rahim ZB, Hossain MA, Al Mamun A, Amin MN, Dash R. Chemotherapeutic potential of Hesperetin for cancer treatment, with mechanistic insights: A comprehensive review. Heliyon. 2022 Jan 1;8(1).
6. Barreca D, Mandalari G, Calderaro A, Smeriglio A, Trombetta D, Felice MR, Gattuso G. Citrus flavones: An update on sources, biological functions, and health promoting properties. Plants. 2020 Feb 26;9(3):288.
7. Khan A, Ikram M, Hahm JR, Kim MO. Antioxidant and anti-inflammatory effects of citrus flavonoid Hesperetin: Special focus on neurological disorders. Antioxidants. 2020 Jul 10;9(7):609.
8. Wdowiak K, Walkowiak J, Pietrzak R, Bazan-Woźniak A, Cielecka-Piontek J. Bioavailability of hesperidin and its aglycone Hesperetin—compounds found in citrus fruits as a parameter conditioning the pro-health potential (neuroprotective and antidiabetic activity)—mini-review. Nutrients. 2022 Jun 26;14(13):2647.
9. Jayaraman R, Subramani S, Abdullah SH, Udaiyar M. Antihyperglycemic effect of Hesperetin, a citrus flavonoid, extenuates hyperglycemia and exploring the potential role in antioxidant and antihyperlipidemic in streptozotocin-induced diabetic rats. Biomedicine & Pharmacotherapy. 2018 Jan 1;97:98-106.
10. Sykuła A, Łodyga-Chruścińska E, Garribba E, Kręgiel D, Dzeikala A, Klewicka E, Piekarska-Radzik L. From the physicochemical characteristic of novel Hesperetin hydrazone to its in vitro antimicrobial aspects. Molecules. 2022 Jan 27;27(3):845.

11. Ren Y, Yu D, Wu J, Mao S, Chen P, Chen S, Gao Q, Ye X, Tian J. Preparation and physicochemical properties characterization of Hesperetin-grafted pectin conjugate. International Journal of Biological Macromolecules. 2023 Jul 15;243:124887.
12. Poyraz S, Cimentepe M, Cimentepe OO, Yildirim M. Innovative Nanoformulation Strategies of Hesperetin and Hesperidin: Pioneering Advances in Pharmaceutical Applications (A Review). Russian Journal of Bioorganic Chemistry. 2024 Dec;50(6):2397-425.
13. Srirangam R. Biopharmaceutic and Pharmacokinetic Evaluation of Hesperidin and Hesperetin for Ocular Delivery.
14. Song B, Hao M, Zhang S, Niu W, Li Y, Chen Q, Li S, Tong C. Comprehensive review of Hesperetin: Advancements in pharmacokinetics, pharmacological effects, and novel formulations. Fitoterapia. 2024 Sep 8:106206.
15. Erlund I. Chemical analysis and pharmacokinetics of the flavonoids quercetin, Hesperetin and naringenin in humans.
16. RIETJENS IM. Stereoselective Conjugation, Transport and Bioactivity of S-and R-Hesperetin Enantiomers in Vitro.
17. Boonpawa R. Physiologically based kinetic modelling based prediction of oral systemic bioavailability of flavonoids, their metabolites, and their biological effects (Doctoral dissertation, Wageningen University and Research).
18. Shete G, Pawar YB, Thanki K, Jain S, Bansal AK. Oral bioavailability and pharmacodynamic activity of Hesperetin nanocrystals generated using a novel bottom-up technology. Molecular pharmaceutics. 2015 Apr 6;12(4):1158-70.
19. Stahr PL, Grewal R, Eckert GP, Keck CM. Investigating Hesperetin nanocrystals with tailor-made sizes for the prevention and treatment of Alzheimer's disease. Drug Delivery and Translational Research. 2021 Apr;11:659-74.
20. Lucas-Abellán C, Pérez-Abril M, Castillo J, Serrano A, Mercader MT, Fortea MI, Gabaldón JA, Núñez-Delicado E. Effect of temperature, pH, β-and HP-β-cds on the solubility and stability of flavanones: Naringenin and Hesperetin. LWT. 2019 Jul 1;108:233-9.
21. Salehi B, Cruz-Martins N, Butnariu M, Sarac I, Bagiu IC, Ezzat SM, Wang J, Koay A, Sheridan H, Adetunji CO, Semwal P. Hesperetin's health potential: Moving from preclinical to clinical evidence and bioavailability issues, to upcoming strategies to overcome current limitations. Critical Reviews in Food Science and Nutrition. 2022 Jun 1;62(16):4449-64.
22. Nakashima M, Goda N, Tenno T, Kotake A, Inotsume Y, Amaya M, Hiroaki H. Pharmacologic Comparison of High-Dose Hesperetin and Quercetin on MDCK II Cell Viability, Tight Junction Integrity, and Cell Shape. Antioxidants. 2023 Apr 18;12(4):952.
23. Martinez S. Pharmacokinetic and pharmacodynamic investigations of select natural products and nutraceuticals for human and veterinary health.
24. Jiang W. Mechanisms of Interplay between UGTs and Efflux Transporters in Flavonoid Disposition.
25. Najmanová I, Vopršalová M, Saso L, Mladěnka P. The pharmacokinetics of flavanones. Critical reviews in food science and nutrition. 2020 Oct 10;60(18):3155-71.
26. Amoabediny G, Haghiralsadat F, Naderinezhad S, Helder MN, Akhoundi Kharanaghi E, MohammadnejadArough J, Zandieh-Doulabi B. Overview of preparation methods of polymeric and lipid-based (niosome, solid lipid, liposome) nanoparticles: A comprehensive review.

International Journal of Polymeric Materials and Polymeric Biomaterials. 2018 Apr 13;67(6):383-400.

27. Choi JS, Cho NH, Kim DH, Park JS. Comparison of paclitaxel solid dispersion and polymeric micelles for improved oral bioavailability and in vitro anti-cancer effects. Materials Science and Engineering: C. 2019 Jul 1;100:247-59.
28. Li C, Schluesener H. Health-promoting effects of the citrus flavanone hesperidin. Critical reviews in food science and nutrition. 2017 Feb 11;57(3):613-31.
29. Ahmed OM, AbouZid SF, Ahmed NA, Zaky MY, Liu H. An up-to-date review on citrus flavonoids: chemistry and benefits in health and diseases. Current Pharmaceutical Design. 2021 Mar 1;27(4):513-30.
30. Actis-Goretta L, Dew TP, Lévèques A, Pereira-Caro G, Rein M, Teml A, Schäfer C, Hofmann U, Schwab M, Eichelbaum M, Crozier A. Gastrointestinal absorption and metabolism of Hesperetin-7-O-rutinoside and Hesperetin-7-O-glucoside in healthy humans. Molecular Nutrition & Food Research. 2015 Sep;59(9):1651-62.
31. Wang M, Zhao H, Wen X, Ho CT, Li S. Citrus flavonoids and the intestinal barrier: Interactions and effects. Comprehensive reviews in food science and food safety. 2021 Jan;20(1):225-51.
32. Akhter S, Arman MS, Tayab MA, Islam MN, Xiao J. Recent advances in the biosynthesis, bioavailability, toxicology, pharmacology, and controlled release of citrus neohesperidin. Critical Reviews in Food Science and Nutrition. 2024 Jun 10;64(15):5073-92.
33. Kim JY, Jung KJ, Choi JS, Chung HY. Hesperetin: a potent antioxidant against peroxynitrite. Free radical research. 2004 Jul 1;38(7):761-9.
34. Brewer MS. Natural antioxidants: sources, compounds, mechanisms of action, and potential applications. Comprehensive reviews in food science and food safety. 2011 Jul;10(4):221-47.
35. Cheng Q, Mao L, Huang H, Tang L, Jiang H, Zhang Y, Mu Q. Hesperetin ameliorates glioblastoma by inhibiting proliferation, inducing apoptosis, and suppressing metastasis. Translational Cancer Research. 2022 Jun;11(6):1781.
36. Tejada S, Pinya S, Martorell M, Capó X, Tur JA, Pons A, Sureda A. Potential anti-inflammatory effects of hesperidin from the genus citrus. Current medicinal chemistry. 2018 Nov 1;25(37):4929-45.
37. Benavente-Garcia O, Castillo J. Update on uses and properties of citrus flavonoids: new findings in anticancer, cardiovascular, and anti-inflammatory activity. Journal of agricultural and food chemistry. 2008 Aug 13;56(15):6185-205.
38. Ren H, Hao J, Liu T, Zhang D, Lv H, Song E, Zhu C. Hesperetin suppresses inflammatory responses in lipopolysaccharide-induced RAW 264.7 cells via the inhibition of NF-κB and activation of Nrf2/HO-1 pathways. Inflammation. 2016 Jun;39(3):964-73.
39. Adan A, Baran Y. Fisetin and Hesperetin induced apoptosis and cell cycle arrest in chronic myeloid leukemia cells accompanied by modulation of cellular signaling. Tumor Biology. 2016 May;37:5781-95.
40. Kim JY, Jung KJ, Choi JS, Chung HY. Modulation of the age-related nuclear factor-κB (NF-κB) pathway by Hesperetin. Aging Cell. 2006 Oct;5(5):401-11.
41. Kim GD. Hesperetin inhibits vascular formation by suppressing of the PI3K/AKT, ERK, and p38 MAPK signaling pathways. Preventive nutrition and food science. 2014 Dec 31;19(4):299.

42. Rajendran P. Unveiling the power of flavonoids: A dynamic exploration of their impact on cancer through matrix metalloproteinases regulation. Biomedicine. 2024 Jun 1;14(2):12.
43. Amawi H, Ashby Jr CR, Samuel T, Peraman R, Tiwari AK. Polyphenolic nutrients in cancer chemoprevention and metastasis: Role of the epithelial-to-mesenchymal (EMT) pathway. Nutrients. 2017 Aug 21;9(8):911.
44. Deldar Abad Paskeh M, Asadi S, Zabolian A, Saleki H, Khoshbakht MA, Sabet S, Naghdi MJ, Hashemi M, Hushmandi K, Ashrafizadeh M, Mirzaei S. Targeting cancer stem cells by dietary agents: an important therapeutic strategy against human malignancies. International Journal of Molecular Sciences. 2021 Oct 28;22(21):11669.
45. Hajialyani M, Hosein Farzaei M, Echeverría J, Nabavi SM, Uriarte E, Sobarzo-Sánchez E. Hesperidin as a neuroprotective agent: a review of animal and clinical evidence. Molecules. 2019 Feb 12;24(3):648.
46. Mirzaei A, Mirzaei A, Khalilabad SN, Askari VR, Rahimi VB. Promising influences of hesperidin and Hesperetin against diabetes and its complications: a systematic review of molecular, cellular, and metabolic effects. EXCLI journal. 2023 Dec 4;22:1235.
47. Zhang J, Song J, Wu D, Wang J, Dong W. Hesperetin induces the apoptosis of hepatocellular carcinoma cells via mitochondrial pathway mediated by the increased intracellular reactive oxygen species, ATP and calcium. Medical Oncology. 2015 Apr;32:1-1.
48. Wang Y, Yu H, Zhang J, Gao J, Ge X, Lou G. Hesperidin inhibits HeLa cell proliferation through apoptosis mediated by endoplasmic reticulum stress pathways and cell cycle arrest. BMC cancer. 2015 Dec;15:1-1.
49. Zughaibi TA, Suhail M, Tarique M, Tabrez S. Targeting PI3K/Akt/mTOR pathway by different flavonoids: a cancer chemopreventive approach. International Journal of Molecular Sciences. 2021 Nov 18;22(22):12455.
50. Samec M, Mazurakova A, Lucansky V, Koklesova L, Pecova R, Pec M, Golubnitschaja O, Al-Ishaq RK, Caprnda M, Gaspar L, Prosecky R. Flavonoids attenuate cancer metabolism by modulating lipid metabolism, amino acids, ketone bodies and redox state mediated by Nrf2. European Journal of Pharmacology. 2023 Jun 15;949:175655.
51. Wei Q, Zhang YH. Flavonoids with anti-angiogenesis function in cancer. Molecules. 2024 Mar 31;29(7):1570.
52. Srirangam R, Hippalgaonkar K, Majumdar S. Intravitreal kinetics of hesperidin, Hesperetin, and hesperidin G: effect of dose and physicochemical properties. Journal of pharmaceutical sciences. 2012 Apr 1;101(4):1631-8.
53. Saeed Y, Zhong R, Sun Z. Advances in traditional herbal formulation based nano-vaccine for cancer immunotherapy: Unraveling the enigma of complex tumor environment and multidrug resistance. International Immunopharmacology. 2024 May 10;132:111948.