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ЭВОЛЮЦИЯ ПРОТИВОРАКОВЫХ СВОЙСТВ РЕСВЕРАТРОЛА: АНАЛИЗ ГЛОБАЛЬНОГО ПАТЕНТНОГО ЛАНДШАФТА

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Ресвератрол – природное фенольное соединение с разнообразной биологической активностью, включая противораковые, противовоспалительные и нейропротекторные эффекты, долгое время сталкивался с препятствиями в клиническом применении из-за низкой биодоступности, химической нестабильности и быстрого метаболизма. На основе глобальных патентных данных данное исследование представляет собой углубленный анализ патентного ландшафта ресвератрола в области терапии рака, с акцентом на конкурентов, технологическую эволюцию и стратегические тенденции развития. Особое внимание уделяется тому, как академические круги и промышленность пытались преодолеть узкие места в применении препаратов посредством модификации молекулярной структуры, синергетической комбинированной терапии и передовых нанодоставочных систем. Предложены стратегические рекомендации для будущего развития и клинического применения противораковых препаратов на основе ресвератрола.

Ключевые слова: патентный анализ; ресвератрол; противораковые препараты; молекулярная оптимизация; повышение биодоступности.

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RESVERATROLS ANTICANCER EVOLUTION: A GLOBAL PATENT LANDSCAPE ANALYSIS

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Resveratrol, a naturally occurring phenolic compound with diverse biological activities including anticancer, anti-inflammatory, and neuroprotective effects, has long faced obstacles in clinical translation due to its low bioavailability, chemical instability, and rapid metabolism. Based on global patent data, this study provides an in-depth analysis of the patent landscape of resveratrol in the field of cancer therapy, focusing on competitive players, technological evolution, and strategic development trends. Particular emphasis is placed on how academia and industry have attempted to overcome application bottlenecks through molecular structural modification, synergistic combination therapies, and advanced nanodelivery systems. This analysis aims to offer strategic insights for the future development and clinical application of resveratrol-based anticancer drugs.

Keywords: patent analysis; resveratrol; anticancer drugs; molecular optimization; bioavailability enhancement

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Introduction

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a non-flavonoid polyphenolic compound widely distributed in nature [1]. Since its first isolation in 1940 from the roots of *Veratrum grandiflorum*, this natural phytoalexin has become a research hotspot in medicinal chemistry and modern oncology [2]. From a botanical perspective, resveratrol is synthesized by higher plants as a self-protective response to environmental stresses such as ultraviolet radiation, mechanical injury, or fungal infection [3]. However, its significance in human medicine was not widely recognized until the «French Paradox» was proposed in 1992, which described the unexpectedly low mortality from cardiovascular diseases among French populations despite a high-fat diet—an observation attributed in part to regular consumption of resveratrol-containing red wine [4]. In 1997, Jang et al. published a landmark study in *Science* demonstrating that resveratrol could prevent skin cancer in mice, formally initiating global research into its anticancer potential [5].

Resveratrol exhibits pronounced pleiotropic biological effects, encompassing antioxidant, anti-inflammatory, neuroprotective, and anti-aging activities, and demonstrates significant intervention potential across all four critical stages of carcinogenesis: initiation, promotion, progression, and metastasis formation [6]. Pharmacological evidence indicates that resveratrol effectively inhibits a wide range of malignancies, including hepatocellular carcinoma, thyroid cancer, lung cancer, breast cancer, colorectal cancer, and various hematological malignancies [7]. Despite these encouraging experimental findings, the clinical translation of resveratrol is severely hampered by a classic «pharmacokinetic paradox» common to natural compounds – extremely low systemic bioavailability, primarily due to poor aqueous solubility, high photosensitivity, chemical instability, and rapid intestinal and hepatic metabolism [8].

To overcome these challenges, pharmaceutical companies and research institutions worldwide have engaged in intensive patent activities. Comprehensive searches and analyses of Himmpat and other global patent databases reveal that resveratrol-based anticancer technologies have converged into three major innovation pathways: structural modification, synergistic combination formulations, and advanced nanodelivery systems. From a patent analytics perspective, this report systematically reviews the global evolution of resveratrol-related anticancer technologies and provides an in-depth interpretation of the latest pharmacological discoveries and formulation innovations emerging between 2016 and 2025.

Data Sources and Methods

Patent data were retrieved from the Himmpat patent search engine using a combination of keywords and International Patent Classification (IPC) codes related to resveratrol and cancer. The search strategy was as follows:(resveratrol OR stilbenotriol OR trihydroxystilbene OR polydatin)/TAC AND (cancer OR tumor OR tumour OR carcinoma)/

TAC,where TAC denotes searches within titles, abstracts, and claims. A total of 4,704 patent records were initially retrieved. After deduplication and consolidation of simple patent families, 1,618 patents remained. These patents were then manually curated and indexed to extract valid technical information for subsequent patent analysis.

Statistical Results

Global Patent Landscape and Macro-Trend Analysis. Patent data not only reflect technological innovation but also serve as indicators of industrial capital flows. Analysis of resveratrol-related anticancer patents provides insights into the maturity and competitive structure of this field.

Over the past two decades, patent applications related to resveratrol's anticancer applications have demonstrated distinct stage-wise growth. Between 2016 and 2024, global patent filings showed an overall upward trend. Following 2018, the rise of nanotechnology and precision medicine accelerated patent activity. In 2024, global applications reached a historical peak of 124 filings, indicating that the technology has entered a deep phase of industrialization. Although post-2024 data appear to decline due to the standard 18-month patent publication lag, actual innovation activity remains robust. This trend suggests a paradigm shift from «functional discovery» to «drugability optimization». Notably, invention patents account for 99.69 % of filings, consistent with the characteristics of the biomedical sector, where core competitiveness lies in novel compounds, new therapeutic uses, and complex formulations rather than incremental device improvements (Fig. 1).

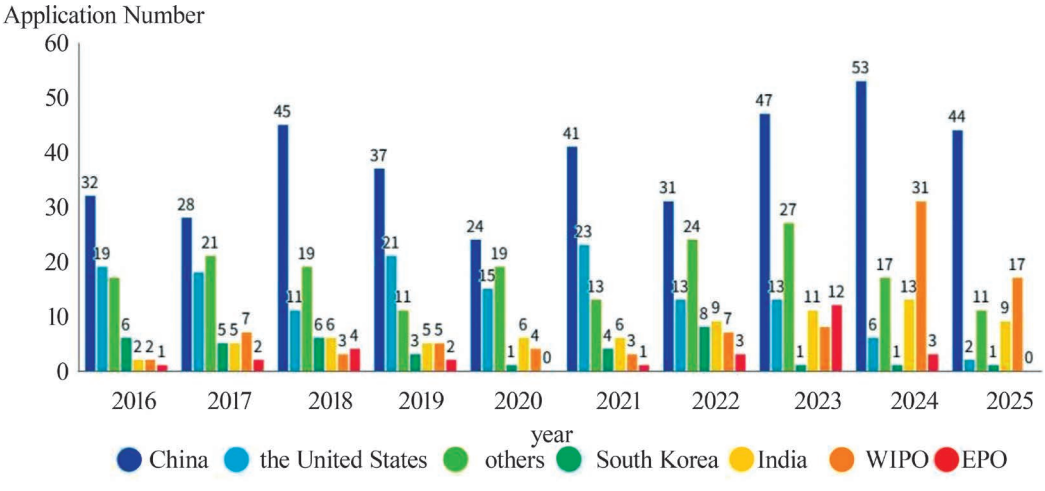


Fig. 1. Trends in patent applications for resveratrol in anti-tumor applications (2016–2025)

Analysis by Patent Office. Analysis of patent publication authorities reveals the target markets and competitive R&D landscape of resveratrol-based anticancer technologies. China dominates this field with 382 patent applications, followed by the United States (141), India (72), and the World Intellectual Property Organization (WIPO, 87). South Korea (36) and Europe (28) also demonstrate active research engagement. These data indicate that, driven by modern pharmacology, resveratrol has become a globally recognized focus in natural anticancer drug development (Fig. 2).

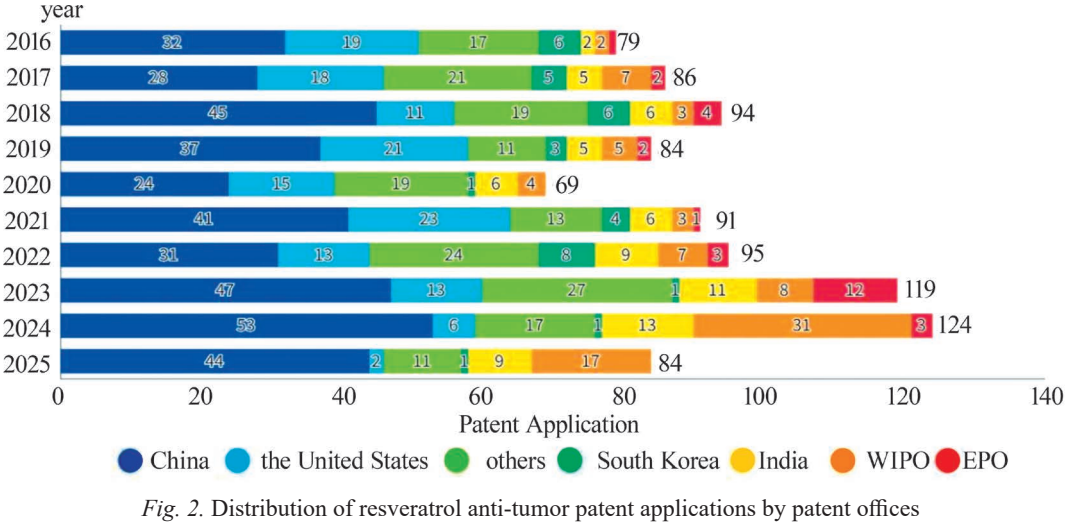


Fig. 2. Distribution of resveratrol anti-tumor patent applications by patent offices

Legal Status of Global Patents. The legal status distribution of resveratrol-related anticancer patents exhibits marked heterogeneity, as shown in Fig. 3. Invalid patents account for 52.16 %, possibly due to technological obsolescence, strategic market realignment, or shifts in R&D focus, leading to discontinuation of maintenance fees. Active and pending patents together represent 45.65 %, indicating substantial remaining R&D and market potential. Additionally, 3.10 % of international applications filed under the Patent Cooperation Treaty (PCT) remain within the designation phase.

Overall, while R&D activity in this field remains vigorous, the high proportion of lapsed patents underscores the importance of optimized patent maintenance and protection strategies in future research and commercialization efforts.

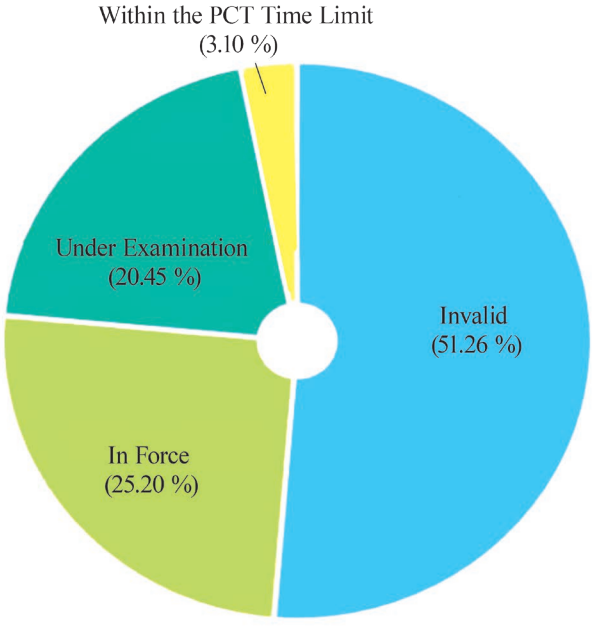


Fig. 3. Global patent legal validity of resveratrol in antitumor applications

Key Research Directions

Structural Modification of Resveratrol. Given its susceptibility to oxidation and phase II metabolism (glucuronidation and sulfation), precise chemical modification of resveratrol represents a core focus of patent activity [9]. By altering physicochemical properties, researchers aim to develop «drug-like» molecules with enhanced bioactivity, metabolic stability, and target specificity.

The three phenolic hydroxyl groups (positions 3, 5, and 4′) are both the source of resveratrol's activity and its instability. Introducing protective groups can effectively reduce first-pass metabolism. One strategy is glycosylation, whereby conjugation of sugar moieties to phenolic hydroxyls improves water solubility and facilitates transporter-mediated cellular uptake. Tom Desmet, et al. [10] disclosed a novel conjugate linking the C-6 position of glucose to resveratrol, which retained anticancer activity while exhibiting improved physicochemical stability and reduced neurotoxicity. Another strategy involves methoxylation. Pterostilbene, a natural dimethyl ether derivative of resveratrol, displays significantly enhanced lipophilicity and metabolic stability, resulting in superior absorption, bioavailability, and blood–brain barrier penetration compared to resveratrol [11].

Additionally, the central double bond of the stilbene scaffold and the substitution patterns of the phenyl rings are critical for activity. Replacing the trans-double bond with alternative linkages has yielded analogues with improved bioavailability. Some studies have developed entirely new structures by substituting the double bond, leading to novel lysine-specific demethylase 1 (LSD1) inhibitors with potent anticancer potential [12].

Synergistic Combination Therapies. Because tumorigenesis involves multiple interconnected signaling pathways, monotherapy is often insufficient. Owing to its low toxicity and pleiotropic effects, resveratrol has become a prominent component in chemosensitization and combination therapy patents.

Studies have shown that co-administration of curcumin and resveratrol produces enhanced cytotoxic effects, associated with increased endoplasmic reticulum stress and upregulation of the pro-apoptotic UPR protein CHOP. This synergy is also linked to curcumin-induced pro-survival autophagy and resveratrol-mediated autophagy inhibition [13]. Other studies indicate that nanoformulations combining resveratrol and quercetin enhance the control of colorectal cancer cell proliferation by modulating CRC-related pathways such as Wnt, PI3K/AKT, caspase-3, MAPK, and NF-κB [14].

Moreover, resveratrol can improve the therapeutic window of conventional chemotherapeutics. For example, combination therapy with doxorubicin (DOX), cyclophosphamide (CP), and resveratrol can prevent chemoresistance, enhance apoptosis, and induce cell cycle arrest. Resveratrol also increases tumor sensitivity to DOX and CP by inhibiting migration and metastasis [15]. Given that DOX-induced cardiotoxicity is a major clinical concern, Alanazi et al. [16] demonstrated that resveratrol confers cardioprotection by modulating oxidative stress, inflammation, S100A1, and sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a).

Nanotechnology-Driven Drug Delivery Systems. The most effective approach to overcoming resveratrol's bioavailability limitations lies in advances in physical encapsulation technologies. Nanodelivery systems, ranging from liposomes to metal–organic frameworks, have become major growth drivers in patent filings.

Amphiphilic block copolymer micelles can encapsulate hydrophobic resveratrol within their core, significantly enhancing dispersion in aqueous environments. Zhang, et al. [17] developed resveratrol-loaded systems using PEO-based and PLGA-based copolymers, achieving sustained release and potent inhibition of breast cancer cell growth.

Beyond synthetic systems, lipid-based carriers, polymeric nanoparticles, nanocrystals, inorganic nanoparticles, nanoemulsions, protein nanoparticles, exosomes, macrophages, and erythrocytes have demonstrated substantial potential for improving solubility, biocompatibility, and therapeutic efficacy [18]. Compared with synthetic carriers, biologically derived vectors exhibit superior biodistribution, cellular uptake, controlled release, and reduced toxicity. However, challenges in large-scale production highlight the need for innovative delivery systems for poorly soluble natural products such as resveratrol. Further studies are required to elucidate pharmacokinetics, biodistribution, toxicity, and *in vivo* performance of resveratrol nanoformulations.

Breakthroughs in Pharmacological Mechanisms (2021–2025)

Over the past five years, resveratrol research has increasingly focused on tumor metabolism and microenvironmental regulation, generating several transformative hypotheses [19].

Tumor cells preferentially rely on aerobic glycolysis – the Warburg effect – even under normoxic conditions [19]. Resveratrol has been shown to downregulate phosphoglycerate kinase 1 (PGK1), disrupting tumor energy supply. In BT-549 breast cancer cells, resveratrol significantly reduced PGK1 accumulation, inducing energy crisis and apoptosis [20]. Resveratrol also interferes with lipid metabolism, inhibiting de novo fatty acid synthesis required for membrane biogenesis, thereby reducing tumor invasiveness and survival [21].

Recent studies reveal that resveratrol induces upregulation and oligomerization of voltage-dependent anion channel 1 (VDAC1), triggering mitochondrial membrane permeabilization and cytochrome C release, thereby activating intrinsic apoptotic cascades [22]. Khanvilkar, et al. [23] reported that chromatin fragments released from dying cancer cells can enter healthy cells and induce mutations leading to metastasis. Resveratrol-copper complexes generate trace reactive oxygen species capable of selectively inactivating these chromatin fragments from dying cancer cells(cfChPs) without damaging genomic DNA, offering a novel strategy for preventing postoperative metastasis.

Thus, the tumor microenvironment is no longer viewed as a passive background but as an active therapeutic target.

Conclusion and Outlook

Despite intense patent activity, a significant gap remains between resveratrol research and clinical translation. A large meta-analysis published in 2025 systematically evaluated the oral bioavailability of resveratrol in humans [24], encompassing 84 clinical dosing regimens. Results showed that even at high oral doses, the mean peak plasma concentration of free resveratrol remained far below the micromolar levels required for anticancer activity in vitro. The study identified an optimal oral dosing window that balances bioavailability and minimal adverse effects.

Future patent strategies should therefore avoid overcrowded apoptotic pathways and instead focus on metabolic reprogramming targets (e.g., PGK1, VDAC1) and tumor microenvironment components such as cancer-associated fibroblasts and cfChPs [25]. Leveraging resveratrol's chemosensitizing properties in combination with immune checkpoint inhibitors or antibody-drug conjugates, as well as developing environmentally responsive smart delivery systems (pH, redox, photothermal), will be critical for concentrating effective drug levels at tumor sites.

Future competition will increasingly shift from wet-lab experimentation to in silico innovation. Artificial intelligence is being employed to predict binding affinities of resveratrol analogues to kinase targets, optimize nanocarrier design, and develop environmentally sustainable synthetic routes free of heavy-metal catalysts.

In summary, resveratrol-based anticancer technologies are undergoing a transformation from broad-spectrum polyphenols to precision microenvironment modulators. Although bioavailability remains a major challenge, advances in nanotechnology and molecular optimization are gradually bridging this gap. This ancient natural compound, empowered by modern molecular biology and nanotechnology, is poised to play an increasingly vital role in the fight against malignant tumors.

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