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Gigantol: a principal bioactive constituent of *Dendrobium* species—multi-target mechanisms, network pharmacology, and therapeutic perspectives

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ABSTRACT

Ethnopharmacological relevance: Gigantol, a naturally occurring bibenzyl compound isolated mainly from *Dendrobium* species, is traditionally used in Chinese and Southeast Asian medicine to nourish Yin, reduce internal heat, and treat inflammation-related diseases. Its broad pharmacological activities support its traditional applications and highlight its potential as a therapeutic agent.

Aim of the study: This review compiles existing evidence regarding the phytochemistry, pharmacological effects, pharmacokinetics, and molecular mechanisms of gigantol, while highlighting critical research gaps and future development directions.

Materials and methods: An extensive literature search was conducted using the PubMed and China National Knowledge Infrastructure (CNKI) databases until June 2025. Data on gigantol extraction, pharmacological activities, *in vitro* and *in vivo* studies, molecular docking, network pharmacology, and pharmacokinetics were collected and analyzed.

Results: Gigantol exhibits polypharmacological properties, including anticancer, antidiabetic, anti-inflammatory, and antioxidant activities. It modulates signaling pathways such as Phosphoinositide 3-kinase/Protein Kinase B (PI3K/Akt), Wingless/Integrated-1/β-catenin (Wnt/β-catenin), Nuclear Factor kappa-B (NF-κB), and Solute Carrier Family 7 Member 11–Glutathione Peroxidase 4 (SLC7A11–GPX4). Key targets identified include Prostaglandin-Endoperoxide Synthase 2 (PTGS2/COX-2), Estrogen Receptor 1 (ESR1), and Heat Shock Protein 90 Alpha Family Class A Member 1 (HSP90AA1). Pharmacokinetic studies have shown rapid absorption, liver accumulation, phase II metabolism, and low toxicity. However, limited oral bioavailability and translational data remain significant challenges.

Conclusions: Gigantol holds promise as a polypharmacological therapeutic agent grounded in ethnopharmacological tradition. Addressing pharmacokinetic limitations and validating its efficacy and safety through rigorous preclinical and clinical studies are essential for its further development.

Abbreviations

12-HETE	12-Hydroxyeicosatetraenoic Acid	iNOS	Inducible Nitric Oxide Synthase

(*continued on next column*)

(*continued*)

AA	Arachidonic Acid	IκBα	Inhibitor of Nuclear Factor Kappa B Alpha
ACC	Acetyl-CoA Carboxylase	JAK-STAT	Janus Kinase-Signal Transducer and

(*continued on next page*)

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(*continued*)

			Activator of Transcription
AChE	Acetylcholinesterase	JNK	c-Jun N-terminal Kinase
Akt	Protein Kinase B	KEGG	Kyoto Encyclopedia of Genes and Genomes
ALDH1A1	Aldehyde Dehydrogenase 1 Family Member A1	Ki-67	Marker of Proliferation Ki-67
AMPK	AMP-activated Protein Kinase	LOX	Lipoxygenase
APC	Adenomatous Polyposis Coli	LRP5/6	Low-Density Lipoprotein Receptor-Related Protein 5/6
AR	Aldose Reductase	MAPK	Mitogen-Activated Protein kinase
Axin	Axis Inhibition Protein	MCM2	Minichromosome Maintenance Complex Component 2
BAX	Bcl-2-associated X protein	MDA	Malondialdehyde
Bcl-2	B-cell lymphoma-2	MMP-9	Matrix Metalloproteinase-9
BP	Biological Process	MTDH	Metadherin
CaM	Calmodulin	mTOR	Mechanistic Target of Rapamycin
Cav-1	Caveolin-1	MYC	Proto-oncogene c-Myc
CC	Column Chromatography	NAC	N-Acetylcysteine
CD133	Cluster of Differentiation 133	NF-κB	Nuclear Factor Kappa B
CDK1	Cyclin-dependent kinase 1	NMR	Nuclear Magnetic Resonance
CDK4	Cyclin-Dependent Kinase 4	NSAIDs	non-steroidal anti-inflammatory drugs
CK1	Casein Kinase 1	NSCLC	Non-Small Cell Lung Cancer
c-Met	Mesenchymal-Epithelial Transition Factor	PBMCs	Peripheral Blood Mononuclear Cells
CNKI	China National Knowledge Infrastructure	PCNA	Proliferating Cell Nuclear Antigen
cPLA2	Cytosolic Phospholipase A2	PDK1	3-Phosphoinositide-Dependent Protein Kinase-1
CSCs	Cancer stem cells	PGE_2	Prostaglandin E2
Cyclin D1	G1/S-specific Cyclin D1	PI3K	Phosphoinositide 3-Kinase
DC	Diabetic Cataract	PIP2	Phosphatidylinositol-4,5-bisphosphate
DN	Diabetic Nephropathy	PIP3	Phosphatidylinositol-3,4,5-trisphosphate
DPPH	2,2-Diphenyl-1-picrylhydrazyl	PPB	Plasma Protein Binding
DR	Diabetic Retinopathy	PPI	protein-protein interaction
DSS	Dextran Sulfate Sodium	PSA	Polar surface area
EGFR	Epidermal Growth Factor Receptor	PTGS2/ COX-2	Prostaglandin-Endoperoxide Synthase 2
EMT	Epithelial-Mesenchymal Transition	PTLC	preparative thin-layer chromatography
ERBB2/ HER2	Erb-B2 Receptor Tyrosine Kinase 2	Rac1	Ras-related C3 Botulinum Toxin Substrate 1
EREs	Estrogen Response Elements	RAS	Rat Sarcoma
ERK	Extracellular Signal-Regulated Kinase	RB	Retinoblastoma
ESR1	Estrogen Receptor 1	rBMSCs	rat bone marrow mesenchymal stem cells
FRAP	Ferric reducing antioxidant power	ROS	Reactive Oxygen Species
GO	Gene Ontology	RPE	Retinal Pigment Epithelium
GPCRs	G protein-coupled receptors	SLC7A11	Solute Carrier Family 7 Member 11
GPX4	Glutathione Peroxidase 4	Slug	Snail Family Transcriptional Repressor 2
GSH	Glutathione	SOD	Superoxide Dismutase

(*continued on next column*)

(*continued*)

GSK3β	Glycogen Synthase Kinase 3 beta	STAT3	Signal Transducer and Activator of Transcription 3
HCC	Hepatocellular Carcinoma	TCF/LEF	T-cell Factor/Lymphoid Enhancer Factor
HIF-1	Hypoxia-Inducible Factor 1	TNF-α	Tumor Necrosis Factor Alpha
HLECs	human lens epithelial cells	UAE	Ultrasound-Assisted Extraction
HPLC	High Performance Liquid Chromatography	UVB	Ultraviolet B
HSP90	Heat Shock Protein 90	VLC	Vacuum Liquid Chromatography
HSP90AA1	Heat Shock Protein 90 Alpha Family Class A Member 1	Wnt	Wingless/Integrated-1
IGF1R	Insulin-like Growth Factor 1 Receptor	XIAP	X-linked Inhibitor of Apoptosis
IKKα/β	Inhibitor of Nuclear Factor Kappa B Kinase Subunit Alpha/Beta	ZO-1	Zonula Occludens-1
IL	interleukin		

1. Introduction

The *Dendrobium* genus, commonly known as “Huangcao” or “Shihu” in Chinese, is one of the largest genera in the Orchidaceae family and is primarily distributed across tropical and subtropical regions of Asia and Oceania (Li et al., 2023). In traditional Chinese medicine (TCM), *Dendrobium* has been esteemed for centuries as a top-grade herb, with historical records in the Compendium of Materia Medica (Bencao Gangmu) and the Pharmacopoeia of the People’s Republic of China highlighting its ability to nourish the stomach and Yin, promote the generation of body fluids, clear internal heat, and relieve symptoms such as dryness, fatigue, and inflammation (Fu et al., 2023; Yan et al., 2015; Yang et al., 2023a). Among the officially recognized species, *Dendrobium officinale*, *D. nobile*, and *D. fimbriatum* are the most frequently used in clinical practice (Li et al., 2023). In addition to Han medicine, various ethnic groups such as the Dai, Yi, and Miao have incorporated *Dendrobium* into folk remedies for fever, eye disorders, and wasting syndromes. The broad therapeutic applications are largely attributed to its rich repertoire of bioactive compounds, including alkaloids, polysaccharides, bibenzyls, phenanthrenes, sesquiterpenes, and trace elements (Chan et al., 2018). In recent years, phenolic constituents, particularly bibenzyls and phenanthrenes, have garnered attention for their diverse pharmacological effects, including antitumor, antidiabetic, and anti-inflammatory activities (Li et al., 2018; Prasad et al., 2017). To date, nearly 90 bibenzyl compounds have been isolated and identified from *Dendrobium* species, some of which have demonstrated antitumor, anti-inflammatory, and antidiabetic activities (He et al., 2020; Teixeira da Silva and Ng, 2017).

Gigantol is a naturally occurring bibenzyl compound primarily isolated from orchidaceous plants, particularly those of the *Dendrobium* genus (He et al., 2020; Thitikornpong et al., 2022; Zhai et al., 2022). Owing to its unique chemical characteristics and broad spectrum of pharmacological activities, gigantol has gained increasing attention as a major phenolic constituent of *Dendrobium* and is often regarded as a marker compound for quality control and bioactivity evaluation (He et al., 2020). A growing body of evidence suggests that gigantol exhibits significant antitumor activity, exerting inhibitory effects on multiple types of cancer, including hepatocellular carcinoma, lung cancer, and breast cancer, through various molecular mechanisms (Avila-Carrasco et al., 2019; Cai et al., 2021; Jimoh et al., 2022; Zhao et al., 2020). In addition, gigantol has demonstrated protective effects against diabetes and its complications (Chen et al., 2019; Li, Z. et al., 2023), as well as notable anti-inflammatory (Chowdhury et al., 2025) and antioxidant

(Ahammed et al., 2021) activities.

Despite its promising pharmacological potential, current research on gigantol remains fragmented and lacks systematic integration. This review aims to provide a comprehensive synthesis and evaluation of the phytochemical properties, pharmacological effects, and pharmacokinetic characteristics of gigantol. This analysis is grounded in a literature review of studies published over the last 25 years (from 2000 to the present), with sources drawn from the China National Knowledge Infrastructure (CNKI) and PubMed databases. Records were retrieved from CNKI and PubMed (2000–June 2025) using the keyword "gigantol". We included peer-reviewed original studies reporting gigantol-specific data on phytochemistry, pharmacology (in vitro/in vivo), pharmacokinetics/toxicology, or computational analyses; non–peer-reviewed items (e.g., conference abstracts, editorials), duplicates, and records without full text were excluded. This is a narrative synthesis; no formal risk-of-bias assessment or meta-analysis was performed Furthermore, we compiled proteins or genes and their corresponding signaling pathways that contribute to the therapeutic properties of gigantol for protein-protein interaction (PPI) analysis. This investigation was combined with molecular docking studies between gigantol and highly connected proteins, alongside comprehensive bioinformatics evaluations, including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis. Collectively, these integrated methodologies may offer novel research trajectories for future studies and potentially facilitate the pharmaceutical development of gigantol, providing new perspectives for future research.

2. Phytochemical characteristics of gigantol

2.1. Chemical structure, physicochemical properties

Gigantol ($C_{16}H_{18}O_4$, Fig. 1) is a bibenzyl-type phenolic compound predominantly found in various species of the *Dendrobium* genus (Li et al., 2023). Structurally, it possesses a bioactive framework composed of two benzene rings connected by an ethylene bridge, forming a bibenzyl skeleton. Bibenzyls are a major class of phenolic constituents in *Dendrobium* species and have attracted increasing attention because of their promising pharmacological properties, including antitumor, antidiabetic, and neuroprotective effects (He et al., 2020). Gigantol contains two hydroxyl (-OH) groups at the 3 and 4 positions on ring A and two methoxy (-OCH_3) groups at the 3′ and 4′ positions on ring B. Structure–activity relationship evidence indicates that gigantol's hydroxyl groups (3,4-positions on ring A) enhance hydrogen bonding and antioxidant potential, while its methoxy groups (3′,4′-positions on ring B) increase lipophilicity and facilitate cell permeability. Comparative studies suggest that altering or removing these substituents markedly reduces cytotoxic and enzyme-inhibitory activities (Hernández-Romero et al., 2004; Nuamnaichati et al., 2025; Wu et al., 2016). Thus, the unique 3,4-dihydroxy/3′,4′-dimethoxy configuration is likely critical for gigantol's polypharmacological profile. In its pure form, gigantol appears as a white to off-white solid or crystalline substance with a molecular weight of 274.31 g/mol. It exhibits a moderate level of lipophilicity (consensus Log P = 2.9002) and has a polar surface area (PSA) of approximately 58.92 $Å^2$. A summary of the physicochemical properties is presented in Table 1. The data in the table are available at https://baike.baidu.com and https://pubchem.ncbi.nlm.nih.gov.

2.2. Natural sources and extraction of gigantol

Gigantol is a bibenzyl-type phenolic compound predominantly isolated from orchid plants, particularly within the genus *Dendrobium*, and is a core component of traditional Chinese and Southeast Asian medicines. The major plant sources include *D. draconis* (Sritularak et al., 2011; Unahabhokha et al., 2016b), *D. chrysotoxum* (Chen et al., 2023; Jie et al., 2023; Xue et al., 2020b), and *D. aurantiacum* var. *Denneanum* (Fang et al., 2015) and *D. officinale* (Ren, G. et al., 2020; Sun et al., 2023; Zhou et al., 2021). Other sources include *Cymbidium ensifolium* (Jimoh et al., 2022) and *Vanda roxburghii* (Ahammed et al., 2021; Uddin et al., 2015). These orchids are distributed throughout tropical and subtropical Asia and have been traditionally used in Chinese, Thai, and Korean ethnomedicine to treat fever, fatigue, inflammation, and metabolic disorders (Bhummaphan and Chanvorachote, 2015; Won et al., 2006). In the Chinese Pharmacopoeia and other classical texts, such as *Bencao Gangmu*, *Dendrobium* stems (known as "Shihu") are classified as Yin-nourishing herbs used to replenish fluids and clear internal heat (Yan et al., 2024). Beyond Chinese records, orchids that contain gigantol are also used in South and Southeast Asia—for example, *Vanda tessellata* for joint/inflammatory conditions and *Rhynchostylis retusa* for pain and skin inflammation (Al-Amin et al., 2023; Padhee et al., 2024). The traditional therapeutic applications of these species conceptually align with modern findings on the antioxidant, anti-inflammatory, and antidiabetic effects of gigantol, suggesting a possible link between the ethnomedical efficacy and phytochemical composition of the extract.

Given its broad distribution and pharmacological relevance, numerous studies have focused on isolating gigantol from various

Table 1
Physical and chemical properties of gigantol.

Name	Gigantol
Synonyms	Phenol, 5-[2-(3-hydroxy-5-methoxyphenyl)ethyl]-2-methoxy-; Gigantol isomer-1; 5-(3-hydroxy-5-methoxyphenethyl)-2-methoxyphenol
Source	Orchidaceae (principally genus *Dendrobium*)
CAS No	67884-30-4
EINECS No	300-009-3
Molecular formula	C16H18O4
Molecular weight	274.31 g/mol
Form	Solid
Colour	White to off-white solid powder or white crystal
Density	1.204 ± 0.06 g/cm^3
Boiling point	452.3 ± 40.0 °C (at 760 mmHg)
Solubility	Soluble in acetone, chloroform, DCM, DMSO, ethyl acetate
Polar surface area	58.92 $Å^2$
LogP	2.9002
pKa	10.09 ± 0.20 (Predicted)
Storage conditions	Store at −20 °C

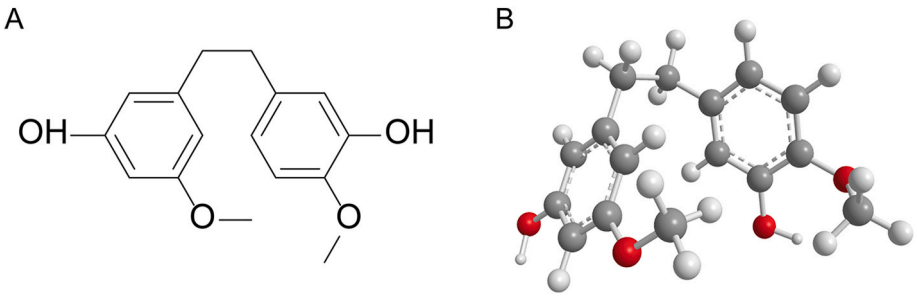

Fig. 1. Diagram of the 2D structure and the 3D optimized configuration of gigantol (PubChem CID: 3085362).

Dendrobium species. However, the relatively low natural abundance of this compound has prompted continuous optimization of extraction strategies. Efficient extraction is essential not only for analytical purposes but also for exploring the therapeutic applications of these compounds on a large scale in the future. Historically, the medicinal stems were used fresh, dried, or subjected to various processing methods, including steaming, roasting, and wine processing (Paozhi). Although rarely quantified in classical texts, these processing techniques may alter the content or bioavailability of chemical constituents, including bibenzyls, such as gigantol. In modern phytochemical practices, gigantol extraction typically involves organic solvents such as methanol or ethanol (Bhummaphan and Chanvorachote, 2015; Fang et al., 2015). Solvent extraction is performed via reflux or maceration (Sun et al., 2020), followed by liquid–liquid partitioning using ethyl acetate and water (Xue et al., 2020b; Zhou et al., 2021). Crude extracts are then subjected to chromatographic techniques, including Vacuum Liquid Chromatography (VLC) (Bhummaphan and Chanvorachote, 2015), silica gel Column Chromatography (CC) (Fang et al., 2015), and Sephadex LH-20 (Khoonrit et al., 2020; Zhao et al., 2016). Final purification is achieved using preparative thin-layer chromatography (PTLC) or high-performance liquid chromatography (HPLC) (Hsieh et al., 2024; Zheng et al., 2018). Emerging techniques, such as Ultrasound-Assisted Extraction (UAE), show promise for improving efficiency and sustainability (Álvarez-Romero et al., 2023; Arya and Kumar, 2021). UAE has demonstrated significantly higher yields in shorter durations than conventional reflux methods (Sun et al., 2023). These greener extraction strategies may be particularly valuable, given the limited natural abundance of gigantol in most plant-derived sources. Structural identification and quantification rely on a combination of techniques, including ˆ1H/ˆ13C Nuclear Magnetic Resonance (NMR) (Ahammed et al., 2021), LC-MS/MS (Zhou et al., 2010), and HPLC (Zheng et al., 2018; Zhou et al., 2010). Representative extraction methods from various plant sources are summarized in Table 2 to emphasize the variations in the solvents, plant parts, and processing techniques used. Chromatographic fingerprints were variably reported, and basic method-validation parameters (linearity, LOD/LOQ, precision, recovery) were rarely documented, constraining quantitative comparisons across sources. Use of authentic gigantol standards with UPLC-DAD or LC-MS/MS and routine validation would strengthen quality control. Where authentic standards were unavailable, tentative identification relied on high-resolution MS fragmentation; nevertheless, a validated quantification method remains desirable for routine profiling.

Given its pharmacological potential and limited natural abundance, significant efforts have been made to isolate and purify gigantol from *Dendrobium* and other related orchids. However, the yield of gigantol varies considerably depending on the species, plant parts, and environmental factors. For instance, stems are preferred in *D. draconis* (Sritularak et al., 2011; Unahabhokha et al., 2016b) and *D. aurantiacum* (Fang et al., 2015), whereas in *D. officinale*, the leaves provide a significantly higher gigantol content (4.79 μg/g) than the stems (0.9 μg/g) (Zheng et al., 2018). Among the documented sources, *D. huoshanense* has been shown to yield exceptional concentrations of gigantol (13.3639 μg/g) (Zheng et al., 2018).

In essence, *Dendrobium* species remain the primary natural reservoirs of gigantol, and their traditional medicinal roles reinforce the pharmacological interest in this compound. Nevertheless, owing to variations in species, plant parts, and environmental conditions, standardized extraction protocols are required to ensure consistent yield and reproducibility for further research and application.

3. Pharmacological properties of gigantol

3.1. Anticancer activity

Carcinogenesis is a multifaceted process that unfolds in several stages, involving changes at both the genetic and epigenetic levels, and includes the initiation, promotion, and progression of cancer. To enhance the survival rates of patients with cancer, a variety of therapeutic approaches have been devised, such as triggering apoptosis in tumor cells and curbing the proliferation, migration, and invasion of cancer cells. To date, gigantol has demonstrated anticancer effects in various cancer cell types and experimental models.

3.1.1. Inhibition of cell proliferation and induction of apoptosis

Uncontrolled growth and proliferation are hallmarks of malignant tumor development. Inhibiting tumor cell proliferation has become a major focus of cancer research (Schiliro and Firestein, 2021). Numerous studies have demonstrated that gigantol effectively inhibits cancer cell growth and proliferation through mechanisms such as the suppression of cell viability, induction of apoptosis, and stimulation of cell cycle arrest (Avila-Carrasco et al., 2019; Jie et al., 2023; Jimoh et al., 2022).

3.1.1.1. Inhibition of MYC and DEK proto-oncogenes. The Proto-oncogene c-Myc (MYC) encodes a family of transcription factors that regulate global gene expression and play critical roles in key cellular processes, including proliferation, differentiation, cell cycle regulation, metabolism, and apoptosis (Llombart and Mansour, 2022). MYC dysregulation is observed in approximately 70 % of human cancers, with compelling evidence indicating its pivotal role in driving tumor initiation and maintenance. Pharmacological inhibition of MYC exerts potent antiproliferative effects and induces sustained tumor regression, positioning MYC as a promising therapeutic target in oncology (Dhanasekaran et al., 2022). Previous studies have indicated that gigantol inhibits the proliferation of human lung cancer cells (Losuwannarak et al., 2020). Proteomic profiling of gigantol-treated cells revealed significant downregulation of MYC, and PPI analysis identified MYC as a central hub. Western blot analysis further confirmed the suppression of MYC expression (Losuwannarak et al., 2020). Mechanistically, MYC degradation is predominantly regulated by the ubiquitin-proteasome system, which requires phosphorylation of Thr58 by Glycogen Synthase Kinase 3 beta (GSK3β) to prime MYC for ubiquitination (Sears, 2004). Gigantol enhances GSK3β activity in lung cancer cells, promoting MYC ubiquitination and subsequent proteasomal degradation, ultimately inhibiting cell proliferation (Losuwannarak et al., 2020).

Another proto-oncogene, DEK, is involved in tumorigenesis through the regulation of DNA repair, cellular differentiation, senescence, and apoptosis (Riveiro-Falkenbach and Soengas, 2010). DEK is ubiquitously expressed in human tissues and is overexpressed in various cancers, including non-small cell lung cancer (NSCLC), where its levels are markedly higher in tumor tissues than in the surrounding non-tumor tissues (Cai et al., 2021; Sandén and Gullberg, 2015). Functional studies have demonstrated that DEK knockdown synergizes with gigantol to suppress NSCLC cell proliferation and enhance apoptosis, whereas DEK overexpression attenuates these effects (Cai et al., 2021). Additionally, gigantol treatment decreases the expression of the Proliferation Ki-67 (Ki-67) and B-cell lymphoma-2 (Bcl-2), while increasing the expression of Bcl-2-associated X protein (BAX) (Cai et al., 2021). Ki-67, a nuclear protein found in proliferating cells, is a well-established indicator of cellular proliferation (Gerdes et al., 1983; Menon et al., 2019). The Bcl-2 protein family governs intrinsic apoptosis by regulating mitochondrial outer membrane permeability, with BAX acting as a key pro-apoptotic effector (Spitz and Gavathiotis, 2022; Suraweera et al., 2022). DEK silencing suppresses Bcl-2 and enhances BAX expression (Hopper et al., 2024; Wise-Draper et al., 2006), suggesting that gigantol may exert its antiproliferative and pro-apoptotic effects through DEK-mediated modulation of these markers (Cai et al., 2021).

Collectively, these findings suggest that gigantol inhibits tumor cell proliferation and induces apoptosis by downregulating MYC via GSK3β-dependent ubiquitin-proteasome degradation and suppressing DEK to disrupt the Bcl-2/BAX balance and reduce Ki-67 expression.

Table 2
Gigantol extraction methods from various plant sources.

Plant Source	Plant Part	Extraction Method	Key Extraction/Purification Steps	References
Dendrobium draconis Rchb. f.	Dried stems	Methanol (MeOH) extraction, VLC, CC	Stems extracted with MeOH. Concentrate purified by VLC and CC to obtain gigantol (>95 % purity).	(Unahabhokha et al., 2016)
Dendrobium draconis Rchb. f.	Dried stems	Methanol extraction, VLC, CC	Stems extracted with MeOH. Concentrate separated by VLC and CC. Structure confirmed by HPLC and NMR. Purity >95 %.	Bhummaphan and Chanvorachote (2015)
Dendrobium chrysotoxum Lindl.	Dried stems	Ethanol extraction, solvent partitioning, CC	Stems extracted with 95 % EtOH. Extract partitioned with EtOAc and n-BuOH. EtOAc fraction subjected to silica gel CC (petroleum ether/acetone gradient), followed by Sephadex LH-20 CC ($CHCl_3$/MeOH) to obtain gigantol.	(Xue et al., 2020)
Cymbidium goeringii (Rchb. f.) Rchb. f.	Whole plant	Methanol extraction, solvent partitioning, CC	Fresh plant extracted with 80 % MeOH. Extract partitioned with EtOAc and n-BuOH. EtOAc fraction subjected to silica gel CC (n-hexane/EtOAc gradient), followed by ODS CC (MeOH/H_2O) to obtain gigantol (>98 % purity, HPLC). Physicochemical properties reported.	Won et al. (2006)
Dendrobium aurantiacum var. *denneanum* (Kerr) Z.H. Tsi	Dried stems	Ethanol extraction, solvent partitioning, CC	Stems extracted with 80 % EtOH. Extract partitioned with EtOAc and n-BuOH. EtOAc fraction purified by silica gel CC (n-hexane/EtOAc and $CHCl_3$/MeOH gradients), followed by ODS CC to obtain gigantol (>98 % purity, HPLC).	Fang et al. (2015)
Dendrobium officinale Kimura et Migo	Leaves	UAE	Powder extracted with 93 % MeOH under optimized UAE conditions (80 W, 42 °C, 27 mL/g, 30 min). Centrifuged, supernatant dried, reconstituted. Quantified by HPLC. Tissue/species differences noted.	Zheng et al. (2018)
Dendrobium officinale Kimura et Migo	Dried stems	Ethanol percolation, solvent partitioning	Stems percolated with 95 % EtOH. Extract concentrated, suspended in H_2O, partitioned with EtOAc. EtOAc fraction subjected to macroporous resin CC (H_2O/EtOH gradient), then further CC (MCI, ODS, Sephadex LH-20, prep-HPLC).	Zhou et al. (2021)
Dendrobium spp. (Nobile type)	Processed stems (Fengdou)	UAE optimized by RSM	Powder extracted with 70 % MeOH under optimized UAE (25 min, RT). Filtered. Method validated (LOD 0.05 μg/mL, LOQ 0.2 μg/mL, recovery 100.8 %). Quantified by HPLC.	Zhou et al. (2010)
Dendrobium gratiosissimum Rchb. f.	Whole plant	Ethanol reflux, solvent partitioning, CC	Plant extracted with 80 % EtOH. Extract partitioned. EtOAc fraction purified by silica gel CC (CH_2Cl_2/MeOH gradient). Active fraction further purified by Sephadex LH-20 CC and prep-HPLC (CH_3CN/H_2O) to obtain gigantol.	Sun et al. (2020)
Dendrobium draconis Rchb. f.	Dried stems	Methanol extraction, VLC, CC	Stems extracted with MeOH (RT). Concentrate separated by VLC (n-hexane/EtOAc gradient). Active fraction purified by silica gel CC and Sephadex LH-20 CC (acetone) to obtain gigantol. Purity confirmed for bioassay.	Sritularak et al. (2011)
Dendrobium chrysotoxum Lindl., *D. nobile* Lindl.	Stems/Leaves	Methanol-water UAE	Powder extracted with 70 % MeOH under UAE (45 min). Filtrate concentrated, freeze-dried for LC-MS/MS analysis (gigantol identified).	Jie et al. (2023)
Dendrobium lindleyi Steud.	Whole plant	Methanol extraction, solvent partitioning, CC	Plant extracted with MeOH (RT). Extract partitioned with EtOAc and n-BuOH. EtOAc fraction subjected to silica gel CC (EtOAc/n-hexane gradient), then Sephadex LH-20 CC (MeOH) to obtain gigantol.	Khoonrit et al. (2020)
Cymbidium ensifolium (L.) Sw.	Aerial parts	Methanol extraction, VLC, CC	Plant extracted with MeOH (RT). Concentrate fractionated by VLC (n-hexane/EtOAc gradient). Active fraction purified by silica gel CC and Sephadex LH-20 CC (acetone) to obtain gigantol.	Jimoh et al. (2022)
Dendrobium moniliforme (L.) Sw.	Whole plant	Methanol extraction, solvent partitioning, CC	Plant extracted with MeOH (RT). Extract partitioned with EtOAc and n-BuOH. EtOAc fraction subjected to silica gel CC (petroleum ether/EtOAc gradient), then MCI CC (H_2O/MeOH gradient), Sephadex LH-20 CC ($CHCl_3$/MeOH), and prep-HPLC to obtain gigantol.	Zhao et al. (2016)
Gastrochilus bellinus (Rchb. f.) Kuntze	Whole plant	Methanol extraction, solvent partitioning, CC	Plant extracted with MeOH. Extract partitioned. EtOAc fraction purified by VLC (CH_2Cl_2/EtOAc gradient), silica gel CC, Sephadex LH-20 CC (acetone), and RP-C18 CC to obtain gigantol.	(San et al., 2021)
Vanda roxburghii R. Br.	Roots	Methanol extraction, solvent partitioning, CC	Roots extracted with MeOH (RT). Extract partitioned. Chloroform fraction purified by silica gel CC (n-hexane/$CHCl_3$/MeOH gradient) and prep-TLC to obtain gigantol.	Ahammed et al. (2021)
Scaphyglottis livida (Lindl.) Schltr.	Whole plant	Dichloromethane-Methanol (1:1) extraction, CC	Plant extracted with CH_2Cl_2/MeOH (1:1, RT). Extract purified by silica gel CC (n-hexane/EtOAc and EtOAc/MeOH gradients). Active subfractions purified by Sephadex LH-20 CC (MeOH) to obtain gigantol. Also synthesized.	Déciga-Campos et al. (2007)
Eria bambusifolia Griff.	Whole plant	Methanol extraction, solvent partitioning, CC	Plant extracted with MeOH (RT). Extract partitioned with EtOAc. EtOAc fraction purified by silica gel CC (petroleum ether/acetone gradient), RP-18 CC (MeOH/H_2O gradient), Sephadex LH-20 CC ($CHCl_3$/MeOH), and silica gel CC to obtain gigantol.	(Zhao et al., 2016)
Dendrobium wardianum R. Warner	Stems	Ethanol reflux, solvent partitioning, CC	Stems extracted with 90 % EtOH. Extract partitioned with EtOAc and n-BuOH. EtOAc fraction purified by silica gel CC ($CHCl_3$/MeOH gradient), Sephadex LH-20 CC (MeOH/H_2O), and prep-HPLC to obtain gigantol.	(Zhang et al., 2017)
Dendrobium scabrilingue Lindl.	Whole plant	Methanol extraction, solvent partitioning, CC	Plant extracted with MeOH (RT). Extract partitioned with EtOAc and n-BuOH. EtOAc fraction fractionated by VLC (EtOAc/n-	Sarakulwattana et al. (2020)

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Table 2 (*continued*)

Plant Source	Plant Part	Extraction Method	Key Extraction/Purification Steps	References
			hexane gradient). Active fraction purified by silica gel CC and Sephadex LH-20 CC (MeOH) to obtain gigantol.	
Cymbidium sp.	Pseudobulbs/ Roots	Ethyl acetate extraction, CC	Pseudobulb/root EtOAc extracts purified by silica gel CC (cyclohexane/EtOAc gradient). Active fractions combined/ further purified by silica gel CC and prep-TLC to obtain gigantol. Structure confirmed by NMR/HRMS.	Axiotis et al. (2022)
Dendrobium brymerianum Rchb. f.	Whole plant	Methanol extraction, VLC, CC	Plant extracted with MeOH (RT). Concentrate fractionated by VLC (n-hexane/EtOAc gradient). Active fraction purified by Sephadex LH-20 CC (acetone) to obtain gigantol. NMR/MS data reported.	Klongkumnuankarn et al. (2015)
Dendrobium chrysotoxum Lindl., *D. nobile* Lindl.	Stems/Leaves	Methanol-water UAE	Powder extracted with 70 % MeOH under UAE (45 min). Filtrate concentrated, freeze-dried for UPLC-Q-TOF-MS/MS analysis (gigantol identified among metabolites).	Chen et al. (2023)
Dendrobium pachyglossum Parish & Rchb. f.	Whole plant	Methanol extraction, solvent partitioning, CC	Plant extracted with MeOH (RT). Extract partitioned with EtOAc and n-BuOH. EtOAc fraction fractionated by VLC (EtOAc/n-hexane gradient). Active fraction purified by Sephadex LH-20 CC (MeOH) to obtain gigantol.	(Warinhomhoun et al., 2021)
Dendrobium candidum Wall. ex Lindl.	Stems	Ethyl acetate reflux, CC	Stems extracted with EtOAc (reflux). Extract purified by silica gel CC (petroleum ether/EtOAc gradient), Sephadex LH-20 CC, and prep-HPLC to obtain gigantol.	(Li et al., 2008)
Epidendrum rigidum Jacq.	Whole plant	Chloroform-Methanol (1:1) extraction, CC	Plant extracted with $CHCl_3$/MeOH (1:1, RT). Extract fractionated by silica gel CC (n-hexane/EtOAc and EtOAc/MeOH gradients). Active fractions purified by silica gel CC and prep-HPLC to obtain gigantol.	(Hernández-Romero et al., 2005)
Dendrobium spp. (Nobile type)	Dried stems	Methanol UAE	Powder extracted with MeOH under UAE (60 min). Concentrate dissolved in MeOH, filtered for UPLC-QToF MS analysis (gigantol identified).	(Nam et al., 2021)
Dendrobium nobile Lindl.	Dried stems	Ethanol reflux	Powder extracted with 95 % EtOH (reflux, 2h x3). Concentrate dissolved in MeOH, filtered for UPLC-ESI-Q-Orbitrap MS analysis (gigantol identified).	Li et al. (2023)
Vanda coerulea Griff. ex Lindl.	Stems	Ethanol-water (9:1) reflux, CH_2Cl_2 partition	Powder extracted with EtOH/H_2O (9:1, reflux). Extract partitioned with CH_2Cl_2. CH_2Cl_2 extract enriched in bibenzyls. Purified by Sephadex LH-20 CC (MeOH/CH_2Cl_2) and prep-HPLC to obtain gigantol (4.01 % in CH_2Cl_2 extract). NMR/HRMS data reported.	Bonté et al. (2011)
Dendrobium capillipes Rchb. f.	Whole plant	Methanol extraction, VLC, CC	Plant extracted with MeOH (reflux/Soxhlet). Concentrate fractionated by VLC (MeOH/EtOAc/CH_2Cl_2 gradient). Active fractions purified by silica gel CC (acetone/petroleum ether or acetone/CH_2Cl_2 gradients) and Sephadex LH-20 CC to obtain gigantol. HRMS/NMR reported.	Kongkatitham et al. (2024)
Nidema boothii (Lindl.) Schltr.	Whole plant	Chloroform-Methanol (1:1) extraction, CC	Plant extracted with $CHCl_3$/MeOH (1:1, RT). Extract fractionated by silica gel CC (n-hexane/EtOAc and EtOAc/MeOH gradients). Active fraction purified by silica gel CC and prep-HPLC to obtain gigantol. NMR/MS confirmed.	Hernández-Romero et al. (2004)
Cyrtopodium macrobulbon (La Llave & Lex.) G.A. Romero & Carnevali	Pseudobulbs	Dichloromethane extraction, CC, TLC	Dried pseudobulbs extracted with CH_2Cl_2 (RT). Extract purified by silica gel CC (n-hexane/EtOAc and EtOAc/MeOH gradients). Active fraction purified by prep-TLC to obtain gigantol. Structure confirmed by comparison.	Morales-Sánchez et al. (2014)
Dendrobium devonianum Paxton	Whole plant	Methanol extraction, solvent partitioning, CC	Plant extracted with MeOH (RT). Extract partitioned with EtOAc and n-BuOH. EtOAc fraction purified by silica gel CC (petroleum ether/EtOAc gradient) and Sephadex LH-20 CC ($CHCl_3$/MeOH) to obtain gigantol.	Sun et al. (2014)
Vanda roxburghii R. Br.	Roots	Methanol extraction, solvent partitioning, CC	Roots extracted with MeOH (RT). Extract partitioned. Chloroform fraction purified by silica gel CC (n-hexane/$CHCl_3$/MeOH gradient) and prep-TLC to obtain gigantol. NMR/UV confirmed.	Uddin et al. (2015)
Rhynchostylis retusa (L.) Blume	Whole plant	Methanol extraction, solvent partitioning, CC	Plant extracted with MeOH (RT). Extract partitioned (n-hexane, $CHCl_3$, MeOH). $CHCl_3$ fraction purified by silica gel CC (CH_2Cl_2/MeOH gradient) and Sephadex LH-20 CC to obtain gigantol.	Al-Amin et al. (2023)
Pholidota pallida Lindl.	Aerial parts	Ethanol extraction, solvent partitioning, CC	Plant extracted with 95 % EtOH (RT). Extract partitioned with EtOAc. EtOAc residue purified by silica gel CC (petroleum ether/acetone or petroleum ether/EtOAc gradients), Sephadex LH-20 CC ($CHCl_3$/MeOH), and prep-TLC to obtain gigantol. NMR confirmed.	(Yu et al., 2021a)
Bulbophyllum wendlandianum (Kraenzl.) Dammer	Whole plant	Ethanol extraction, solvent partitioning, CC	Plant extracted with 95 % EtOH (RT). Extract partitioned with EtOAc. EtOAc residue purified by silica gel CC (petroleum ether/EtOAc gradient) and Sephadex LH-20 CC ($CHCl_3$/MeOH) to obtain gigantol. NMR confirmed.	(Yu et al., 2021b)
Dendrobium officinale Kimura et Migo	Leaves	Ethanol extraction, resin chromatography	Leaves extracted with 95 % EtOH (RT). Extract purified sequentially by HP-20 macroporous resin CC (EtOH/H_2O gradient), MCI CHP-20P resin CC (EtOH/H_2O gradient), Sephadex LH-20 CC (MeOH or MeOH/H_2O), and prep-HPLC to obtain gigantol.	Ren et al. (2020)
Dendrobium officinale Kimura et Migo	Stems	UAE	Freeze-dried stem slices dry-ground. Powder extracted with 95 % MeOH under UAE (200 W, 30 min). Optimized UADG (15 min	Sun et al. (2023)

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Table 2 (*continued*)

Plant Source	Plant Part	Extraction Method	Key Extraction/Purification Steps	References
			grinding) gave 65 % extraction yield, superior to heat reflux (50 %). Mechanism: particle size reduction & cell disruption.	
Dendrobium fimbriatum Hook.	Stems	Ethyl acetate extraction, CC, PTLC	Stems extracted with EtOAc. Extract purified by silica gel CC (n-hexane/acetone gradient). Active fraction purified by prep-TLC (CH_2Cl_2/acetone) to obtain gigantol. HPLC-ESI-qTOF-MS/MS and NMR confirmed.	Hsieh et al. (2024)
Dendrobium venustum Teijsm. & Binn.	Not specified	Methanol extraction, CC, Prep-TLC/HPLC	Plant material extracted with MeOH. Concentrate purified by multiple CC steps (silica gel, Sephadex LH-20) and final purification by Prep-TLC or prep-HPLC to obtain gigantol (>98 % purity). MS and NMR confirmed.	Nuamnaichati et al. (2025)

3.1.1.2. Suppression of Wnt/β-catenin signaling. The Wingless/Integrated-1/β-catenin (Wnt/β-catenin) signaling pathway, a canonical pathway critical for embryonic development and adult tissue homeostasis, regulates diverse physiological processes, including proliferation, differentiation, apoptosis, migration, and invasion (Liu, J. et al., 2022). However, aberrant activation of this pathway drives tumorigenesis by promoting cancer stem cell renewal, uncontrolled proliferation, and therapeutic resistance (Zhang and Wang, 2020). Emerging evidence has identified gigantol as a potent inhibitor of Wnt/β-catenin signaling in multiple cancer models (Cai et al., 2021; Kang et al., 2022; Yu et al., 2018).

When Wnt ligands are not present, the "destruction complex," which includes Axis Inhibition Protein (Axin), Adenomatous Polyposis Coli (APC), GSK3β, and Casein Kinase 1 (CK1), phosphorylates cytoplasmic β-catenin. This phosphorylation results in β-catenin being ubiquitinated by β-TrCP and subsequently degraded by the proteasome, thus inhibiting the pathway's activity (Liu, J. et al., 2022; Zhang and Wang, 2020). In contrast, when Wnt ligands bind to Frizzled and Low-Density Lipoprotein Receptor-Related Protein 5/6 (LRP5/6) receptors, dishevelled is drawn to the membrane, leading to the destabilization of the destruction complex, which stabilizes β-catenin, allowing its nuclear translocation to interact with T-cell Factor/Lymphoid Enhancer Factor (TCF/LEF) transcription factors and activate pro-tumorigenic genes (e.g., G1/S-specific Cyclin D1(Cyclin D1), MYC, Survivin) (Liu, J. et al., 2022; Zhang and Wang, 2020). Survivin, an apoptosis inhibitor frequently overexpressed in cancers, is directly upregulated by Wnt/β-catenin signaling, thereby enhancing tumor cell survival (Ye et al., 2019). In NSCLC, gigantol inactivates Wnt/β-catenin signaling by downregulating Wnt10b and β-catenin expression in a DEK-dependent manner, as DEK overexpression reverses these effects (Cai et al., 2021). In breast cancer, gigantol selectively reduces phosphorylated LRP6, total LRP6, and cytoplasmic β-catenin levels in tumor cells (e.g., MDA-MB-231 and MDA-MB-468), suppressing downstream targets Axin2 and Survivin while sparing non-tumorigenic mammary epithelial cells (Yu et al., 2018). Similarly, in cervical cancer (HeLa) cells, gigantol inhibits cell viability in a concentration-dependent manner by attenuating Wnt1/β-catenin signaling (Kang et al., 2022). This is accompanied by increased Reactive Oxygen Species (ROS) generation, lipid peroxidation, mitochondrial membrane depolarization (ΔΨm loss), and nuclear fragmentation, which are hallmarks of apoptosis. Gigantol also enhances GSK3β activity, promoting β-catenin degradation and reducing nuclear transcription of proliferative (Cyclin D1, MYC) and anti-apoptotic (Bcl-2) markers, while elevating pro-apoptotic factors (BAX, cytochrome C, caspases 9/3) (Kang et al., 2022).

Gigantol synergizes with temozolomide (chemotherapy) and radiotherapy in glioma models, markedly enhancing cytotoxicity (Tao et al., 2021). *In vivo*, gigantol combined with these therapies suppressed tumor growth and prolonged survival, highlighting Wnt/β-catenin inhibition as a strategy to enhance the efficacy of conventional treatments.

3.1.1.3. Blockade of PI3K/Akt/mTOR pathway. The Phosphatidylinositol 3-Kinase (PI3K)/Akt pathway, which is frequently hyperactivated in cancers, plays a central role in tumorigenesis by regulating cell proliferation, survival, and apoptosis (Fresno Vara et al., 2004). This pathway can be dysregulated through multiple mechanisms, with genomic alterations leading to PI3K-mediated phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3, 4,5-trisphosphate (PIP3). PIP3 recruits oncogenic signaling proteins, including Akt, which phosphorylate downstream substrates to promote cancer progression and suppresses apoptosis (He et al., 2021). Previous studies have demonstrated that gigantol inhibits hepatocellular carcinoma (HCC) cell proliferation and induces apoptosis by targeting the PI3K/Akt signaling pathway (Li, S. et al., 2022).

The PI3K/Akt/Mechanistic Target of Rapamycin (mTOR) axis, which is commonly mutated in cancers, integrates proliferative and survival signals (Hanker et al., 2019; Thorpe et al., 2015). Heat shock protein 90 (HSP90) stabilizes the oncogenic PI3K/Akt/mTOR complex, thereby preventing proteasomal degradation (Giulino-Roth et al., 2017). Cyclin-dependent kinase 1 (CDK1), a critical mitotic regulator, specifically phosphorylates 3-phosphoinositide-dependent protein kinase-1 (PDK1), thereby influencing the PI3K/Akt signaling pathway (Wang et al., 2017). Molecular docking and experimental validation revealed that gigantol targets Heat Shock Protein 90 Alpha Family Class A Member 1 (HSP90AA1), Estrogen Receptor 1 (ESR1), and X-linked Inhibitor of Apoptosis (XIAP), suppressing HCC progression via the HSP90/Akt/CDK1 axis (Li, S. et al., 2022). Additionally, Nuclear Factor kappa-B (NF-κB), a transcription factor activated by PI3K/Akt, drives tumor angiogenesis, metastasis, and chemoresistance by regulating apoptotic genes (e.g., p53, BAX, Bcl-2, Caspase-3) (Azijli et al., 2013; Kim et al., 2009; Yu et al., 2017). Gigantol inhibits PI3K/Akt/NF-κB signaling in HCC, reducing phosphorylated Akt (p-Akt) levels while activating pro-apoptotic markers (Caspase-3, PARP, and p53) (Brown et al., 2009; Chen et al., 2017; Kulkarni et al., 2013). In breast cancer, gigantol synergizes with cisplatin by suppressing the PI3K/Akt/mTOR signaling (Huang et al., 2021). Gigantol inhibited the activity of MDA-MB-231 cells with an IC_{50} value of 64.2 ± 1.1 μM (Al-Amin et al., 2023). Network pharmacology and molecular docking analyses revealed that gigantol binds to PI3K, Akt, and mTOR via hydrogen bonds and π-π interactions. This reduces p-PI3K, p-Akt, and p-mTOR expression, enhancing cisplatin-induced apoptosis through the activation of BAX, Caspase-9/7, and PARP (Huang et al., 2021).

3.1.1.4. Targeting cancer stem cell markers. Cancer stem cells (CSCs) are a subset of tumor cells that possess self-renewal capacity, can differentiate into multiple cancer cell types, and promote tumor growth and diversity. CSCs are known for their enhanced DNA repair mechanisms and increased drug efflux activity, contributing to chemotherapy resistance (Batlle and Clevers, 2017). The biological activity of CSCs is regulated by pluripotency transcription factors, including OCT4, Nanog, and MYC (Yang et al., 2020). Additionally, several intracellular signaling pathways, such as Wnt, NF-κB, Notch, Hedgehog, Janus kinase/signal transducers and activators of transcription (JAK-STAT), and PI3K/Akt/mTOR, have been identified as critical regulators of CSCs function. Gigantol reduces CSC markers (Cluster of Differentiation 133 (CD133) and Aldehyde Dehydrogenase 1 Family Member A1 (ALDH1A1)) in lung cancer, impairing anchorage-independent growth

and spheroid formation at non-toxic concentrations (Bhummaphan and Chanvorachote, 2015). It downregulates Akt signaling, diminishing the pluripotency factors Oct4 and Nanog (Bhummaphan and Chanvorachote, 2015). In parallel, gigantol disrupts the PI3K/Akt/mTOR and JAK/STAT pathways while activating JNK, thereby weakening CSC viability and tumor integrity (Losuwannarak et al., 2019). Preclinical studies in xenograft models have confirmed that gigantol-pretreated cells exhibit reduced tumorigenicity, with decreased tumor weight and Ki-67-positive proliferating cells (Losuwannarak et al., 2019).

Gigantol exerts significant antiproliferative and pro-apoptotic effects in multiple cancer types by targeting various oncogenic pathways. It promotes MYC degradation via GSK3β activation and suppresses DEK to disrupt the Bcl-2/BAX axis. Additionally, gigantol inactivates Wnt/β-catenin signaling and downregulates key effectors such as Cyclin D1, Survivin, and β-catenin. It also inhibits the PI3K/Akt/mTOR and PI3K/Akt/NF-κB pathways, enhancing pro-apoptotic signals, including caspase-3 and p53. Furthermore, gigantol reduces cancer stemness by downregulating CSC markers and pluripotency factors, while impairing self-renewal and tumorigenicity.

3.1.2. *Anti-migration and invasion*

Metastasis, responsible for over 90 % of cancer-related deaths, is propelled by tumor cell migration and invasion, which enable malignant cells to disseminate from primary sites to distant organs (Kaewmeesri et al., 2022; Lambert et al., 2017; Mehlen and Puisieux, 2006; Šeklić et al., 2022). Therefore, inhibiting tumor cell migration and invasion plays an important role in suppressing tumor progression.

3.1.2.1. Regulation of EMT via the Wnt/β-catenin signal pathway. Epithelial-mesenchymal transition (EMT) is closely associated with cancer cell migration and invasion. EMT facilitates metastasis by decreasing cell adhesion molecules, such as E-cadherin, and triggering mesenchymal markers, such as N-cadherin and vimentin, thereby enhancing motility and invasiveness (Lüönd et al., 2021). The Wnt/β-catenin signaling pathway is intricately linked to the breakdown of the extracellular matrix, cancer cell migration and adhesion, and tumor angiogenesis, all of which are associated with cancer invasion (Basu et al., 2018). Wnt/β-catenin signaling promotes EMT via GSK3β-mediated stabilization of β-catenin, which suppresses E-cadherin expression and activates pro-invasive genes (Jong et al., 2005). Notably, gigantol inhibits HCC migration and invasion by downregulating the expression of proliferation markers (Proliferating Cell Nuclear Antigen (PCNA) and Minichromosome Maintenance Complex Component 2 (MCM2)) and EMT proteins (N-cadherin and vimentin) while restoring E-cadherin levels (Li, S. et al., 2022). In bladder cancer, gigantol preferentially targets low-grade cells (SW780 and 5637), suppressing Wnt/EMT markers (Axin2, Survivin, Snail Family Transcriptional Repressor 2 (Slug), and vimentin) and reducing invasiveness (Zhao et al., 2020). The preferential activity of gigantol against low-grade bladder cancer cells (e.g., SW780, 5637) may be explained by their stronger dependence on Wnt/EMT signaling, which is effectively suppressed by gigantol. In contrast, high-grade bladder cancer often harbors additional oncogenic mutations such as TP53 and RB1, leading to signaling redundancy and reduced responsiveness. This context-dependent vulnerability may account for the observed selectivity of gigantol in bladder cancer models (Chi et al., 2022; Zhao et al., 2020). In lung cancer, gigantol significantly inhibited the migration of H460 cells at non-cytotoxic concentrations (Klongkumnuankarn et al., 2015; Unahabhokha et al., 2016b). Slug, a major regulator of EMT, acts as a molecular switch by blocking the expression of genes that inhibit E-cadherin expression (Ang et al., 2023; Ye et al., 2010). Gigantol attenuates migration by upregulating E-cadherin and degrading Slug via proteasomal pathways, coupled with GSK3β activation and β-catenin suppression (Unahabhokha et al., 2016a, 2016b).

3.1.2.2. c-Met/Akt signaling crosstalk. Akt, a serine/threonine kinase, is widely activated by growth signals and participates in various important signaling pathways, such as the PI3K pathway (Revathidevi and Munirajan, 2019). Akt is centrally located in many signaling pathways and is often deregulated in various human cancers, contributing to tumor cell invasion and migration, making it an important target for cancer therapy (Chi et al., 2022; Song et al., 2019; Yao et al., 2020). Proteomic analysis revealed that gigantol (20 μM, 24 h) altered the expression of adhesion- and migration-related proteins in H460 lung cancer cells, with mesenchymal-epithelial transition factor (c-Met) identified as a hub target (Aksorn et al., 2021). c-Met, a receptor tyrosine kinase activated by hepatocyte growth factor, stimulates the PI3K/Akt and Wnt/β-catenin pathways to promote proliferation and invasion (Imura et al., 2016; Pilotto et al., 2017; Zhang, T. et al., 2022). Gigantol suppresses c-Met-driven PI3K/Akt signaling, thereby inhibiting lung cancer metastasis. Concurrently, it downregulates EMT markers, inactivates survival pathways (Akt, Extracellular Signal-Regulated Kinase (ERK), Caveolin-1 (Cav-1)), and enhances anoikis-mediated cell death by impairing pseudopodia formation via Cdc42 inhibition (Aksorn et al., 2021; Charoenrungruang et al., 2014; Unahabhokha et al., 2016a). Importantly, gigantol selectively inhibits the migration of malignant cells (H460 and H292) without affecting normal keratinocytes (HaCaT) (Charoenrungruang et al., 2014). In retinoblastoma (RB), gigantol suppresses tumor cell viability and downregulates multiple pro-invasive proteins in RB tissues, highlighting its broad-spectrum anticancer potential (Zhang et al., 2021).

Gigantol effectively suppresses cancer cell migration and invasion by targeting multiple pathways associated with metastasis. It inhibits EMT progression by downregulating mesenchymal markers and restoring E-cadherin, primarily through Wnt/β-catenin pathway inactivation and Slug degradation. Additionally, gigantol interferes with c-Met/Akt signaling, impairing pro-invasive cascades and cytoskeletal remodeling in cancer cells. These actions not only reduced cellular motility but also sensitized tumor cells to anoikis. Its selectivity for malignant cells over normal cells further highlights the potential of gigantol as a safe, polypharmacological anti-metastatic agent.

3.1.3. *Induction of ferroptosis*

Ferroptosis is a distinct type of programmed cell death triggered by the excessive accumulation of lipid peroxides in an iron-dependent manner (Jiang et al., 2021; Li et al., 2020). It is characterized by intracellular free iron overload, ROS bursts, and abnormal lipid peroxidation, ultimately leading to disruption of cell membrane structure and cell death. In recent years, an increasing number of studies have demonstrated the important role of ferroptosis in cancer therapy (Jiang et al., 2021; Zhang, C. et al., 2022; Zhou et al., 2024). Tumor cells often exhibit high iron loads, elevated metabolic activity, and impaired antioxidant systems, making them more susceptible to ferroptosis and thus a potential target for anticancer treatments (Jiang et al., 2021). Recent studies have shown that gigantol can suppress tumor growth by inducing ferroptosis in lung cancer (Chen, P. et al., 2024). *In vitro*, gigantol reduced the viability of of H460 and A549 lung cancer cells in a concentration- and time-dependent manner at 50–150 μM and induced significant cell death. *In vivo*, daily intraperitoneal administration of gigantol (30 or 60 mg/kg for 12 days) markedly suppressed xenograft tumor growth in nude mice without apparent systemic toxicity. Mechanistic studies showed that gigantol caused intracellular iron accumulation, ROS bursts, enhanced lipid peroxidation, and loss of mitochondrial cristae. At the molecular level, gigantol directly inhibited the cystine transporter SLC7A11, thereby reducing cystine uptake, depleting intracellular cysteine and glutathione (GSH), and subsequent impairing both the activity and expression of the antioxidant enzyme GPX4. Importantly, ferroptosis inhibitors (Liproxstatin-1, Ferrostatin-1) and N-acetylcysteine (NAC), a precursor of cysteine, significantly reversed gigantol's anticancer effects and the associated oxidative damage, confirming that gigantol exerts its antitumor activity by

inducing ferroptosis through the SLC7A11-GPX4 axis (Chen, P. et al., 2024).

Collectively, current evidence indicates that gigantol inhibits cancer cell proliferation, migration, and survival through diverse mechanisms, including regulation of PI3K/Akt/mTOR, Wnt/β-catenin, c-Met, and NF-κB signaling pathways (Fig. 2). Reported IC_{50} values are generally in the micromolar range, for example ~20–40 μM in bladder cancer cells (SW780, 5637) (Zhao et al., 2020) and ~50–150 μM in lung cancer cells (H460, A549) (Chen et al., 2024), suggesting moderate potency across different malignancies. However, many studies did not provide IC_{50} values, limiting direct cross-comparison. Although gigantol regulates pathways such as EMT and PI3K/Akt that are closely linked to drug resistance, no published studies have directly examined its effects in chemoresistant models. Future work should therefore systematically evaluate IC_{50} values across cancer types and investigate whether gigantol can overcome chemotherapy resistance to better define its therapeutic window and clinical potential.

3.2. Anti-diabetic and its complications

Diabetes mellitus, a chronic endocrine disorder characterized by hyperglycemia, has emerged as one of the fastest-growing global health challenges (Cho et al., 2018). Microvascular complications, including diabetic nephropathy (DN), diabetic retinopathy (DR), and diabetic cataracts (DC), significantly contribute to increased mortality, blindness, renal failure, and reduced quality of life (Cole and Florez, 2020; Obrosova et al., 2010; Yu, M.G. et al., 2024). Gigantol demonstrates promising therapeutic potential for managing diabetes and its complications through multifaceted mechanisms, as evidenced by recent research.

3.2.1. Diabetes

Type 2 diabetes mellitus is a metabolic disorder characterized by persistent hyperglycemia due to insulin resistance and β-cell dysfunction, often accompanied by lipid metabolism disturbances. Effective glycemic control, especially postprandial glucose regulation and improvement of insulin sensitivity, remains a cornerstone of diabetes management (Magkos et al., 2020; Singh et al., 2025). Recent studies have demonstrated that gigantol exerts dual antidiabetic effects by enhancing glucose uptake and inhibiting carbohydrate digestion. In skeletal muscle cells (L6 myotubes), gigantol significantly increases glucose uptake under both basal and insulin-stimulated conditions, mediated by activation of the AMP-activated Protein Kinase (AMPK) which promotes GLUT4 translocation, and by regulation of lipid

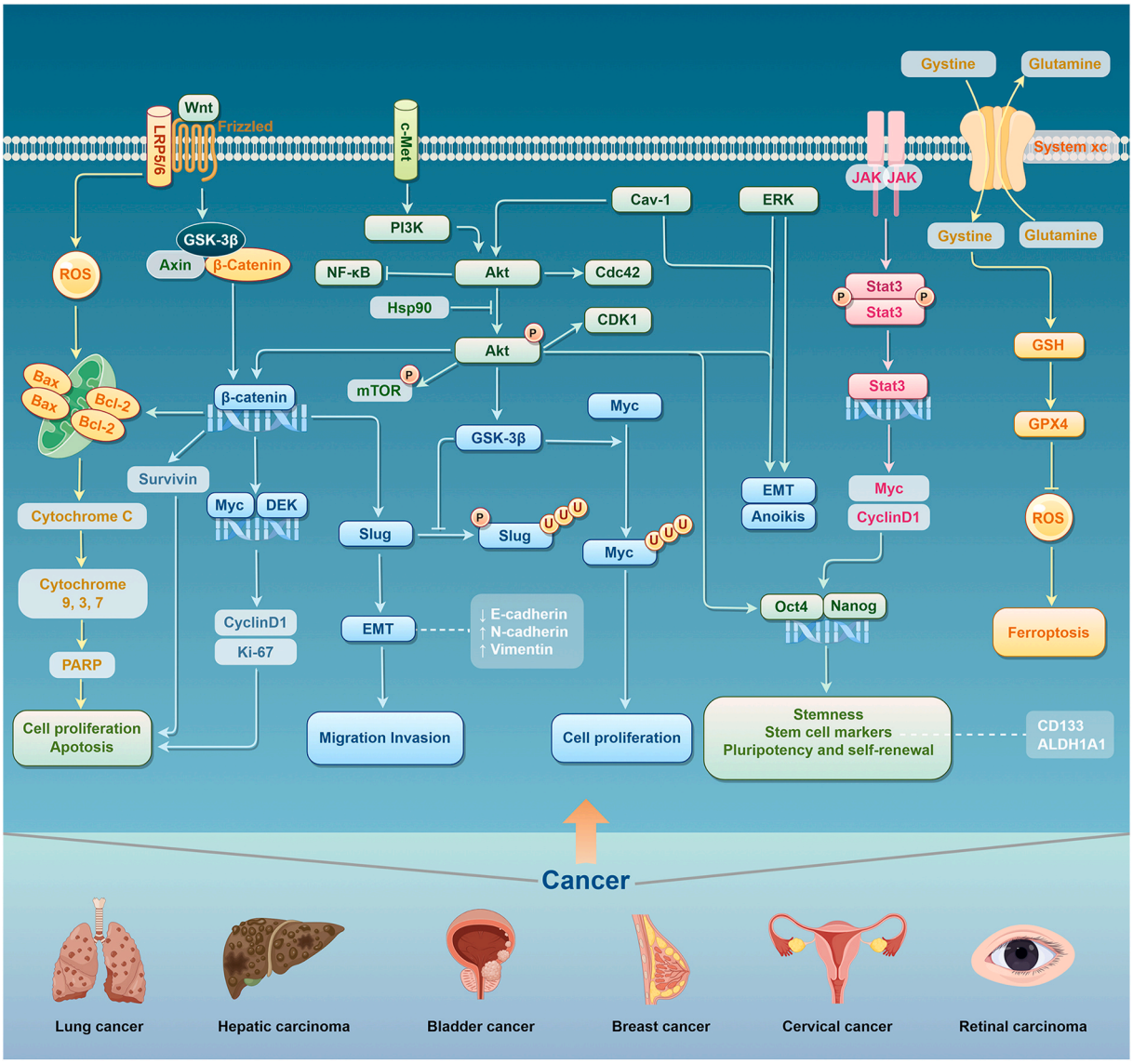

Fig. 2. A summary of the processes through which gigantol exerts its antitumor effects across various cancer types.

metabolism via Acetyl-CoA Carboxylase (ACC) (Nuamnaichati et al., 2025). In parallel, gigantol also inhibits the Akt/GSK-3β pathway, further improving insulin sensitivity. In contrast, gigantol exhibits potent α-glucosidase inhibitory activity, which is essential to control postprandial hyperglycemia (Hsieh et al., 2024; Sarakulwattana et al., 2020). At 437.5 μM, it achieves 36.7 % inhibition of α-glucosidase, surpassing the standard drug acarbose (29.9 %) in a dose-dependent manner (Sun et al., 2014). Collectively, these findings indicate that current evidence primarily supports gigantol's therapeutic relevance in type 2 diabetes , particularly through improving insulin sensitivity and attenuating postprandial glucose excursions.

3.2.2. Diabetic nephropathy

Diabetic nephropathy, a common cause of end-stage renal disease, is characterized by increased oxidative stress, which triggers various pathological processes, including inflammation, podocyte damage, extracellular matrix accumulation and glomerulosclerosis (Jin et al., 2023). Excessive production of (ROS) and free radicals under hyperglycemic conditions leads to the destruction of the body's antioxidant defenses and depletion of GSH, exacerbating oxidative stress (Rani et al., 2016; Volpe et al., 2018). In high-glucose-treated mesangial cells (MES-13), gigantol mitigates oxidative damage by suppressing ROS/Mitogen-Activated protein kinase (MAPK)/NF-κB signaling (Chen et al., 2019; Li, Z. et al., 2023). Pretreatment with gigantol restores glutathione levels, reduces malondialdehyde (MDA) production, and alleviates mitochondrial dysfunction—evidenced by preserved membrane potential, ATP replenishment, and inhibition of cytochrome *c* release. Additionally, gigantol modulates the Bax/Bcl-2 balance and attenuates caspase-9/3 activation, thereby blocking apoptosis in renal cells (Chen et al., 2019). These findings highlight the potential of interrupting the "oxidative stress-inflammation" vicious cycle in DN.

3.2.3. Diabetic retinopathy

DR is one of the most prevalent complications of diabetes, involving oxidative stress, inflammation, and vascular dysfunction (Seo et al., 2025). High glucose-induced oxidative stress and inflammation significantly contribute to retinal pigment epithelial (RPE) cell damage, a hallmark of DR (Tosi et al., 2021; Willermain et al., 2018). In ARPE-19 cells (high-pigment epithelial cells), gigantol enhances cell viability, reduces apoptosis, and alleviates oxidative and inflammatory damage (Chen, Y. et al., 2024). Mechanistically, gigantol downregulated metadherin (MTDH) expression in a dose-dependent manner, thereby inactivating the NF-κB signaling pathway. Overexpression of MTDH partially reversed these protective effects, confirming MTDH as a critical mediator of the action of gigantol (Chen, Y. et al., 2024). This dual modulation of oxidative stress and inflammation positions gigantol as a potential therapeutic agent for DR.

3.2.4. Diabetic cataracts

The incidence of cataracts is markedly higher in patients with diabetes, with a reported fivefold increase over non-diabetic populations, and is particularly high in younger patients with type 2 diabetes (Obrosova et al., 2010). The key pathogenesis underlying DC is the accumulation of sorbitol in the lens and oxidative damage triggered by the action of aldose reductase (AR) (Pollreisz and Schmidt-Erfurth, 2010). Gigantol has been shown to directly inhibit AR activity (IC_{50} = 65.67 μg/mL) and suppresses AR gene expression by 51.2 % in human lens epithelial cells (HLECs) (Fang et al., 2015; Wu et al., 2017; Yang et al., 2019). Molecular docking and atomic force microscopy have revealed that gigantol interacts with AR at catalytic residues (Trp111, His110, Tyr48, and Trp20), as well as with Iinducible Nitric Oxide Synthase (iNOS) at Ile195 and Gln257, thereby reducing oxidative stress and lens opacification (Fang et al., 2015; Yang et al., 2019). Gigantol combined with syringic acid synergistically enhances AR inhibition and sorbitol reduction, as demonstrated by enzyme kinetics and mutant AR (Asn160Ala) studies (Wu et al., 2016). These actions preserve lens transparency in streptozotocin-induced diabetic rats, validating the traditional use of gigantol for cataract prevention (Fang et al., 2015).

Gigantol exerts significant efficacy against diabetes and its microvascular complications by concurrently regulating glucose homeostasis, oxidative stress, and inflammatory cascades (Fig. 3). It directly inhibits α-glucosidase to blunt postprandial hyperglycemia while concurrently activating the AMPK/ACC pathway and inhibiting Akt/GSK-3β signaling within skeletal muscle and adipocytes, facilitating glucose uptake and reducing lipogenic activity, thereby mitigating both insulin resistance and dyslipidemia commonly observed in type 2 diabetic conditions. For diabetic complications, gigantol silences ROS/MAPK/NF-κB signaling to quench oxidative stress and mitochondrial apoptosis in mesangial cells in nephropathy; in retinopathy, it downregulates the MTDH/NF-κB nexus to shield the retinal pigment epithelium from hyperglycemic damage; and in cataracts, it sterically blocks AR at catalytic residues to halt sorbitol accumulation and lens opacification, synergizing with syringic acid to potentiate AR inhibition. These findings validate the traditional use of *Dendrobium* species for "Xiaoke" (diabetes) and eye disorders (Li, M. et al., 2022), positioning gigantol as a promising lead compound for ethnopharmacological development against diabetic complications. Overall, available data indicate that gigantol primarily targets mechanisms of type 2 diabetes, with limited but emerging evidence of benefit in type 1 diabetes complications.

3.3. Anti-inflammatory activity

Inflammation is a protective physiological response of the host to tissue damage, restoring homeostasis and combating infections, although it may also occur under sterile conditions. While acute inflammation is protective, chronic inflammation can lead to tissue damage and contribute to autoimmune and inflammatory diseases (Alessandri et al., 2013). The inflammatory cascade involves immune cell recruitment (e.g., leukocytes), activation of macrophages/mast cells, and the release of mediators, such as cytokines and chemokines. Persistent stimuli may result in chronic inflammation, which is characterized by granuloma formation and T-cell infiltration (Medzhitov, 2008). Growing evidence highlights the therapeutic potential of gigantol in diverse inflammatory models (Al-Khayri et al., 2023; Chowdhury et al., 2025), with key mechanisms outlined below.

NF-κB, a master regulator of inflammation, operates via canonical (IKKβ-mediated IκB degradation) and non-canonical (IKKα-dependent p100 processing) pathways, driving pro-inflammatory cytokine production (Tumor Necrosis Factor Alpha (TNF-α), interleukin (IL)-1β, IL-6) and enzyme expression (iNOS and COX-2 (PTGS2,Prostaglandin-Endoperoxide Synthase 2) (Medzhitov, 2008). In chronic inflammation, NF-κB exerts harmful effects by inducing the expression of pro-inflammatory mediators that coordinate and maintain the inflammatory response, leading to tissue damage (Tornatore et al., 2012). Gigantol inhibits LPS-induced NF-κB activation in RAW 264.7 macrophages, reducing NO, Prostaglandin E2 (PGE_2), and TNF-α levels by suppressing iNOS and COX-2 mRNA transcription (Won et al., 2006). During inflammation, large amounts of pro-inflammatory mediators, such as NO and PGE_2, are produced by the inducible isoforms of iNOS and COX-2 (Vane et al., 1994). Therefore, the inhibition of NO and PGE_2 release may result from suppressed mRNA transcription of iNOS and COX-2. NF-κB is essential for controlling genes that ensure cell survival and manage the production of pro-inflammatory enzymes and cytokines, including iNOS, COX-2, TNF-α, IL-1β, and IL-6 (Surh et al., 2001). Further studies have shown that gigantol inhibits NF-κB activation, which explains the downregulation of iNOS, COX-2, and cytokine expressions (Won et al., 2006). This effect was independent of cytotoxicity at 150 μg/mL concentration (Won et al., 2006). Additionally, another study found that gigantol extracted from *Rhynchostylis retusa* (L.) Blume inhibited RAW 264.7 cell viability with an IC_{50} value of 45.7 ± 0.6 μM (Al-Amin et al., 2023). *Rhynchostylis retusa* has traditionally been used to treat pain, inflammation, and skin diseases, suggesting that gigantol has

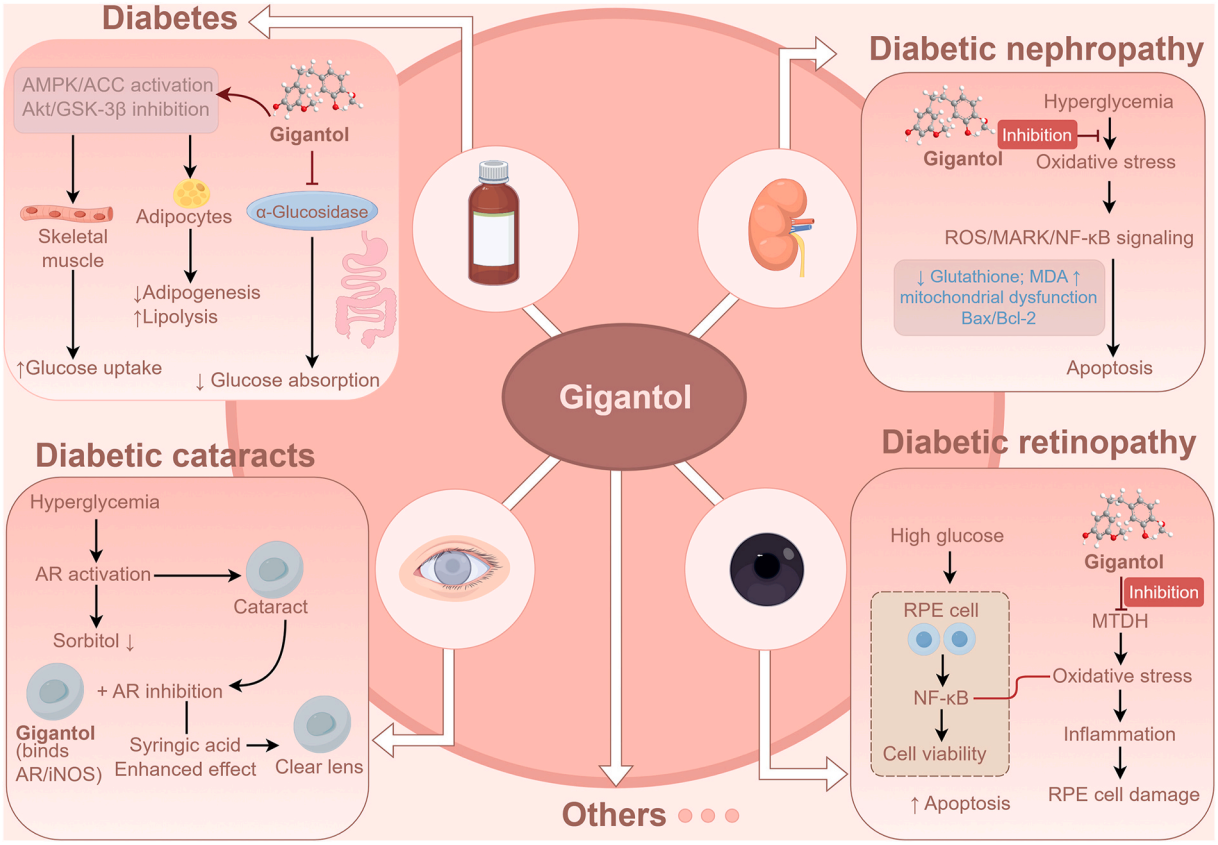

Fig. 3. Schematic representation of gigantol-mediated protection in diabetes and related pathologies.

potential therapeutic applications in pain- and inflammation-related disorders (Al-Amin et al., 2023). In UVB-irradiated HaCaT keratinocytes, gigantol (≥2.87 μM) attenuates PGE_2 release and COX-2 protein expression without directly inhibiting COX-2 enzymatic activity, suggesting transcriptional regulation (Simmler et al., 2010). PGE_2, catalyzed by COX-2, plays a crucial role in UVB-induced skin inflammation by promoting skin erythema, swelling, and other inflammatory responses (Tripp et al., 2003). Gigantol's ability to inhibit UVB-induced PGE_2 release is notable, indicating its potential for use in anti-inflammatory and photoprotective skincare products.

Similarly, in dextran sulfate sodium (DSS)-induced colitis mice, gigantol inhibits NF-κB activation by reducing p65/IKKα/β phosphorylation, elevating IκBα, and alleviating colonic inflammation by upregulating tight junction proteins (Zonula Occludens-1 (ZO-1) and occludin), mucus-related genes (*Muc1/2/4*), and suppressing TNF-α, IL-1β, and IL-6 (Yu, W. et al., 2024). Furthermore, Gigantol disrupts β2 integrin-mediated macrophage adhesion and chemotaxis in RAW 264.7 cells (Yu, W. et al., 2024). β2 integrin is an important member of the integrin family that plays a critical role in immune cell adhesion, migration, and activation, particularly in immune responses and inflammation (Wen et al., 2022). β2 integrin mediates leukocyte adhesion and transendothelial migration by binding to ligands, such as ICAM-1, on endothelial cells, activating downstream signaling pathways that induce Vav1 phosphorylation, which subsequently promotes Ras-related C3 Botulinum Toxin Substrate 1 (Rac1) activation through its guanosine triphosphate (GTP)-activating protein function (Ni et al., 2023; Wen et al., 2022). By binding β2 integrin, it reduces ICAM-1 affinity, suppresses Vav1 phosphorylation, and inhibits Rac1-driven cytoskeletal remodeling, thereby blocking leukocyte migration (Yu, W. et al., 2024). These findings highlight the potent anti-inflammatory ability of gigantol, which involves not only the inhibition of the classical NF-κB signaling pathway but also the targeting of β2 integrin, blocking macrophage chemotaxis and migration, and regulating cytoskeletal remodeling in macrophages. This provides theoretical support for its application in the treatment of ulcerative colitis and other inflammation-related conditions.

Gigantol is one of the four key active components of *Vanda tessellata* for treating osteoarthritis (alongside Vanillin, Daucosterol, and Syringaldehyde) (Padhee et al., 2024). Studies have revealed that gigantol exerts significant antiosteoarthritis activity through a polypharmacological synergistic mechanism. It inhibits the nuclear translocation of NF-κB and phosphorylation of MAPK/Signal Transducer and Activator of Transcription 3 (STAT3) signaling, effectively reducing the expression of inflammatory factors (IL-6, TNF-α) to alleviate joint inflammation (Padhee et al., 2024). Simultaneously, it suppresses the activity of matrix metalloproteinases, such as Matrix Metalloproteinase-9 (MMP-9) (with mRNA expression reduced by 6.65-fold), thereby preventing cartilage matrix degradation. These effects are further reinforced by its high-affinity binding to hub targets, including BCL2 (binding affinity: 9.5 kcal/mol), ESR1 (−9.3 kcal/mol), and MMP9 (−9.3 kcal/mol), which modulate apoptosis, estrogen signaling, and the hypoxia-inducible factor-1 (HIF-1) pathway, ultimately mediating joint protection through multiple signaling pathways (Padhee et al., 2024).

Arachidonic acid (AA) is a fatty acid that affects various physiological functions, including body temperature regulation, cardiovascular function, pain induction, immune response, and inflammation (Kaur et al., 2019). The AA pathway produces proinflammatory mediators that orchestrate the inflammatory response (Joshi et al., 2016). Research indicates that CCl_4 activates the JNK pathway and phosphorylates cytosolic phospholipase A2 (cPLA2), which releases AA and generates pro-inflammatory metabolites, such as 12-hydroxyeicosatetraenoic acid (12-HETE), via the 12-lipoxygenase (LOX) pathway, leading to liver damage (Xue et al., 2020a). Gigantol reduces immune cell activity,

inhibits JNK and cPLA2 activation, and alleviates liver damage by modulating AA metabolism, particularly via the 12-LOX-12-HETE pathway (Xue et al., 2020a). It also inhibits the expression of 12-LOX genes and proteins, with effects similar to those of pan-LOX inhibitors (Xue et al., 2020a). Overall, gigantol mitigated CCl_4-induced liver inflammation by targeting the JNK/cPLA2/12-LOX signaling axis and modulating the immune cell phenotypes. Another study found that gigantol downregulated complement component C9 expression, preventing C5b-9 formation, and reducing its deposition in the liver vasculature, thereby alleviating CCl_4-induced liver injury (Xue et al., 2020b). Moreover, gigantol dose-dependently inhibited inflammatory edema in a carrageenan-induced rat inflammation model, demonstrating its anti-inflammatory effects similar to those of classic non-steroidal anti-inflammatory drugs (NSAIDs) (Déciga-Campos et al., 2007).

Gigantol mitigates inflammation by coordinating multiple pathways—limiting β2-integrin/Vav1/Rac1–dependent leukocyte trafficking, restraining MAPK/STAT3 phosphorylation, reprogramming arachidonic-acid metabolism via the JNK/cPLA2/12-LOX axis with downstream suppression of COX-2/PGE_2, and modulating complement activation—as demonstrated in colitis, UVB-induced skin injury, and liver damage models (Fig. 4). NF-κB signaling is consistently attenuated across these settings; however, the precise node of interference—whether at IκBα phosphorylation, p65 nuclear translocation, or DNA binding—remains undefined, underscoring the need for further mechanistic study.

3.4. Antioxidant activity

Recent studies have demonstrated the potent antioxidant properties of gigantol. Oxidative stress, a critical pathological mechanism underlying various diseases such as cardiovascular disorders, neurodegenerative diseases, cancer, and diabetes (Bai et al., 2022; Liguori et al., 2018), arises from an imbalance between free radical generation and the endogenous antioxidant defense system, leading to cellular damage. Gigantol mitigates oxidative stress by scavenging free radicals, suppressing ROS production, and enhancing intrinsic antioxidant defense. Gigantol extracted from *Dendrobium* fimbriatum exhibited excellent 2,2-Diphenyl-1-picrylhydrazyl (DPPH) and ABTS free radical scavenging abilities, as well as ferric reducing antioxidant power (FRAP) iron reduction ability (Padhee et al., 2024). *In vitro* studies have revealed that gigantol displays significant DPPH radical scavenging capacity (Sritularak et al., 2011), with IC_{50} values of 14.01 ± 1.69 mM (DPPH), 0.157 ± 0.039 mM (NOH), and 20.6 mM (intracellular ROS) in H_2O_2-induced HaCaT keratinocytes (Simmler et al., 2010). Additionally, gigantol markedly reduced ROS generation in lithocholic acid-treated human and primary hepatocytes and enhanced cell viability (Xue et al., 2020b). *In vivo*, gigantol attenuated CCl_4-induced hepatic oxidative stress by lowering MDA levels and elevating superoxide dismutase (SOD) activity, thereby exerting hepatoprotective effects (Xue et al., 2020b). Notably, gigantol pretreatment dose-dependently protected rat bone marrow mesenchymal stem cells (rBMSCs) from H_2O_2-induced apoptosis. It reduced intracellular ROS accumulation, suppressed morphological alterations, and decreased apoptosis. Mechanistically, gigantol activated the PI3K/Akt pathway, upregulating (p-Akt and the anti-apoptotic protein Bcl-2 while downregulating pro-apoptotic proteins (Bax, caspase-3, and caspase-9). This protective effect was partially reversed by the PI3K inhibitor LY294002, confirming pathway dependency (Chen et al., 2018). These findings highlight the potential of gigantol to enhance mesenchymal stem cell survival in ischemic disease treatment (Chen et al., 2018).

In a separate study, gigantol was extracted from *Vanda roxburghii*, a plant traditionally used to treat neurological disorders. This study found that several phenolic compounds extracted from this plant, including

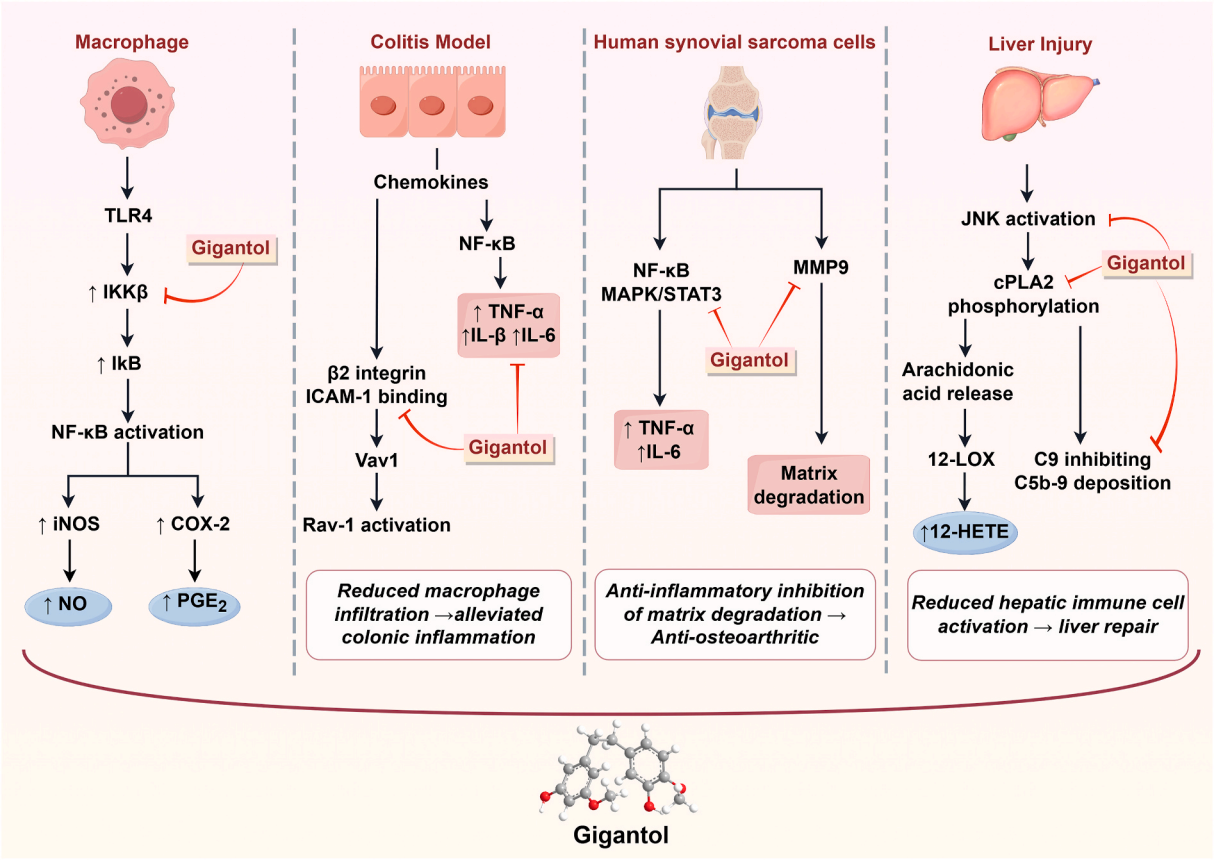

Fig. 4. Mechanisms of gigantol involved in the anti-inflammatory activity.

gigantol, exhibit strong antioxidant activities (Ahammed et al., 2021; Uddin et al., 2015). Gigantol, extracted from *Dendrobium* fimbriatum, exhibited acetylcholinesterase (AChE) inhibitory activity (IC_{50} = 176.05 μM), with binding sites including typical AChE activity center residues, such as Trp86, Tyr337, and Ser203 (Hsieh et al., 2024).

Gigantol exerts multifaceted antioxidant effects through ROS scavenging, enzymatic regulation, and the PI3K/Akt signaling pathway, suggesting its therapeutic potential in oxidative stress-related pathologies and neurodegenerative diseases.

3.5. Other pharmacological activities

Beyond its anticancer, antidiabetic, and anti-inflammatory effects, gigantol has also shown preliminary neuroprotective, hepatoprotective, and antimicrobial activities, although these remain less systematically studied. It exhibits potent smooth muscle relaxant activity, markedly inhibiting spontaneous contractions in the guinea pig ileum, with an IC50 value of 0.26 μM (Hernández-Romero et al., 2004). Gigantol also antagonizes acetylcholine-, histamine-, and barium chloride-induced contractions (Gutierrez and Solis, 2009). In both endothelium-intact and denuded rat aortic rings, gigantol concentration-dependently suppressed norepinephrine-induced contractions, with IC_{50} values of 1.68×10^6 M and 9.43×10^5 M, respectively (Estrada-Soto et al., 2006).

Smooth muscle relaxation is partially mediated by the NO/cGMP signaling pathway. Gigantol elevates cGMP levels in rat ileal rings and enhances NO signaling, effects that are attenuated by the nitric oxide synthase inhibitor L-NAME and the guanylate cyclase inhibitor ODQ (Estrada-Soto et al., 2006; Gutierrez and Solis, 2009; Hernández-Romero et al., 2004). Furthermore, gigantol inhibits calmodulin (CaM) activity, disrupting CaM-dependent enzymes (e.g., phosphodiesterase) and blocking contractile signaling (Gutierrez and Solis, 2009; Hernández-Romero et al., 2004). Furthermore, gigantol induced sustained vasorelaxation in denuded aortic rings, indicating endothelium-independent actions that may involve the blockade of α/β-adrenergic receptors (Estrada-Soto et al., 2006).

Gigantol also exerts peripheral analgesic effects by prolonging nociceptive response latency in mice (Déciga-Campos et al., 2007; Morales-Sánchez et al., 2014). This analgesia is partially reversed by the opioid receptor antagonist naloxone but is unaffected by L-NAME or the ATP-sensitive K^+ channel blocker glibenclamide, indicating partial opioid receptor dependency without NO or K^+ channel involvement (Déciga-Campos et al., 2007). Notably, gigantol enhances TNF and IL-6 production in LPS-stimulated human Peripheral Blood Mononuclear Cells (PBMCs) and unstimulated monocytes, suggesting its immunomodulatory potential under specific conditions (Khoonrit et al., 2020; Kongkatitham et al., 2024).

Additionally, gigantol enhances steroidogenesis by upregulating cholesterol/steroid synthesis-related genes (e.g., *StAR* and *Fdx1*), thereby promoting progesterone production in MA-10 Leydig cells (Basque et al., 2022). It also re-sensitizes multidrug-resistant gram-negative bacteria to colistin by suppressing *mcr-1* expression and enzymatic activity, demonstrating synergistic therapeutic efficacy and safety in preclinical models (Huang et al., 2023). Moreover, gigantol exhibits dose-dependent tyrosinase inhibition, ameliorates cell cycle arrest, and delays senescence in normal human fibroblasts (Axiotis et al., 2022; Bonté et al., 2011).

In summary, gigantol is a naturally occurring bioactive compound with a wide array of pharmacological activities, including anticancer, antidiabetic, anti-inflammatory, and antioxidative activities (Fig. 5). The anticancer and other biological activities of gigantol are

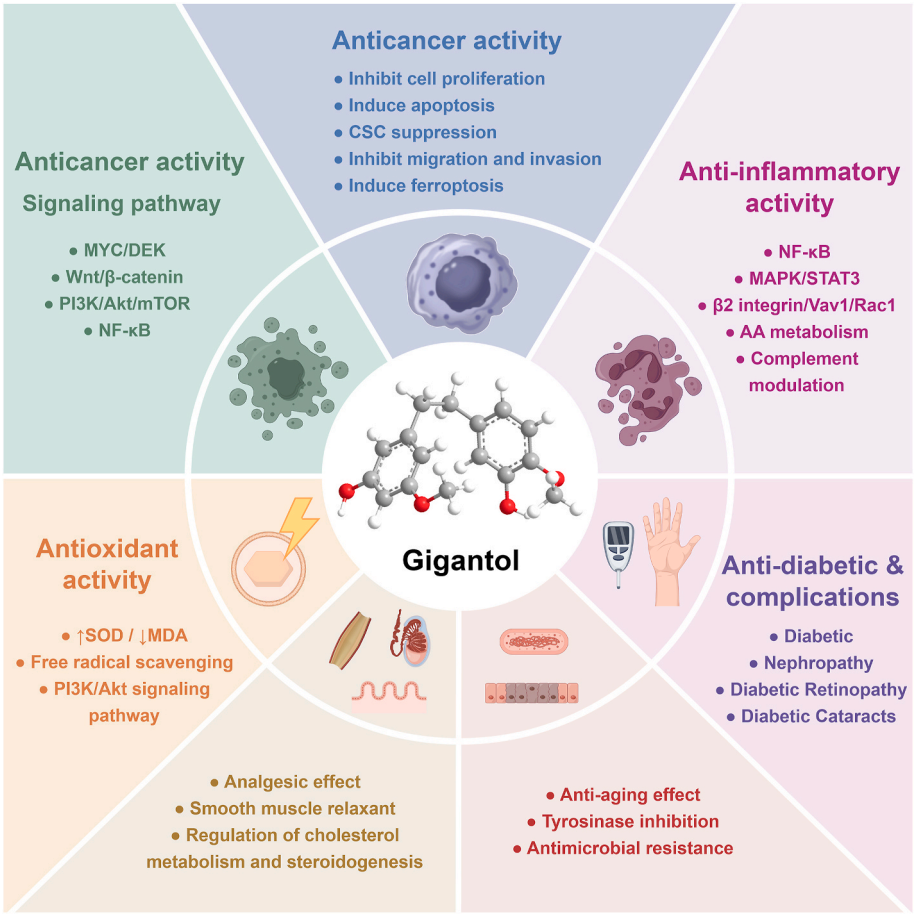

Fig. 5. Summary diagram of the pharmacological properties of gigantol.

systematically summarized in Tables 3 and 4. Notably, its antitumor effects are mediated by the modulation of key signaling pathways, such as NF-κB, Wnt/β-catenin, PI3K/Akt, and GSK3β/MYC, exerting anti-proliferative and antimigratory effects across various cancer models. These findings underscore the potential of gigantol for the treatment of multiple diseases. However, many *in vivo* studies reported significant effects without providing sufficient details on statistical analyses, control group sizes, or standardized dosing regimens, and the use of positive controls or reference inhibitors was seldom included. These limitations reduce comparability across studies and highlight the need for more rigorously designed experiments. Furthermore, current evidence is predominantly derived from *in vitro* and animal studies, necessitating further clinical trials to confirm its effectiveness and safety in humans.

4. Pharmacokinetics of gigantol

Pharmacokinetic evaluation is essential for characterizing the absorption, distribution, metabolism, and excretion (ADME) properties of active ingredients isolated from traditional Chinese medicine. Such studies provide a scientific basis for understanding their *in vivo* dynamics, optimizing clinical dosing strategies, and ensuring their efficacy and safety for therapeutic use. Gigantol exhibits ADME properties, as evidenced by recent experimental studies (Fig. 6).

Pharmacokinetic experiments in ICR mice have shown that gigantol is rapidly absorbed following both oral and intravenous administration, with plasma concentrations peaking within 5 min. However, its absolute oral bioavailability is relatively low (~11.5 %), likely due to significant first-pass hepatic metabolism (Xue et al., 2020b). In silico ADME predictions (e.g., SwissADME) indicate favorable gastrointestinal absorption, supported by moderate molecular weight, appropriate lipophilicity, and moderate water solubility (Chowdhury et al., 2025). These findings suggest that the low oral bioavailability of gigantol is primarily attributable to rapid metabolism rather than poor intestinal permeability. To date, no studies have directly assessed the contribution of efflux transporters such as P-glycoprotein (P-gp) to gigantol disposition, representing a relevant gap for future investigation. A key feature of gigantol is its pronounced hepatic accumulation:after oral or intravenous dosing, liver concentrations greatly exceed plasma, with liver-to-plasma C_max and $AUC_{0-24\ h}$ ratios of ~26-fold and ~375-fold, respectively (Xue et al., 2020b). This hepatic enrichment aligns with its hepatoprotective and anti-inflammatory pharmacodynamic profiles. By contrast, no experimental data are currently available regarding blood–brain barrier (BBB) permeability. In silico properties (moderate molecular weight, high plasma-protein binding, and only moderate lipophilicity) do not favor efficient BBB penetration, although this requires experimental verification.Metabolic studies have consistently demonstrated predominant phase II conjugation for gigantol. In rat urine, 11 metabolites have been identified—exclusively phase II products such as glucuronides and glutathione (GSH) conjugates— with no phase I intermediates detected (Fan et al., 2014). Complementary *in vitro* studies using hepatocytes from rats, dogs, monkeys, and humans further confirmed that glucuronidation is the major metabolic pathway across species; additional metabolic transformations include hydroxylation, followed by glucuronidation or GSH conjugation, and demethylation, followed by GSH conjugation. Among identified metabolites, glucuronides are the most abundant in all species, and monkey hepatocytes show the closest profile to human, supporting their suitability as preclinical models (Wang, J. et al., 2020). However, the specific UGT or SULT isoforms responsible for these conjugations remain undefined, limiting predictions of drug–drug interactions and interindividual variability. Urinary excretion is the primary route of elimination for gigantol metabolites: multiple conjugated metabolites are detected in rat urine, whilethe parent compound appears present only in trace amounts, indicating extensive hepatic metabolism before elimination (Fan et al., 2014). In mice, elimination is rapid, with short half-lives of 0.17 h (oral) and 0.06 h (i.v.), and a predicted clearance of 12.81 mL/min/kg consistent with moderate cleared compounds (Chowdhury et al., 2025; Xue et al., 2020b). A high predicted plasma-protein binding (PPB) of ~97.2 % may further modulate free drug levels and distribution kinetics (Chowdhury et al., 2025).

In silico toxicological profiling predicts a high LD_{50} (2260 mg/kg; toxicity category 5) andow risk of hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, or cytotoxicity (Chowdhury et al., 2025).These predictions, however, lack *in vivo* or clinical confirmation; thus, the safety profile of gigantol remains preliminary and warrants comprehensive acute, chronic, and organ-specific toxicology studies.

Given the rapid metabolism and low oral bioavailability, formulation and medicinal-chemistry strategies—such as nanocarriers or prodrug approaches—may be required to enhance systemic exposure and enable translation.

5. Network pharmacology and molecular docking analysis

Network pharmacology provides a systems-level view that links gigantol's diverse molecular interactions to disease modules, complementing experimental pharmacology. By integrating target prediction, disease association mining, PPI topology, and functional enrichment, this analysis helps rationalize the polypharmacological profile observed in cancer and inflammation models.

5.1. Network pharmacology analysis

First, 100 putative targets of gigantol were identified using the SwissTargetPrediction platform based on ligand structure similarity (Supplementary Table S1). Considering the reported pharmacological activities of gigantol, particularly its anticancer, antidiabetic, anti-inflammatory, and antioxidant effects, disease-related genes were retrieved from the GeneCards database using the keywords "cancer," "diabetes mellitus," "inflammation," and "oxidative stress," with a relevance score threshold of ≥10. After merging and deduplication, 6765 disease-associated genes were identified. The intersection between the predicted targets and disease genes yielded 89 overlapping targets (Fig. 7A), of which 83 were associated with cancer (Fig. 7B), suggesting that gigantol may exert significant antitumor effect. The overlap with diabetes-related genes was limited (37 genes; Fig. 7C); therefore, subsequent analyses focused on the total and cancer-specific target gene subsets only.

To explore the interactions among these targets, PPI networks were constructed using the STRING database (https://string-db.org/) with a medium confidence score threshold (≥0.4). The network was derived from 89 disease-related targets (Fig. 7D and E) comprised 89 nodes with an average degree of 11.76, betweenness centrality of 101.91, and closeness centrality of 0.0055, indicating a moderately dense regulatory structure. To prioritize biologically meaningful nodes, we operationally defined "hub targets" as proteins ranking within the top 10 % for degree and within at least the top quartile for betweenness in the corresponding network. Under these criteria, HSP90AA1, PTGS2, ESR1, Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2), CDK4, MAPK8emerged as hubs, consistent with their roles in oncogenic signaling, chaperone stress responses, prostaglandin synthesis, and hormone-dependent pathways. The cancer-specific subnetwork (83 targets; Fig. 7F and G) displayed slightly greater cohesion (average degree 12.13, betweenness 90.35, closeness 0.0061), with hub proteins including HSP90AA1, ESR1, CDK4, and insulin-like growth factor 1 receptor (IGF1R), further highlighting potential mechanisms involving cell cycle control and oncogenic signaling.

Functional enrichment analysis of the intersecting targets was conducted using DAVID. GO analysis focused on biological processes (BP), while KEGG pathway enrichment provided mechanistic insight. The top 25 GO (BP) terms and KEGG pathways are shown in Fig. 8, and the complete enrichment results are listed in Supplementary Table S2–S5. For the 89 overlapping genes between gigantol and all disease-

Table 3
Antitumor pharmacological effects of gigantol.

Diseases	Pharmacological effects	Types	Animal/cell	Dosage	Effects	References
NSCLC	Inhibition of cell proliferation and induction of apoptosis	*In vitro*	A549 cells	25, 50, 100 μM	Gigantol inhibited cell proliferation and promoted apoptosis by targeting DEK; gigantol decreased the expression levels of Ki-67 and Bcl-2, increased the expression level of Bax, and inactivated the Wnt/β-catenin signaling pathway.	Cai et al. (2021)
NSCLC	Anti-migration and invasion	*In vitro*	H460 cells	5, 10, 20 μM	Gigantol inhibited filopodia formation by down-regulating Cav-1 and activating ATP-dependent tyrosine kinase (Ser 473 phosphorylated Akt) and Cdc42.	Charoenrungruang et al. (2014)
Lung cancer	Inhibition of cell proliferation and induction of apoptosis	*In vitro*	H460, A549, H292 cells	5, 10, 20 μM	Gigantol inhibited lung cancer proliferation through induction of GSK3β-mediated MYC ubiquitin-proteasome degradation.	Losuwannarak et al. (2020)
Lung cancer	Induction of ferroptosis	*In vitro/in vivo*	H460, A549 cells; subcutaneous tumor model in BALB/c nude mice	50, 100, 150 μM; 30, 60 mg/kg	Gigantol induced ferroptosis in lung cancer cells by targeting the SLC7A11-GPX4 signaling axis.	Chen et al. (2024)
Lung cancer	Inhibition of cell proliferation and induction of apoptosis	*In vitro/in vivo*	H460, A549, H292 cells; subcutaneous tumor model in BALB/c nude mice	10, 20, 50, 100, 200 μM	Gigantol weakened CSCs and reduced tumor integrity by inhibiting PI3K/AKT/mTOR and JAK/STAT-related pathways and enhancing JNK signaling.	Losuwannarak et al. (2019)
Lung cancer	Inhibition of cell proliferation and induction of apoptosis	*In vitro*	H460 cells	1, 5, 10, 20 μM	Gigantol significantly reduced the expression of CSC markers, including CD133 and ALDH1A1; gigantol reduces the stemness of cancer cells by inhibiting the activation of Akt signaling, thereby reducing cell pluripotency and cellular levels of the self-renewal factors Oct4 and Nanog.	Bhummaphan and Chanvorachote (2015)
Lung cancer	Anti-migration and invasion	*In vitro*	H460 cells	1, 2, 5, 10, 20 μM	Gigantol attenuated the activity of ATP-dependent tyrosine kinase (AKT), thereby inhibiting the expression of Slug, a major EMT transcription factor, by reducing its transcription and increasing its degradation, thereby inhibiting lung cancer metastasis.	Unahabhokha et al. (2016b)
Lung cancer	Anti-migration and invasion	*In vitro*	H460 cells	5, 10, 20 μM	Gigantol inhibited the metastasis and migration of lung cancer cells by inhibiting c-Met and its downstream PI3K/AKT signaling pathway.	Aksorn et al. (2021)
Lung cancer	Anti-migration and invasion	*In vitro*	H460 cells	1, 5, 10, 20 μM	Significant reduction of EMT markers, including N-cadherin, Vimentin, and Slug, resulted in significant inhibition of AKT, ERK, and Cav-1 survival pathways in the isolated state.	Unahabhokha et al. (2016a)
Lung cancer	Anti-migration and invasion	*In vitro*	H460 cells	0.1 μg/ml	Gigantol exhibited appreciable cytotoxic properties against H460 cells.	Klongkumnuankarn et al. (2015)
Hepatic carcinoma	Inhibition of cell proliferation and induction of apoptosis	*In vitro*	HepG2 cells	1, 40, 150 μM	Gigantol enhanced the activities of caspase-3, PARP and p53, down-regulated the expression of p-Akt/Akt, and induced growth inhibition and apoptosis of hepatoma cells through the PI3K/Akt/NF-κB signaling pathway.	Chen et al. (2017)
Hepatic carcinoma	Inhibition of cell proliferation and induction of apoptosis; anti-migration and invasion	*In vitro*	SMMC-7721, Hep3B and HCC-LM3 cells	25, 50, 100 μM	gigantol may inhibit the progression of HCC through HSP90/Akt/CDK1 pathway.	Li et al. (2022)
Bladder cancer	Inhibition of cell proliferation and induction of apoptosis	*In vitro*	SW780, 5637, and T24 cells	40, 80, 160 μM	The expressions of Axin2, Survivin, Slug and Vimentin were significantly decreased in SW780 and 5637 cells treated with gigantol. gigantol may inhibit the invasion and migration of bladder cancer cells by inhibiting Wnt/EMT signaling pathway.	Zhao et al. (2020)
Breast cancer	Inhibition of cell proliferation and induction of apoptosis	*In vitro*	MDA-MB-468, MCF-7 cells	20, 40, 60 μM	Gigantol enhanced the DDP-induced anticancer effect by down-regulating the PI3K/Akt/mTOR signaling pathway in Breast cancer cells.	Huang et al. (2021)
Breast cancer	Inhibition of cell proliferation and induction of apoptosis	*In vitro*	MDA-MB-231, MDA-MB-468 cells	10, 25, 50, 75, 100 μM	Gigantol inhibited Wnt/β-catenin signaling by down-regulating phosphorylated LRP6 and cytoplasmic β-catenin in breast cancer cells.	Yu et al. (2018)
Breast cancer	Inhibition of cell proliferation and induction of apoptosis	*In vitro*	MDA-MB-231 cells	–	Gigantol could inhibit the activity of MDA-MB-231 cells with an IC_{50} value of 64.2 ± 1.1 μM.	Al-Amin et al. (2023)

(*continued on next page*)

Table 3 (*continued*)

Diseases	Pharmacological effects	Types	Animal/cell	Dosage	Effects	References
Cervical cancer	Inhibition of cell proliferation and induction of apoptosis	*In vitro*	HeLa cells	10, 20 μM	Gigantol inhibited HeLa cell proliferation and enhanced oxidative stress to induce apoptosis by regulating Wnt/β-catenin signaling pathway.	Kang et al. (2022)
Retinoblastoma	Anti-migration and invasion	*In vitro*	Y79 SO-RB50 cells	50, 60, 100, 120, 180, 200 mM	Gigantol suppressed tumor cell viability and downregulated multiple pro-invasive proteins in RB tissues, highlighting its broad-spectrum anticancer potential.	Zhang et al. (2021)
Glioma	Inhibition of cell proliferation and induction of apoptosis	*In vitro/in vivo*	LN229, T98G cells; subcutaneous tumor mouse model	100 μM; 10 mg/kg	Gigantol inhibited Wnt/β-catenin signaling pathway, increased the efficacy of chemotherapy drugs, and significantly inhibited tumor development when combined with chemotherapy or radiotherapy.	Tao et al. (2021)

associated targets, GO analysis revealed significant enrichment in processes such as platelet-derived growth factor receptor-beta signaling, peptidyl-tyrosine phosphorylation, protein phosphorylation, regulation of kinase activity, and response to oxidative stress (Fig. 8A). These biological processes align closely with the reported effects of gigantol on apoptosis, kinase signaling, and redox homeostasis. KEGG pathway analysis of this target set further highlighted critical signaling pathways, including PI3K-Akt, MAPK, ErbB, TNF, and cytokine–cytokine receptor interactions (Fig. 8B). These pathways are involved in tumor growth, survival, inflammation, and angiogenesis, supporting the multifunctional pharmacological profile of gigantol. A focused enrichment of the 83 targets overlapping with cancer-related genes revealed similar GO terms related to cell proliferation, transmembrane receptor protein kinase activity, and negative regulation of apoptotic signaling, further validating the predicted anti-cancer functions of gigantol (Fig. 8C). KEGG analysis of the cancer-specific subset again emphasized the PI3K-Akt, ErbB, p53, and pathways in cancer, suggesting that gigantol may exert its antitumor activity by interfering with classical oncogenic signaling axes (Fig. 8D). Overall, GO and KEGG analyses indicated convergent enrichment in PI3K–Akt, NF-κB, HIF-1, estrogen signaling, and arachidonic-acid metabolism, offering a network-level rationale for the experimentally observed anticancer and anti-inflammatory effects.

5.2. Molecular docking analysis

Molecular docking analysis was conducted to further confirm the interaction between gigantol and its anticipated core targets, assessing the binding affinity and interaction patterns at the molecular level. Docking was performed using AutoDock Vina 1.1.2 to evaluate the binding affinity between gigantol and four hub protein targets (ESR1, HSP90AA1, IGF1R and PTGS2). Three-dimensional structures of the target proteins were obtained from the RCSB Protein Data Bank. Protein preparation was conducted using AutoDock Tools and PyMOL, which included the removal of water molecules and co-crystallized ligands, addition of polar hydrogens, and assignment of Gasteiger charges. The chemical structure of gigantol was retrieved from PubChem (CID: 3085362) and energy-minimized using ChemDraw prior to docking. The docking grid was defined to cover the entire protein structure of the target. Docking simulations generated nine binding poses per receptor, and the conformation exhibiting the lowest binding energy and highest frequency within the cluster was chosen as the most likely binding mode for each receptor. The conformation exhibiting the lowest binding energy and highest frequency within the cluster was chosen as the most likely binding mode for each receptor. The final docking results were visualized using PyMOL and analyzed using PLIP to visualize ligand–receptor interactions, including hydrogen bonds and key contacts.

As shown in Fig. 9, gigantol adopts favorable binding modes within the active sites of four target proteins (PTGS2, ESR1, HSP90AA1, and IGF1R), with distinct interaction patterns driving its its broad target-binding profile. In terms of binding energy, PTGS2 demonstrated the strongest interaction (−8.1 kcal/mol), suggesting that gigantol forms the most stable complex with this inflammation-related target. ESR1 followed closely (−7.5 kcal/mol), indicating a high affinity and potential relevance to hormone-related cancers. HSP90AA1 showed moderate binding (−7.1 kcal/mol), whereas IGF1R exhibited a relatively weaker interaction (−6.6 kcal/mol), although still within the biologically active threshold (≤−5.0 kcal/mol). The key binding parameters, interacting residues, and proposed mechanisms of gigantol with the four selected targets are summarized in Supplementary Table S6.

PTGS2 (COX-2), a classical pro-inflammatory enzyme, plays an important role in many inflammation-related diseases (Ma et al., 2023). COX-2 is a nodal enzyme in the inflammatory cascade, linking upstream pro-inflammatory signaling (NF-κB, MAPK) to the production of prostanoids that act through specific G protein-coupled receptors (GPCRs) to drive and resolve inflammation (Li, X. et al., 2025; Ren, Q. et al., 2020; Zhang et al., 2023). Its tightly regulated expression and function make it a strategic target for pharmacological control of inflammatory disorders. COX-2 exhibited the strongest binding affinity with gigantol (−8.1 kcal/mol). Structural analysis revealed that gigantol forms a robust hydrogen bond triad with HIS39A, ARG44A, and GLU465A, anchoring it deep within the catalytic pocket. Gigantol exerts anti-inflammatory effects by targeting the key regulators of COX-2 expression and signaling. It suppresses NF-κB activation, thereby reducing *COX-2* transcription and PGE_2 production in macrophages and keratinocytes (Simmler et al., 2010; Won et al., 2006). Gigantol also inhibits MAPK and STAT3 phosphorylation, further downregulating *COX-2* expression (Padhee et al., 2024; Yu, W. et al., 2024). Although it does not directly inhibit COX-2 enzymatic activity, molecular docking suggests a stable interaction that potentially influences enzyme conformation or accessibility. Additionally, gigantol modulates upstream arachidonic acid metabolism by inhibiting the $cPLA_2$ and 12-LOX pathways, thereby reducing inflammatory lipid mediators (Xue et al., 2020a). Thesepolypharmacological effects converge on the COX-2/PGE_2 axis, positioning COX-2 as a central effector in gigantol-mediated inflammation control. Collectively, these findings suggest that gigantol suppresses inflammation through multiple mechanisms, prominently by downregulating COX-2 expression via inhibition of the NF-κB and MAPK/STAT3 signaling pathways, rather than directly targeting COX-2 enzymatic function. It has a stable binding to COX-2 and the ability to reduce PGE_2 synthesis. These properties underscore the potential of gigantol as an anti-inflammatory agent acting through multiple signaling pathways, with therapeutic value in diseases such as colitis, UV-induced skin damage, and hepatic inflammation.

ESR1 is a ligand-dependent nuclear transcription factor involved in the progression of hormone-dependent cancers such as breast cancer. In the classical genomic pathway, estrogen (E2) binding promotes ESR1 dimerization and recruitment to estrogen response elements (EREs), activating genes related to the cell cycle, apoptosis inhibition, and metabolism (Cao et al., 2019; Nie et al., 2024; Wang et al., 2014).

Table 4
Other pharmacological effects of gigantol.

Pharmacological effects	Types	Animal/cell	Dosage	Effects	References
Anti-diabetes and its complications	*In vitro*	Mouse 3T3-L1 pre-adipocytes; human PCS-210-010 pre-adipocytes; and rat skeletal muscle L6 myoblasts	5, 15 and 25 μM	Gigantol exhibits potent metabolic regulatory effects by enhancing glucose uptake and inhibiting adipogenesis through modulation of GLUT expression and AMPK/Akt signaling pathways.	Nuamnaichati et al. (2025)
	In vitro	–	–	Gigantol inhibited α-glucosidase activity with an IC_{50} value of 103.1 ± 0.8 μM, significantly outperforming the reference drug acarbose with an IC_{50} value of 1076.4 ± 30.6 μM.	Sarakulwattana et al. (2020)
	In vitro	–	–	The inhibition of α-glucosidase (IC_{50} = 469.72 μM) was similar to that of the control drug Acarbose (IC_{50} = 490.00 μM).	Hsieh et al. (2024)
	In vitro	–	–	Gigantol inhibited α-glucosidase activity by 36.7 % at the concentration of 437.5 μmol/L, and its activity was concentration-dependent.	Sun et al. (2014)
	In vitro	MES-13 cells	1, 5, 10 and 20 μM	gigantol inhibited high glucose-induced renal dysfunction in MES-13 cells by inhibiting ROS/MAPK/NF-κB signaling pathway.	Chen et al. (2019)
	In vitro	ARPE-19 cells	5, 10 and 20 μM	Gigantol protected against high glucose-induced apoptosis, oxidative stress and inflammation by inhibiting the MTDH-mediated NF-kB signaling pathway.	Chen et al. (2024)
	In vitro	SRA01/04 cells	1 μg/mL	Gigantol inhibited the expression of the AR gene by interacting with the AR gene through insertion binding, thereby exerting its anti-cataract activity.	Wu et al. (2017)
	In vitro/in vivo	Streptozotocin-induced diabetic cataract rat model	1.1–10 mM; 2 mg/mL, 3 drops each time	gigantol inhibited AR activity and protected streptozotocin-induced DC.	Yang et al. (2019)
	In vitro/in vivo	Rat lenses/intraperitoneal injection of 50 % D-galactose - induced diabetic cataract rat model	2, 4 and 6 mg/mL; 4 mg/kg, 50 μL each time	Gigantol inhibited the lens opacity induced by galactose *in vitro* and *in vivo*, and inhibited the activity and gene expression of aldose reductase (AR) and inducible nitric oxide synthase (iNOS).	Fang et al. (2015)
	In vitro/in vivo	SRA01/04 cells/streptozotocin-induced diabetic cataract rat model	0.1, 0.5, 1.0 and 2.0 μg/mL; 4 mg/mL, 50 μL each time	Combined treatment with gigantol and syringic acid inhibits AR activity, down-regulated AR expression through impaired transcription, and decreases sorbitol levels, which synergistically protected both human lens epithelial cells cultured *in vitro* and streptozotocin-induced DC formation in rats.	Wu et al. (2016)
Anti-inflammatory activity	*In vitro*	LPS induced-RAW 264.7 cells	25, 50 and 100 μg/mL	Gigantol inhibited the expression of iNOS and COX-2 induced by LPS through inhibiting the activation of NF-κB, thereby reducing the production of NO and PGE_2; gigantol also inhibited the release of TNF-α, IL-1β, and IL-6.	Won et al. (2006)
	In vitro	RAW 264.7 cells	–	Gigantol could inhibit the activity of RAW 264.7 cells with an IC_{50} value of 45.7 ± 0.6 μM.	Al-Amin et al. (2023)
	In vitro	UVB-induced HaCaT cells	0.1 mM–100 mM	Gigantol inhibited PGE-2 production in a concentration-independent manner. The protein expression of COX-2 was inhibited, but its enzyme activity was not inhibited.	Simmler et al. (2010)
	In vivo	Carrageenan induced inflammation model in rats	25, 50 and 100 mg/kg	Gigantol inhibited the inflammatory edematous response in a dose-dependent manner.	Déciga-Campos et al. (2007)
	In vitro/in vivo	RAW 264.7 cells; DSS-induced ulcerative colitis model in mice	20 μM; 20 and 60 mg/kg	Gigantol inhibited NF-κB signaling pathway, targets β2 integrin, blocked macrophage chemotaxis and migration, and regulated cytoskeleton remodeling.	Yu et al. (2024)
	In vitro	IL-1β-induced human synovial sarcoma cells (SW982)	50–100 μg/ml (equivalent gigantol dosage)	Gigantol exerts anti-osteoarthritic effects by suppressing NF-κB/MAPK-driven inflammation and MMP-9-mediated cartilage degradation, while synergistically modulating apoptosis (via BCL2), estrogen signaling (ESR1), and HIF-1 pathways.	Padhee et al. (2024)
	In vivo	CCl_4 induced acute liver injury model in mice	40 mg/kg	Gigantol alleviated CCl_4-induced acute liver injury by inhibiting the JNK/cPLA2/12-LOX inflammatory pathway, reducing the generation of AA metabolites, and modulating the phenotype of immune cells.	Xue et al. (2020a)
	In vitro/in vivo	L929 cell, Rat primary hepatocytes, CCl_4 induced acute liver injury model in mice	0.1–250 μM; 10, 20 and 40 mg/kg	Gigantol attenuated CCl_4-induced inflammatory responses by inhibiting the expression of complement component C9 and the formation of the terminal complement complex C5b-9, as well as the production of proinflammatory cytokines such as TNF-α, IL-6, and IL-1β and the expression of chemokines such as MCP-1 and ICAM-1.	Xue et al. (2020b)

(*continued on next page*)

Table 4 (*continued*)

Pharmacological effects	Types	Animal/cell	Dosage	Effects	References
Antioxidant activity	*In vitro/in vivo*	Human induced hepatocytes, Bone marrow-derived macrophages CCl_4 induced acute liver injury model in mice	0.1–250 μM; 10, 20 and 40 mg/kg	Gigantol significantly alleviated CCl_4-induced liver oxidative damage by reducing the content of MDA and increasing the level of SOD.	Xue et al. (2020b)
	In vitro	Rat bone marrow mesenchymal stem cell	1, 10, 40, 80 and 100 μM	Gigantol inhibited H_2O_2 -induced apoptosis of rBMSCs by activating PI3K/Akt signaling pathway, reducing ROS production and regulating the expression of apoptosis-related proteins.	Chen et al. (2018)
	In vitro	–	6.25, 12.5, 25, 50 and 100 μg/mL	Gigantol showed strong antioxidant effects in terms of free radical scavenging, reducing power, total antioxidant capacity, and inhibition of lipid peroxidation.	Ahammed et al. (2021)
	In vitro	–	3.12, 6.25, 12.5, 25, 50 and 100 μg/mL	Gigantol has a strong free radical scavenging activity and shows an inhibitory effect on lipid peroxidation in rat brain homogenate.	Uddin et al. (2015)
	In vitro	HaCaT cells	–	Gigantol showed some free radical scavenging ability in terms of antioxidant activity.	Simmler et al. (2010)
	In vitro	–	–	Gigantol showed strong antioxidant activity in the experiments with an IC_{50} value of 17.7 μM.	Sritularak et al. (2011)
	In vitro	–	–	Gigantol exhibited excellent DPPH, ABTS free radical scavenging ability, FRAP iron reduction ability and AChE inhibitory activity.	Hsieh et al. (2024)
Smooth muscle relaxant effect	*In vitro*	Guinea-pig ileum model	0.14–2.36 μM	Gigantol significantly inhibited the spontaneous contraction of the guinea-pig ileum, with an IC50 value of 0.26 ± 0.10 μM, and inhibits the activity of CaM-dependent PDE (IC50 = 7.0 μM); it could bind to CaM and inhibit its function.	Hernández-Romero et al. (2004)
	In vitro	Guinea-pig ileum model	50–300 μg/mL	Gigantol inhibited spontaneous contractions of guinea pig ileum and antagonized contractions induced by three types of spasmogens: acetylcholine, histamine, and $BaCl_2$.	Gutierrez and Solis (2009)
	In vitro	Intact endothelial and endothelium-denuded rat aortic rings	0.01–100 μg/mL	Gigantol could significantly inhibit the contraction of rat aortic rings induced by norepinephrine in a concentration-dependent manner. The IC50 values in aortic rings with intact and removed endothelium were 1.68×10^{-6} M and 9.43×10^{-5} M, respectively.	Estrada-Soto et al. (2006)
Immunomodulatory effects	*In vitro*	LPS-stimulated PBMCS	1, 5, 10 and 20 μM	Gigantol induced the production of proinflammatory cytokines TNF and IL-6.	Kongkatitham et al. (2024)
	In vitro	PBMCs, monocytes	5, 10 and 20 μM	The expression of TNF and IL-6 was increased after Gigantol treatment.	Khoonrit et al. (2020)
Analgesic Effect	*In vivo*	acetic acid-induced writhing mouse model; hot-plate test mouse model	25, 50 and 100 mg/kg	Gigantol could significantly prolong the latency of nociceptive response in mice and has a peripheral analgesic effect.	Déciga-Campos et al. (2007)
Regulation of cholesterol metabolism and steroidogenesis	*In vitro*	Mouse MA-10 Leydig cells	1, 10, 100 μM	Gigantol promoted progesterone synthesis in MA-10 Leydig cells by upregulating genes involved in cholesterol metabolism and steroid synthesis.	Basque et al. (2022)
Antimicrobial resistance	*In vitro/in vivo*	Galleria mellonella infection model; mouse peritonitis-sepsis infection model	32–64 μg/mL; 10, 20 mg/kg	Gigantol restored and enhanced the antimicrobial efficacy of colistin against *mcr*-carrying resistant bacteria by boosting colistin's membrane-damaging action, curbing the expression of LPS-modification-related bacterial genes, and directly inhibiting MCR-1 enzyme activity.	Huang et al. (2023)
Tyrosinase inhibition	*In vitro*	–	25, 100, 250 μM	gigantol exhibited significant anti-tyrosinase activity.	Axiotis et al. (2022)
Anti-aging effect	*In vitro*	normal human fibroblasts	–	The extract containing gigantol significantly improved cell cycle arrest and delayed the senescence process.	Bonté et al. (2011)

Crosstalk between ESR1 and growth factor receptors (such as Epidermal Growth Factor Receptor (EGFR) and HER2) contributes to endocrine resistance (Jeselsohn et al., 2015). Clinically, mutations in the ligand-binding domain (e.g., Y537S and D538G) and ESR1 amplification lead to ligand-independent activity and therapy resistance. Molecular docking revealed that gigantol binds to ESR1 with a binding energy of −7.5 kcal/mol. It forms hydrogen bonds with GLU353A, ARG394A, and HIS524A and engages in π–π stacking with PHE404A, residues located within the canonical ligand-binding pocket. These interactions suggest a competitive mechanism by which gigantol interferes with estrogen signaling and ESR1-mediated transcriptional programs. Previous studies combining molecular docking and experimental validation identified ESR1 and HSP90AA1 as potential targets of gigantol, linking its antitumor effects in hepatocellular carcinoma to the disruption of the HSP90/Akt/CDK1 signaling axis (Li, S. et al., 2022). In addition, gigantol inhibits the Wnt/β-catenin and PI3K/Akt/mTOR pathways in breast cancer cells (Huang et al., 2021; Yu et al., 2018), supporting its therapeutic potential in ESR1-positive cancers. These results indicate that gigantol may suppress both genomic and non-genomic ESR1 signaling, offering therapeutic potential for overcoming hormone therapy resistance and treating ESR1-driven cancers.

HSP90AA1 functions as a molecular chaperone that is crucial for the conformational maturation and stability of various oncogenic proteins. It functions in an ATP-dependent manner, facilitating the proper folding of nascent polypeptides and maintaining the stability of mature client proteins, including various kinases and transcription factors

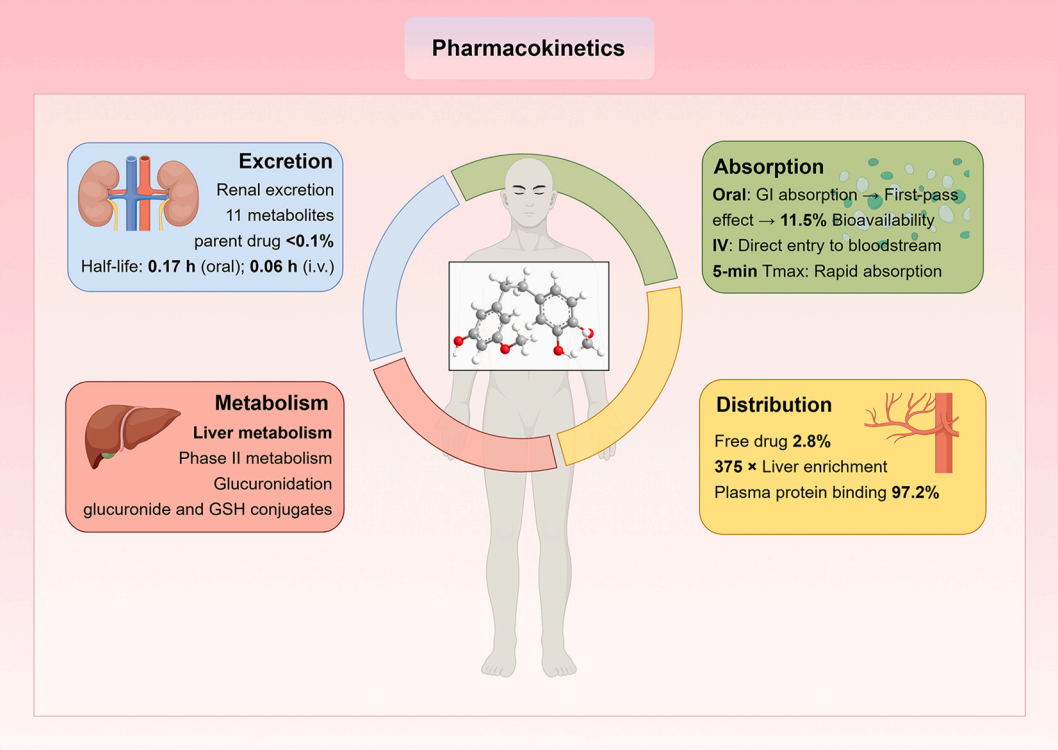

Fig. 6. Schematic representation of gigantol pharmacokinetics.

(Lorenzo-Gómez et al., 2023; Yang, S. et al., 2023). In multiple cancer types, HSP90AA1 promotes tumor progression by stabilizing oncoproteins, thereby enhancing proliferation, invasion, and drug resistance. Therefore, it is widely recognized as a promising therapeutic target in oncology (Chen et al., 2025; Li, Y. et al., 2025; Xiao et al., 2018). Molecular docking revealed that gigantol binds to HSP90AA1 with moderate affinity (−7.1 kcal/mol). It is accommodated within a hydrophobic cavity formed by residues such as LEU107A and PHE138A and establishes multiple hydrogen bonds with key residues ASN51A and SER52A located near the ATP-binding pocket. These interactions may interfere with the ATPase activity of HSP90, thereby disrupting its chaperone function and impairing downstream cancer-promoting signaling pathways, providing a potential mechanistic basis for its antitumor effect.

IGF1R is a transmembrane tyrosine kinase receptor that serves as a key regulator of growth. It promotes cell proliferation and inhibits apoptosis, thereby contributing to tissue development and maintaining homeostasis (Iams and Lovly, 2015). IGF1R is frequently overexpressed or hyperactivated in various malignancies, including lung, endometrial, and pancreatic cancers, where it facilitates tumor progression through the PI3K-Akt and Rat Sarcoma (RAS)-MAPK pathways while also enhancing resistance to chemotherapeutic agents (Liu, Z. et al., 2022; Stalnecker et al., 2022; Wang, Y. et al., 2020; Werner et al., 2018). Consequently, IGF1R is regarded as a promising therapeutic target in cancer treatment. Molecular docking analysis showed that gigantol exhibited the weakest binding affinity (−6.6 kcal/mol) among the four targets, yet remained within a biologically relevant range. The interaction pattern involved hydrophobic contacts with TRP404A and TYR508A, a hydrogen bond with GLN399A, and dual π–π stacking interactions with TRP404A. These features suggest a potential allosteric mode of inhibition that could suppress IGF1R kinase activity and downstream tumor-promoting signaling pathways.

Integrating target prediction with disease associations and PPI topology (cytoHubba degree/betweenness), we prioritized hub candidates (e.g., HSP90AA1, PTGS2, ESR1, ERBB2, IGF1R, CDK4, MAPK8), and GO/KEGG enrichment converged on PI3K–Akt, NF-κB, HIF-1, estrogen signaling, and arachidonic-acid metabolism, consistent with experimental pharmacology. Docking to the prioritized proteins yielded plausible poses aligned with pocket features but remains predictive; orthogonal validation—such as reference-ligand redocking/RMSD, score benchmarking, and binding/engagement assays (SPR/ITC, CETSA/DARTS) with site-directed perturbation—will be required to establish target engagement and causality.

6. Conclusion and future perspectives

Gigantol is a bibenzyl-type phenolic compound predominantly derived from *Dendrobium* species and is a promising focus of modern ethnopharmacological. Classical records (e.g., Shennong Bencao Jing ; the Compendium of Materia Medica) describe *Dendrobium* as “nourish Yin,” “brighten the eyes,” “clear internal heat,” and “relieve thirst,”notions that map onto chronic inflammation, oxidative stress, and metabolic imbalance in contemporary terms (Fu et al., 2023; Li et al., 2023) These historical uses are consistent with pharmacological findings showing that gigantol counters oxidative injury, regulates glucose metabolism, and attenuates pro-inflammatory signaling, providing a rational bridge from tradition to mechanism.

Pharmacologically, gigantol exerts robust biological activities against cancer, diabetes and its complications, inflammatory conditions, and oxidative stress. As demonstrated by a growing body of evidence, its anticancer efficacy is attributed to its ability to inhibit proliferation, migration, invasion, and cancer stemness, while inducing apoptosis and ferroptosis. Notably, gigantol modulates key oncogenic signaling pathways, including PI3K/Akt/mTOR, Wnt/β-catenin, MYC/DEK, c-Met, and NF-κB. It also disrupts redox balance and lipid metabolism via the SLC7A11-GPX4 ferroptosis axis, representing a novel anticancer mechanism. These pharmacological activities reinforce the historical use of *Dendrobium* for “heat clearance” and systemic detoxification. Importantly, the traditional use of *Dendrobium* for eye conditions invites further investigation of gigantol in modern retinal disease models, particularly in diabetic retinopathy, which features oxidative vascular damage and metabolic dysregulation.

In addition to its disease-specific effects, gigantol exhibits a multi-

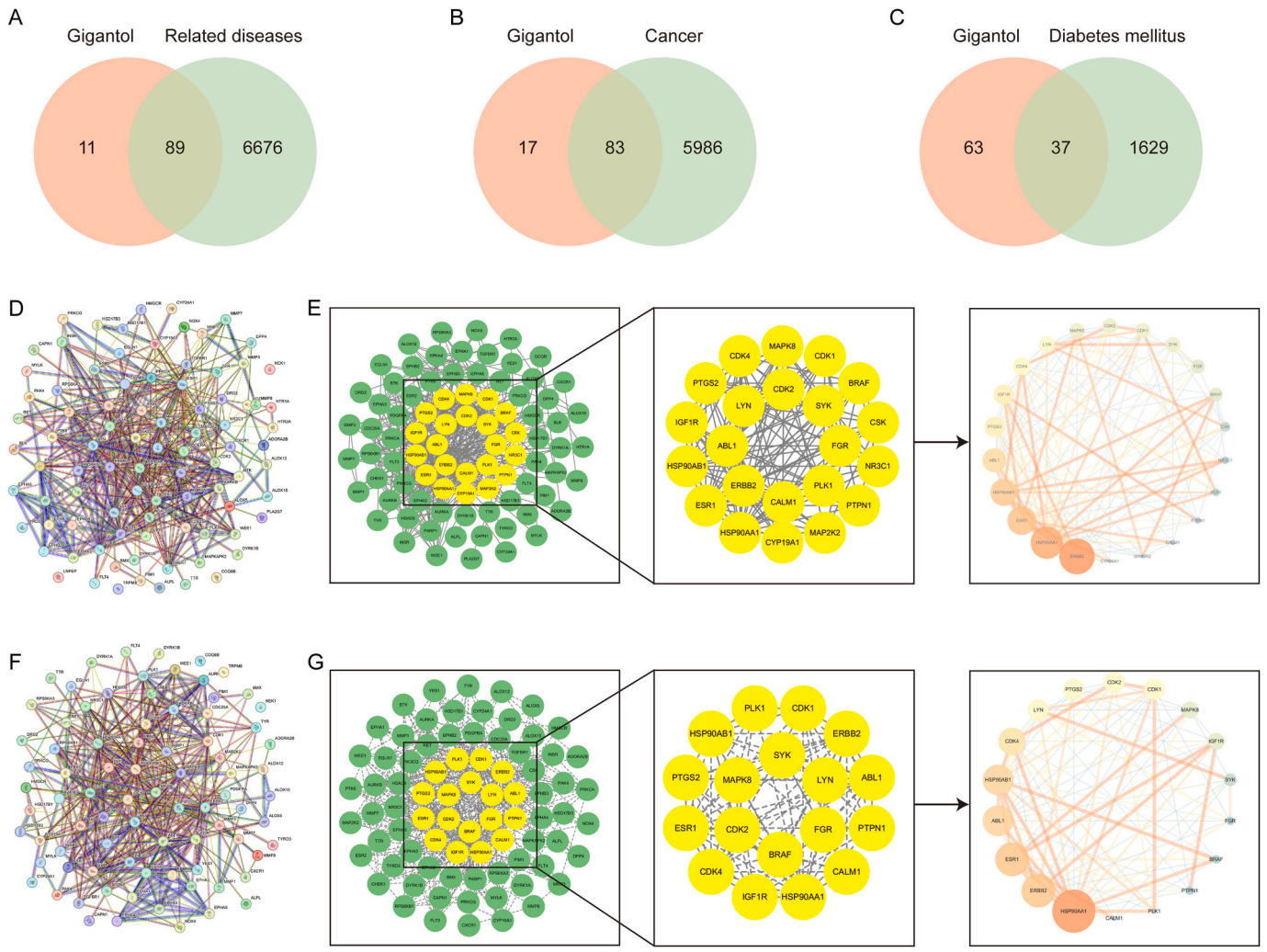

Fig. 7. Protein–protein interaction (PPI) networks of gigantol-related targets.
(A–C) Venn diagrams of predicted gigantol targets and disease-related genes (A: total diseases; B: cancer only; C: diabetes mellitus only). (D–E) PPI network of 89 intersecting targets between gigantol and all disease-related genes. (F–G) PPI network of 83 intersecting targets between gigantol and cancer-related genes. All networks were constructed using the STRING database (https://string-db.org/) with a medium confidence score cutoff (≥0.4). Nodes represent proteins, and edge thickness reflects interaction confidence.

mechanistic pharmacodynamic profile that reflects the traditional concept of "holistic regulation" in East Asian medicine. Ethnomedical theories emphasize the restoration of internal balance rather than blocking a single pathogenic target. Gigantol's ability to modulate inflammation, apoptosis, oxidative stress, and ferroptosis through multiple signaling pathways supports its potential in treating complex systemic diseases, such as metabolic syndrome and cancer-related cachexia. This polypharmacology, rather than being a liability, may enable broader therapeutic coverage and better reflect traditional treatment strategies.

Network pharmacology highlights hub proteins—including including PTGS2 (COX-2), ESR1, HSP90AA1, and IGF1R—linking gigantol to inflammation, hormone-dependent tumors, proteostasis, and growth-factor signaling. GO/KEGGanalyses converge on PI3K-Akt, MAPK, ErbB, cytokine signaling and oxidative stress pathways, aligning with experimental data. Docking suggests plausible binding modes (hydrogen bonding and π–π contacts) within canonical pockets of these prioritized targets; however, these are predictive hypotheses and warrant orthogonal validation (e.g., redocking/RMSD benchmarks, biochemical binding or cellular engagement assays).

Gigantol is rapidly absorbed (T_{max} ≈ 5 min), preferentially accumulates in the liver (liver/plasma $AUC_{0-24\ h}$ ≈ 375-fold), and exclusively undergoes Phase II metabolism via glucuronidation and glutathione conjugation, withrenal elimination. Absoluteoral bioavailability is low (~11.5 %) and systemic clearance is rapid ($t_{1/2}$ ≈ 0.17 h), consistent with extensive first-pass metabolism. Formulation and medicinal-chemistry approaches (e.g., advanced delivery systems or prodrug strategies) may be required to enhance exposure and optimize target-tissue delivery. Current toxicological evidence is largely in silico (predicting high LD_{50} and low risks for major toxicities); comprehensive *in vivo* toxicology remains limited and should be established before translation.

Gigantol—an ethnopharmacologically grounded, polypharmacological agent—modulates cancer-, metabolic-, and inflammation-related pathways, yet critical translational gaps persist. Current evidence relies predominantly on *in vitro* studies, with inadequate validation in physiologically relevant *in vivo* models to substantiate its broad bioactivities. Additionally, despite gigantol's multi-target properties, there is a notable research gap in systematically evaluating its synergistic effects with standard therapeutic agents like metformin or NSAIDs. Its low oral bioavailability further challenges drug delivery, mirroring the limitations observed with other plant-derived phenolics. To advance this ethnopharmacological candidate, (1) rigorous *in vivo* efficacy studies must verify disease-modifying effects, (2) novel

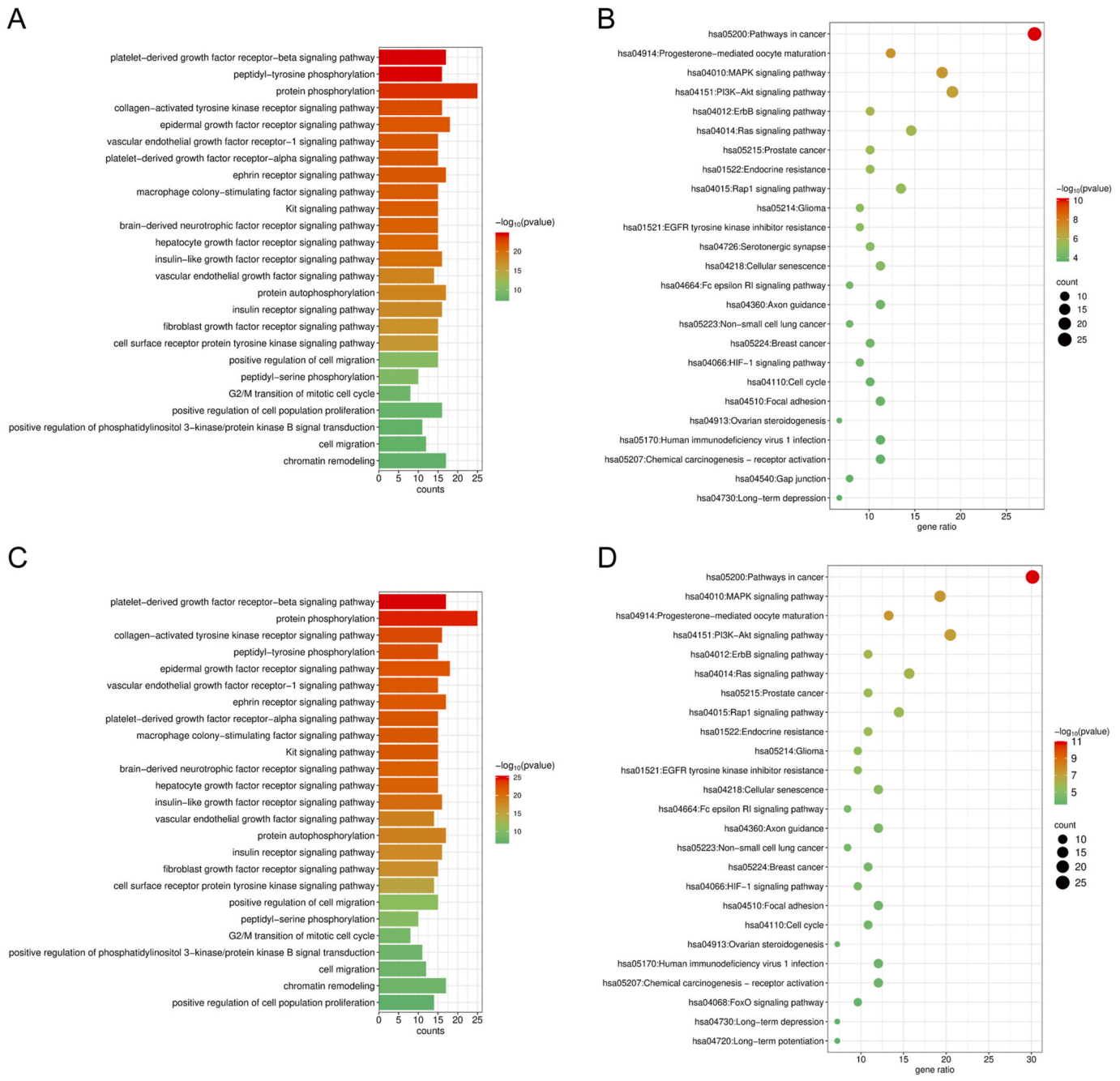

Fig. 8. GO and KEGG enrichment analysis of gigantol-related target genes. (A–B) GO biological process (BP) and KEGG pathway enrichment results of intersecting genes between gigantol and total disease-related targets (n = 89). (C–D) GO BP and KEGG pathway enrichment results of gigantol and cancer-specific target overlaps (n = 83). Enrichment analysis was performed using the DAVID database (https://david.ncifcrf.gov/). The top 25 significantly enriched terms (ranked by P-value) were selected for visualization.

formulations should address pharmacokinetic shortcomings, and (3) preclinical safety profiles require comprehensive evaluation. Addressing these priorities will translate traditional knowledge into modern therapeutics and better position gigantol for the treatment of complex diseases.

CRediT authorship contribution statement

Sha Shi: Writing – original draft. **Chengkai Zhu:** Investigation. **Jiaqi Xu:** Investigation. **Qi Sui:** Methodology. **Shanhao Zhu:** Methodology. **Jingnan Zhang:** Resources. **Peng Chen:** Writing – review & editing. **Guang Liang:** Funding acquisition, Resources. **Yi Zhang:** Funding acquisition, Writing – review & editing.

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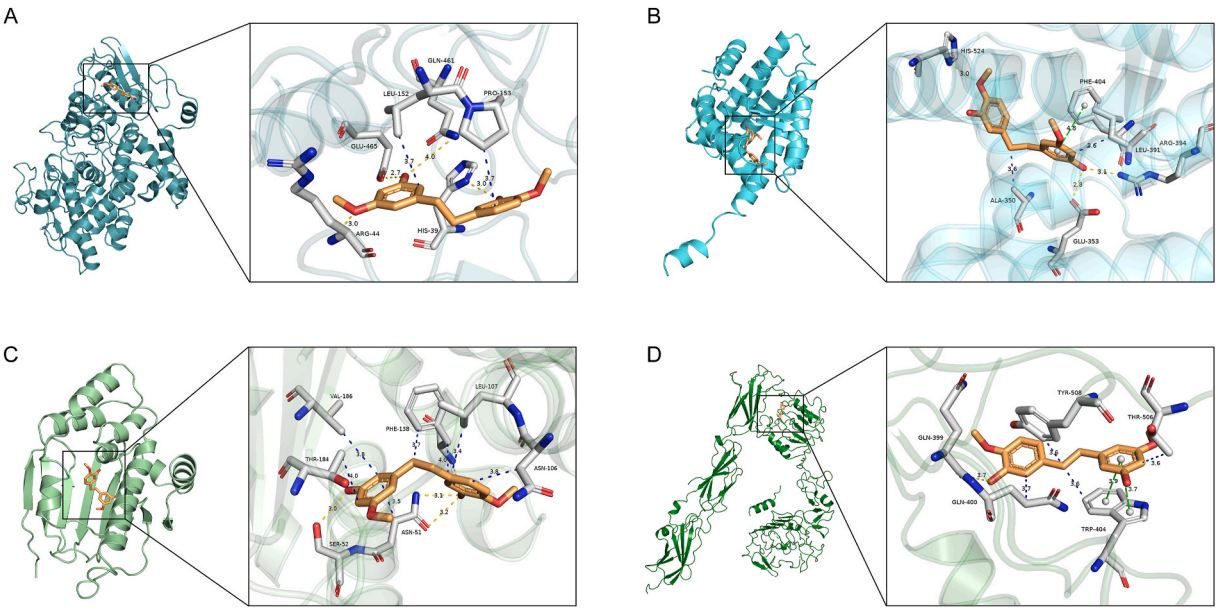

Fig. 9. Molecular docking of gigantol and core targets. (A) Gigantol-PTGS2. (B) Gigantol-ESR1. (C) Gigantol-HSP90AA1. (D) Gigantol-IGF1R.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The primary figures were created using Figdraw (www.figdraw.com).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2025.120595.

Data availability

Data will be made available on request.

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