

Antitumor Effects of Ginsenoside Rh2: Mechanistic Insights

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Abstract

Cancer is one of the leading causes of death worldwide, and its clinical treatment often involves comprehensive strategies such as chemotherapy, radiotherapy, and surgery. Although these methods continue to advance, they still face numerous challenges, including the severe toxic side effects of chemotherapy and the emergence of drug resistance in targeted therapies. Therefore, identifying highly effective, low-toxicity agents from traditional Chinese medicine has become an area of active research. As a well-known traditional Chinese herb, ginseng has garnered significant attention for its potent antitumor properties, primarily driven by its active components, ginsenosides. Ginsenoside Rh2, a low-glycosylated dammarane-type saponin monomer extracted from ginseng, has attracted research attention due to its remarkable antitumor potential. Rh2 exists as two stereoisomers, 20(S)-Rh2 and 20(R)-Rh2, which exhibit both similarities and differences in antitumor activity. For example, most *in vitro* experiments have demonstrated that 20(S)-Rh2 possesses stronger proliferation-inhibiting capability, whereas some *in vivo* studies suggest that 20(R)-Rh2 may offer distinct antitumor advantages by regulating apoptosis-related proteins, such as B-cell lymphoma 2. This article systematically reviews the molecular mechanisms by which ginsenoside Rh2 exerts its antitumor effects through interventions in multiple signaling pathways, such as phosphoinositide 3-kinase/AKT/mammalian target of rapamycin, Wnt/ β -catenin, signal transducer and activator of transcription 3, and nuclear factor kappa B, as well as through the regulation of mitochondrial function and induction of programmed cell death. This synthesis of recent research advances provides a theoretical basis for future studies and clinical development of Rh2.

Keywords: ginsenosides; neoplasms; signal transduction; stereoisomerism

1. Introduction

Cancer, also referred to as malignant neoplasms, is one of the leading causes of death globally. It is characterized by the uncontrolled growth and division of abnormal cells that can invade and destroy surrounding tissues. These abnormal cells may also spread to other parts of the body through the blood or lymphatic system, a process known as metastasis [1]. Cancer can develop in various locations within the body and encompasses numerous types, including lung [2,3], bowel [4,5], blood [6], pancreatic [7], liver [8,9], cervical [10], and breast [11] cancers. Consequently, addressing the challenges posed by cancer has become a significant concern in contemporary healthcare. Common therapeutic approaches in clinical practice include chemotherapy, radiotherapy, immunotherapy, surgery, and hormone therapy, which are often administered in combination [12]. Despite advancements in medical science, several issues remain unresolved, necessitating ongoing efforts to enhance cancer treatment. In response, oncology research is dedicating substantial resources to discovering new and effective therapies aimed at alleviating the severe side effects associated with conventional treatments [13]. As our understanding of cancer's pathogenesis deepens, many researchers are increasingly focusing on the potential of traditional Chinese medicine.

Traditional Chinese medicine, along with its active ingredients, demonstrates a wide range of pharmacological effects. For many years, ginseng has been utilized as a traditional herbal remedy in Eastern countries for dietary supplementation and the treatment of various health conditions [14]. Ginsenoside Rh2, a key component of ginseng, exhibits antioxidant, anti-inflammatory, and antitumor properties that enhance the body's immune response, exerting both direct and indirect antitumor effects [15]. Regarding its antioxidant mechanism, Rh2 reduces cellular damage caused by oxidative stress. In its anti-inflammatory role, Rh2 inhibits the production of inflammatory mediators. Given that oxidative stress and excessive inflammatory responses can lead to tissue damage closely associated with cancer, Rh2 is regarded as an inhibitor of various cancer cell types [16,17]. Due to its distinct spatial structures, Rh2 exists in two stereoisomeric forms at the C20 position, specifically 20(S)-Rh2 and 20(R)-Rh2, as illustrated in Fig. 1 [18]. As a cancer therapeutic adjuvant, Rh2, found in ginseng, demonstrates notable efficacy and exhibits anticancer activity by modulating cellular and molecular targets, thereby inhibiting or treating tumors [19,20,21]. Furthermore, unlike targeted therapies, ginsenosides interact with multiple targets and exhibit anticancer activity through various mechanisms, including the



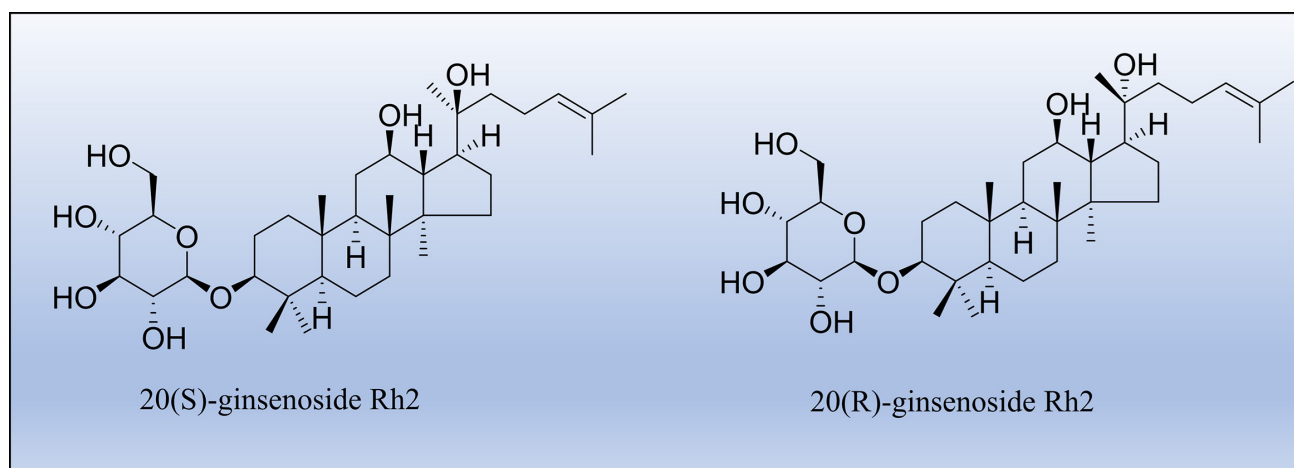


Fig. 1. The two stereostructures of ginsenoside Rh2, with the S-type on the left and the R-type on the right. The picture is drawn by ChemBioDraw Ultra (version: 14.0.0.117; PerkinElmer). Rh2, 20(S)-ginsenoside Rh2 and 20(R)-ginsenoside Rh2.

modulation of signaling pathways such as estrogen receptor beta (ER β)/tumor necrosis factor alpha (TNF- α) and inhibitor of apoptosis proteins (IAPs)/annexin A2/nuclear factor kappa B (NF- κ B) [11,22,23]. In specific experimental settings, such as doxorubicin-induced cellular senescence models, 20(S)-Rh2 has shown more pronounced activity than its R-isomer in alleviating pro-tumorigenic secretory phenotypes [24]. Conversely, in other experimental systems, particularly in hepatocellular carcinoma models *in vivo*, the R-configuration has shown comparable or even superior antitumor efficacy. Both isomers significantly suppress H22 tumor growth *in vivo*, with inhibition rates of 42.2% for 20(S)-Rh2 and 46.8% for 20(R)-Rh2 ($p < 0.05$). This suggests that 20(R)-Rh2 possesses stronger anticancer activity than 20(S)-Rh2, as evidenced by its ability to downregulate the mRNA expression of the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2) [9]. Although both stereoisomers of Rh2 exhibit unique anticancer strengths, most data demonstrate that the S configuration of Rh2 demonstrates greater efficacy than the R configuration. Unspecified references to Rh2 in the literature typically imply the presence of both S- and R-configurations. The chemical structure is shown in Fig. 1.

2. Ginsenoside Rh2 as a Potential Anticancer Agent

Ginsenoside Rh2, a diol-type saponin derived from *Panax ginseng*, has demonstrated broad-spectrum anticancer activity across various tumor types through *in vitro* and *in vivo* experimental models, with its therapeutic efficacy closely associated with its stereoisomeric configuration. In lung cancer treatment, Rh2 exerts potent antiproliferative effects via dual mechanisms: inducing ROS-mediated endoplasmic reticulum stress-dependent apoptosis in H1299 cells, and synergizing with miR-28-5p inhibitors to activate the serine/threonine kinase 4 (STK4) tumor suppressor and inhibit the Wnt/ β -catenin signaling

pathway in A549 and H1650 cells. In colorectal cancer (CRC), 20(S)-ginsenoside Rh2 downregulates interleukin 6 (IL-6)-induced signal transducer and activator of transcription 3 (STAT3) activation and inhibits key matrix metalloproteinases (MMPs), namely MMP-1, MMP-2, and MMP-9, thereby suppressing cancer cell invasion. Additionally, its chemically modified derivative Rh2E2 disrupts energy metabolism by interfering with glycolysis, fatty acid β -oxidation, and the tricarboxylic acid cycle, leading to S-phase arrest in CRC cells and exhibiting significant tumor-suppressive effects on azoxymethane (AOM)/dextran sodium sulfate (DSS)-induced mouse models. In hepatocellular carcinoma (HCC) cells (HepG2 and H22 cells), both 20(S)-Rh2 and 20(R)-Rh2 induce apoptosis by downregulating Bcl-2 expression and modulating the Fas/poly ADP-ribose polymerase axis, with *in vivo* studies demonstrating tumor inhibition rates of 42.2% and 46.8%, respectively. In breast cancer, 20(S)-Rh2 suppresses cell proliferation through the ER β /TNF- α pathway and inhibits tumor growth in BALB/c mouse models via a free radical-mediated mechanism. Beyond its effects on hematological malignancies, Rh2 suppresses tumor progression via diverse molecular pathways. Specifically, it drives caspase-3 activation and mitophagy in K562 chronic myeloid leukemia cells; triggers mitochondrial dysfunction and upregulates voltage-dependent anion channel 1 (VDAC1) expression in HeLa cervical cancer cells; exerts antiproliferative effects on PANC-1 pancreatic cells through glycosylation changes; and induces apoptosis in DU145 prostate cancer cells by upregulating peroxisome proliferator-activated receptor delta (PPAR- δ) and modulating the p-STAT3/STAT3 pathway. Integrating these research findings, 20(S)-ginsenoside Rh2 acts as a multi-target anticancer agent by regulating key signaling pathways, specifically phosphoinositide 3-kinase (PI3K)/AKT, Wnt/ β -catenin, and STAT3, along with driving mitochondrial apoptosis. This positions it as a highly promising

broad-spectrum adjuvant for cancer therapy. Table 1 (Ref. [2,3,4,5,6,7,8,9,10,11,25,26,27,28]) summarizes the medical applications of ginsenoside Rh2 in cancer treatment, both *in vitro* and *in vivo*.

3. Potential Anticancer Mechanisms of Rh2

The process by which normal cells become cancerous is intricate and involves multiple contributing factors, with oxidative stress serving as a major contributor. This damage is primarily induced by reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can damage cells. Additionally, the inflammatory response triggered by pro-inflammatory cytokines, such as TNF- α , IL-1 β , IL-6, nitric oxide (NO), and prostaglandin E2 (PGE2) [17,29], plays a critical role in this transformation. These perturbations ultimately converge on core signaling networks that regulate cell cycle, survival, and apoptosis, leading to the emergence and progression of malignant cells.

One feature that distinguishes cancer cells from normal cells is their ability to produce more ROS and their increased dependence on antioxidant defense systems. In this context, Rh2 functions as a redox modulator: in cancer cells, it promotes ROS accumulation to induce apoptosis, whereas in normal cells, it alleviates oxidative stress by enhancing antioxidant capacity [30]. During this period, several key signaling pathways play significant roles in mediating these effects. Oxidative stress is defined as a cellular imbalance between the production of ROS/RNS and the body's antioxidant defense mechanisms. This condition, driven by either excess ROS/RNS accumulation or diminished antioxidant capacity, stems from both endogenous and exogenous factors [31,32]. Oxidative stress is widely recognized as a harmful process, causing significant damage to cellular structures and biomolecular functions. By breaking the natural, dynamic balance between the production and elimination of ROS during metabolism [30], it directly or indirectly contributes to the development of various diseases, including cancer [33]. When cells experience oxidative stress, excessive ROS levels can lead to irreversible damage to cellular macromolecules, such as proteins, lipids, and DNA, resulting in cellular defects, lesions, and potentially tumor development [16]. While oxidative stress is widely acknowledged as a detrimental byproduct of normal metabolic reactions, it is essential to recognize that ROS also play a vital physiological role in supporting the biological functions of both normal and cancer cells [34].

Inflammation causes damage through mechanisms distinct from those of oxidative stress. While oxidative stress injury is primarily mediated by ROS, inflammation is primarily influenced by inflammatory mediators. For instance, an excessive or unbalanced production of pro-inflammatory factors disrupts the equilibrium of tissue homeostasis, which is normally regulated through their interaction with *in vivo* anti-inflammatory agents, such as IL-2, IL-4, and IL-10 [14]. Serious inflammatory diseases in-

clude diabetes and cancer, as well as cardiovascular and neurological disorders [35,36,37]. As early as the first century AD, the Roman physician Aulus Cornelius Celsus defined inflammation as “rubor” (redness), swelling, “calor” (heat), and “dolor” (pain) [33]. Modern medicine views inflammation as the body's natural, non-specific defense mechanism against injury, pathogens, and harmful stimuli, acting as a critical, rapid response to initiate tissue healing. This process involves a variety of cellular and molecular mechanisms designed to eliminate noxious stimuli, repair damaged tissues, and restore normal physiological functions, thereby maintaining tissue homeostasis [38]. In recent years, studies have found that inflammation can also initiate or promote the transmission of apoptotic signals. However, Rh2—a ginseng-derived protopanaxadiol-type saponin—possesses strong anti-inflammatory properties, effectively modulating key inflammatory mediators and pathways including IAPs/annexin A2/NF- κ B, mammalian target of rapamycin (mTOR), and Wnt signaling.

It is clear that the clinical efficacy of direct Rh2 administration relies on critical targets and signaling pathways that drive its antitumor effects. Research has shown that ginsenoside Rh2 exerts its anticancer effects through the targeted regulation of molecules or the integrated management of multiple regulatory pathways [39]. Network pharmacology analysis indicates that Rh2 may target 217 different genes or proteins. Identifying several of these targets is essential for understanding the mechanisms by which Rh2 impacts cancer cells, particularly because cancer onset is driven by multiple genes and risk factors [2]. A signaling pathway is a series of enzymatic reactions that convert extracellular signals into intracellular responses by transmitting information across the cell membrane. These extracellular signals include hormones, growth factors, cytokines, neurotransmitters, and other small-molecule compounds. A drug target is the specific biological structure—usually a protein like an enzyme, receptor, or ion channel—that a drug interacts with within an organism. Fig. 2 summarizes the pathway diagrams included in this article.

From the perspective of its mechanism of action, ginsenoside Rh2 exerts its antitumor effects through a hierarchical network of signaling pathways, which ultimately target the hallmark characteristics of cancer. As shown in Fig. 2, Rh2 primarily targets three categories of signaling pathways: proliferation and survival pathways—PI3K/AKT/mTOR and Src/phosphorylated extracellular signal-regulated kinase 1/2 (p-ERK1/2) pathways, the inhibition of which leads to slowed cell growth and G1 phase arrest; oncogenic driver pathways (such as Wnt/ β -catenin and STAT3 pathways), the suppression of which can limit metastasis, angiogenesis, and chemoresistance; and stress and death pathways including Kelch-like ECH-associated protein 1 (Keap1)/nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated antioxidant responses, TNF- α -induced apoptosis, and IAPs/annexin A2/NF- κ B-regulated inflammatory responses. Furthermore, Rh2 directly modulates

Table 1. Anticancer applications of ginsenoside Rh2.

Saponin type	<i>In vitro/</i> <i>in vivo</i>	Cancer type	Experimental model	Mechanisms of influence	Reference
20(S)/(R)-Rh2	<i>In vitro</i>	Lung cancer	A549 and H1650 lung cancer cells; NSCLC cells	Synergizes with an miR-28-5p inhibitor to enhance NSCLC cell apoptosis and inhibit Wnt signaling by targeting STK4	[2]
	<i>In vitro</i>	Lung cancer	H1299 lung cancer cells	Inhibits lung cancer cell proliferation by inducing endoplasmic reticulum stress-dependent apoptosis through ROS production	[3]
20(S)-Rh2	<i>In vitro</i>	CRC	CRC cells	Downregulation of IL-6-induced signal transducers, STAT3 and MMPs (MMP-1, MMP-2 and MMP-9)	[4]
20(R)-Rh2	<i>In vivo</i>	CRC	Male BALB/c mice; AOM/DSS-induced CRC model	Alteration of Rh2 (Rh2E2) increases cellular toxicity and leads to S-phase cell cycle arrest by impairing key metabolic enzymes in glycolysis, fatty acid β -oxidation, and the tricarboxylic acid cycle	[5]
	<i>In vitro</i>	Lung cancer	LLC-1 lung cancer cells	Rh2E2 downregulates cell adhesion, cell invasion, and angiogenesis through downregulation of α -enolase	[5]
20(S)-Rh2	<i>In vitro</i>	Hematological cancer	K562 chronic myeloid leukemia cells	Reduces caspase-3 activation and induces cellular autophagy through the mitochondrial signaling pathway	[6]
20(S)/(R)-Rh2	<i>In vitro</i>	Pancreatic cancer	PANC-1 human pancreatic cancer cells	Regulates cell proliferation by increasing the number of glycosyl groups through chemical transformation	[7]
20(S)-Rh2	<i>In vitro</i>	Liver cancer	Male Sprague-Dawley rats; HepG2 HCC cells	Inhibits the expression of Bcl-2, transmembrane protein (Fas) and cleaved poly (ADP-ribose) polymerase by inducing cytotoxicity and autophagy	[8]
20(R)-Rh2	<i>In vivo</i>	Liver cancer	Female H22 HCC-loaded mice	Reduces Bcl-2 expression by inducing apoptosis in HCC cells; Reduces microvessels and necrotic cells	[9]
20(S)/(R)-Rh2	<i>In vitro</i>	Cervical cancer	HeLa human cervical cancer cells	Promotes apoptosis of cervical cancer cells by inducing mitochondrial dysfunction	[10]
	<i>In vivo</i>	Breast cancer	Female BALB/c mice	Generates semi-stable diazonium ions to initiate free radical reactions	[11]
20(S)-Rh2	<i>In vitro</i>	Liver cancer	HepG2 HCC cells	Transcriptional activity of NF- κ B was inhibited by targeting annexin A2, which in turn promoted apoptosis in cancer cells	[25]
	<i>In vivo</i>	CRC	BALB/c-nu mice; HCT116 CRC cells	By directly interacting with the receptor tyrosine kinase (AXL) and obstructing the AXL signaling pathway in CRC cells, the proliferation of HCT116 cells is inhibited, leading to apoptosis and cell cycle arrest	[26]
20(S)/(R)-Rh2	<i>In vivo</i>	Skin cancer	BALB/c nude mouse; A375 melanoma cells	Enhancement of autophagy-induced cell death by enhanced antitumor activity of a small molecule serine or threonine kinase inhibitor (SMI-4a) and reduced phosphorylation levels of AKT and mTOR	[27]
	<i>In vitro</i>	Prostate cancer	DU145 prostate cancer cells	The upregulation of PPAR- δ induces apoptosis in DU145 prostate cancer cells, subsequently leading to down-regulation of intracellular oxidative stress via the p-STAT3/STAT3 pathway	[28]

NSCLC, non-small cell lung cancer; STK4, serine/threonine kinase 4; ROS, reactive oxygen species; CRC, colorectal cancer; IL-6, interleukin 6; STAT3, signal transducer and activator of transcription 3; MMPs, matrix metalloproteinases; AOM, azoxymethane; DSS, dextran sodium sulfate; HCC, hepatocellular carcinoma; PPAR- δ , peroxisome proliferator-activated receptor delta; Bcl-2, B-cell lymphoma 2; NF- κ B, nuclear factor kappa B; mTOR, mammalian target of rapamycin.

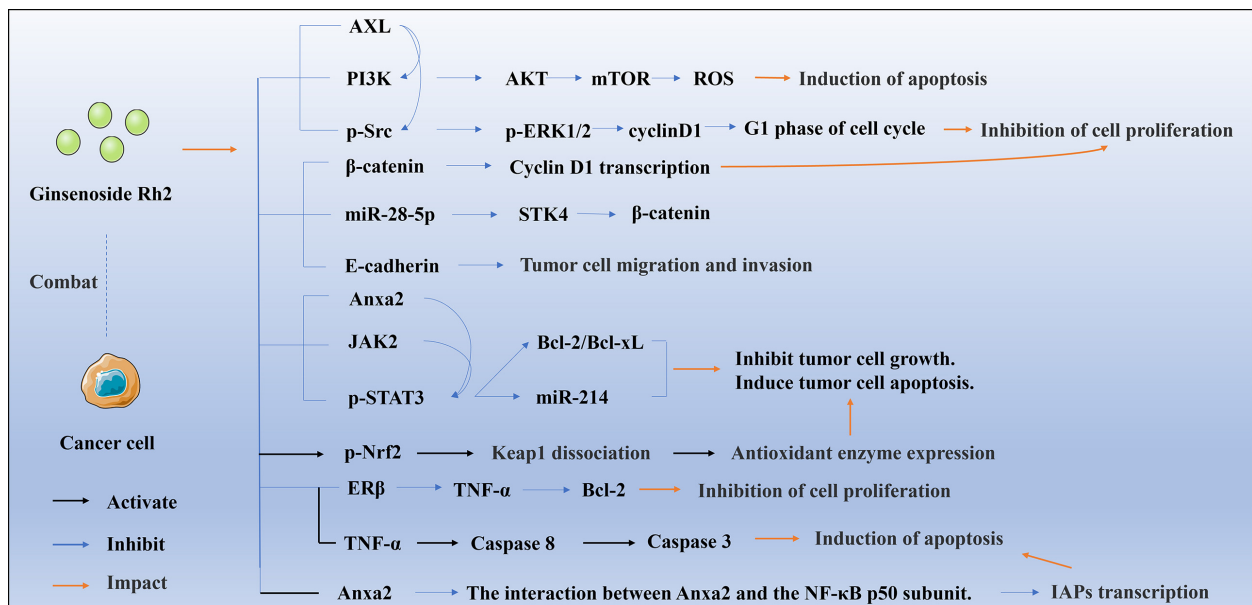


Fig. 2. Six signaling pathways are highly associated with the antitumor activity of ginsenoside Rh2. The picture is drawn by PowerPoint (version: 2606 Build 16.0.20131.20086; Microsoft). PI3K, phosphoinositide 3-kinase; p-ERK1/2, phosphorylated extracellular signal-regulated kinase 1/2; ER β , estrogen receptor beta; TNF- α , tumor necrosis factor alpha; IAPs, inhibitor of apoptosis proteins.

mitochondrial function by regulating the Bcl-2 family of proteins, disrupting the mitochondrial membrane potential, and promoting cytochrome c release, thereby amplifying the apoptotic cascade. This multi-tiered regulatory mechanism enables Rh2 to simultaneously block protumor signals and activate tumor-suppressive pathways, providing compelling theoretical evidence for its broad-spectrum anticancer activity.

3.1 Inhibiting PI3K/AKT/mTOR and Src/p-ERK1/2 Signaling Pathways

AKT, also known as protein kinase B, is a serine/threonine protein kinase with an approximate molecular weight of 60 kDa, predominantly found in mammals. Abnormal activation of the AKT signaling pathway is frequently associated with tumor development, progression, and drug resistance. PI3K is a crucial intracellular kinase that regulates signaling pathways, influencing various biological processes such as cell growth, proliferation, and survival, which are essential for normal cellular function. Bioinformatics analyses of predicted targets indicated that the PI3K/AKT signaling pathway is the primary signaling mechanism implicated in the therapeutic action of Rh2 [2]. This pathway is crucial for cancer treatment and plays a key regulatory role in many biological processes, including cell proliferation and cell cycle regulation [40,41,42].

Recent studies have identified AXL receptor tyrosine kinase as a direct molecular target of 20(S)-Rh2, acting upstream of identified signaling pathways in CRC cells [26]. By directly interacting with AXL, Rh2 obstructs its kinase activity and blocks downstream signaling cascades, including the PI3K/AKT and Src/ERK1/2 pathways. This di-

rect targeting mechanism provides a molecular basis for the observed antitumor effects of Rh2 in CRC. *In vitro* experiments have shown that Rh2 inhibits the proliferation of cervical cancer cells by suppressing the AKT signaling pathway [43]. It affects the growth and survival of human retinoblastoma cell lines Y79 and RBL-13 by inactivating the mTOR pathway via the PI3K/AKT pathway [4]. Furthermore, Rh2 treatment leads to the inactivation of p85, 3-phosphoinositide-dependent kinase 1, and AKT, confirming that Rh2 can induce apoptosis in cancer cells by inhibiting the PI3K/AKT signaling pathway [2]. Additionally, the primary downstream effector of the PI3K/AKT signaling pathway is mTOR, a serine/threonine kinase that couples nutrient and growth factor sensing to cell growth by regulating translation, anabolic metabolism, and autophagy [44]. Evidence indicates that the antioxidant and anti-inflammatory activities of Rh2 are mediated through signaling pathways such as PI3K/AKT, with ROS playing a crucial role in this mechanism [34]. Hyperactivation of the mTOR pathway has been associated with increased ROS production, whereas inhibition of mTOR decreases ROS levels [44]. Kim et al. [45] showed that Rh2 can protect cells from damage caused by oxidative stress by reducing intracellular ROS levels through the mTOR signaling pathway. In 2018, Hsieh et al. [46] demonstrated that Rh2 improves LPS-induced acute lung injury in mice by dose-dependently regulating the PI3K/AKT/mTOR signaling pathway. This aligns with findings from Baatar et al. [47], who demonstrated that Rh2 dose-dependently inhibited NO production and increased the proliferation of LPS-stimulated RAW 264.7 mouse macrophages [48].

The Src family consists of a group of non-receptor tyrosine kinases that play a crucial role in cell signaling, particularly in regulating cell growth, differentiation, and motility. Research indicates that Rh2 significantly downregulates the expression of p-Src and p-ERK1/2 in CRC cells both *in vitro* and *in vivo*, thereby modulating cell proliferation and inducing cell cycle arrest [26,49]. Consistent with the direct targeting of AXL mentioned above, the suppression of Src and ERK1/2 phosphorylation represents a key downstream consequence of Rh2-mediated AXL inhibition [26]. It is well known that dysregulation of the cell cycle and excessive cell proliferation are key hallmarks of cancer. Overactive cyclin-dependent kinases (CDKs) can bypass normal cell cycle checkpoints, allowing cells to proliferate despite unrepaired DNA damage and increasing carcinogenic risk. Therefore, Rh2 serves as a vital inhibitor by restoring cell cycle control and regulating cell proliferation [50]. *In vitro* experiments have shown that in CRC cell lines, the Src signaling pathway is significantly downregulated after treatment with 20(S)-Rh2, leading to a reduction in cell cycle regulatory proteins such as cyclin E1, cyclin D1, and two G0/G1-promoting kinases, CDK4 and CDK6 [26,51]. There is also evidence indicating that the PI3K/Akt/mTOR signaling pathway mediates a reduction in cell growth and induces G1 cell cycle arrest following treatment with 20(S)-Rh2 [52]. Li et al. [53] found that ginsenoside Rh2 induces cell cycle arrest by downregulating CDK4 and cyclin D, significantly decreasing the level of p-AKT. Therefore, ginsenoside Rh2 inhibits human A172 glioma cells by regulating the CDK4/cyclin D complex and AKT expression. It is worth mentioning that recent research into the therapeutic potential of Rh2 for CRC has increasingly highlighted the significance of the receptor tyrosine kinase AXL. By establishing AXL as a direct target in CRC treatment, Rh2 is able to modulate multiple downstream pathways, including the PI3K/AKT and Src signaling pathways, as illustrated in Fig. 3. Furthermore, although AXL has been confirmed as a direct target of Rh2, subsequent inhibition of downstream pathways such as PI3K/AKT and Src/ERK1/2 may involve both direct and indirect mechanisms. The direct binding of Rh2 to AXL disrupts its kinase activity, leading to reduced phosphorylation of downstream effectors. However, given that these signaling pathways are part of complex regulatory networks with multiple feedback loops and crosstalk, it is plausible that the observed suppression of cell cycle regulators (cyclin D1, CDK4/6) and induction of apoptosis may result from a combination of direct AXL inhibition and indirect downstream effects, such as secondary changes in gene expression and kinase activities [26]. Future studies employing proteomic and transcriptomic approaches may help differentiate direct from indirect effects, offering a more comprehensive understanding of Rh2's mechanism of action.

3.2 Inhibiting the Wnt/ β -Catenin Signaling Pathway

While the Wnt-related signaling pathway plays a crucial role in cell proliferation, differentiation, and stem cell maintenance, its abnormal activation acts as a major driver of tumorigenesis and cancer progression. Recent evidence has demonstrated that Rh2 suppresses the Wnt signaling pathway, including the Wnt/ β -catenin pathway, which is frequently overactive in various cancers. This overactivity leads to increased cell proliferation and tumor growth; thus, inhibiting this pathway may help prevent the excessive proliferation of tumor cells [54]. There is evidence that Rh2 can dose dependently inhibit the growth of HCC cells, reduce the expression of β -catenin in HCC cells, and increase autophagy [54,55].

Research indicates that Rh2 inhibits non-small cell lung cancer (NSCLC) by targeting microRNAs (miRNAs), specifically by decreasing the expression of miR-28-5p. This downregulation of miR-28-5p, in turn, inactivates Wnt signaling in NSCLC cells [23]. STK4 was identified among 66 potential mRNA targets of miR-28-5p as a tumor suppressor in NSCLC that negatively regulates the Wnt signaling pathway [56]. In NSCLC cells, Rh2 induces the upregulation of STK4 by decreasing the expression of its target miRNA, miR-28-5p. In the Wnt/ β -catenin signaling pathway, E-cadherin plays a crucial role in suppressing tumor metastasis and serves as a major regulator of the pathway's transcriptional activity. Additionally, Rh2 can upregulate E-cadherin expression and related transcription factors, thereby inhibiting tumor invasion and metastasis [57,58]. Although direct molecular targets of Rh2 in the Wnt/ β -catenin pathway have not yet been identified, emerging evidence from studies on other ginsenosides suggests that modulation of this pathway may be a common feature among ginsenosides. For instance, ginsenoside Rh4—a structurally related compound—has been shown to inhibit esophageal squamous cell carcinoma metastasis by suppressing the Wnt/ β -catenin signaling pathway and downregulating the expression of its downstream target c-Myc [59]. Given the structural similarities between Rh2 and Rh4, it is plausible that the antitumor effects of Rh2 are mediated, at least in part, by the direct or indirect modulation of Wnt signaling components.

3.3 Inhibiting the STAT3 Signaling Pathway

Recent studies have identified 20(S)-Rh2 as an effective agent for treating cancers, such as CRC [4] and NSCLC [60], by inhibiting the abnormal STAT3 activity that drives tumor development. STAT3 can be activated through receptors on the cell surface, particularly in response to cytokines such as IL-6. This activation leads to phosphorylation, the subsequent formation of homo- or heterodimers, translocation into the nucleus, and direct binding to DNA to regulate the transcription of target genes. Ginsenoside Rh2 alleviates ulcerative colitis by modulating the STAT3/miR-214 signaling pathway; specifically, Rh2 effectively inhibits IL-

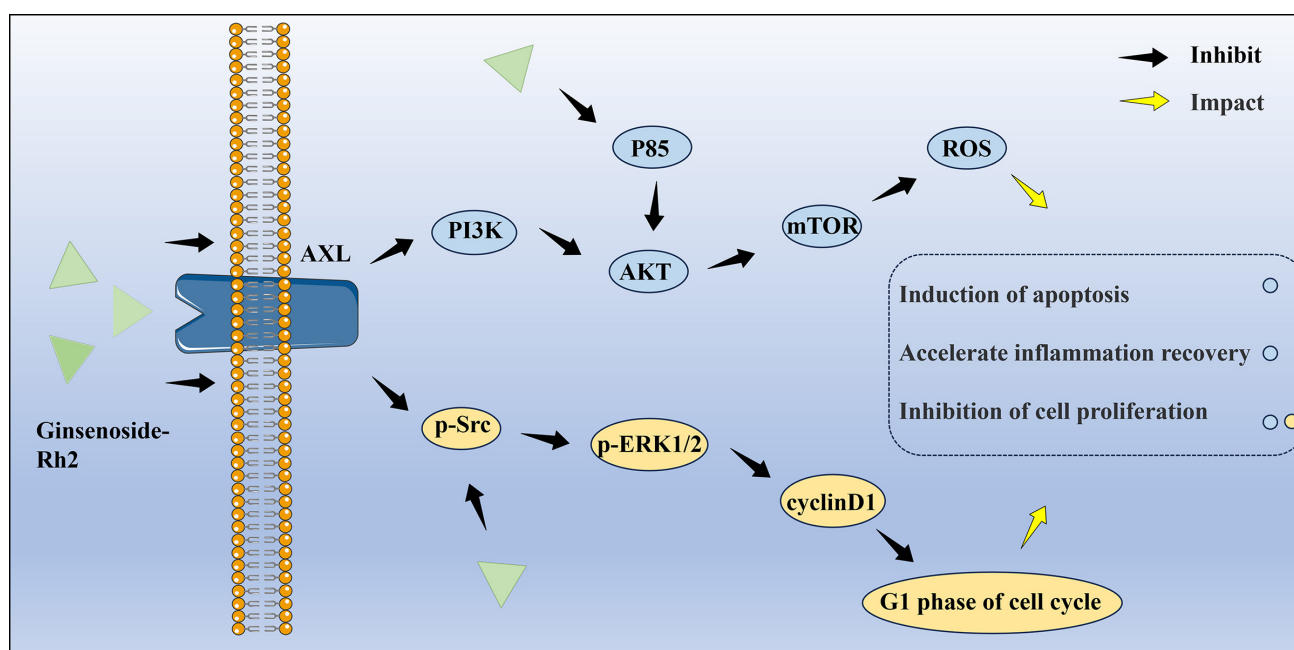


Fig. 3. Ginsenoside Rh2 exerts antitumor effects by inhibiting the PI3K/AKT/mTOR and Src/p-ERK1/2 signaling pathways. (AXL has been identified as the direct target of Rh2 in CRC cells, facilitating the suppression of these two pathways). The picture is drawn by PowerPoint.

6-induced STAT3 phosphorylation and downregulates the levels of STAT3/miR-214 [52]. Studies have demonstrated that 20(S)-Rh2 inhibits STAT3 activation by directly targeting annexin A2, a multifunctional calcium-dependent phospholipid-binding protein that is overexpressed in various cancers and contributes to tumor progression by regulating signaling pathways, including STAT3. Using affinity chromatography and surface plasmon resonance, Wang et al. [61] identified annexin A2 as a direct binding partner of 20(S)-Rh2, showing that Rh2 binds to annexin A2 with high affinity [62]. In addition, annexin A2 is highly expressed in patients with breast cancer, and Rh2 is expected to target and promote the proliferation and metastasis of tumor cells [63]. These findings establish annexin A2 as a critical molecular target through which Rh2 exerts its inhibitory effects on STAT3 signaling, providing a mechanistic basis for its anticancer activity in cancers driven by aberrant STAT3 activation. Recent *in vitro* and *in vivo* experiments have further established that the two configurations of Rh2 exhibit therapeutic effects in triple-negative breast cancer. By reducing activation of the Janus kinase 2/STAT3 signaling pathway and inhibiting the expression levels of anti-apoptotic proteins Bcl-2 and B-cell lymphoma-extra large (Bcl-xL), they suppress tumor growth *in vivo*, with the S-configuration showing superior efficacy compared to the R-configuration [64]. Additionally, studies on gastric cancer have confirmed that Rh2 is a highly potent inhibitor of p-STAT3 [65]. Therefore, some of the observed antitumor effects may be indirectly mediated through these downstream networks, highlighting the complexity of Rh2's multi-target pharmacology.

3.4 Activating the Keap1/Nrf2 Signaling Pathway

Nrf2 is a critical transcription factor that maintains redox homeostasis by regulating both endogenous and exogenous inducers of oxidative stress. Because it aids cancer cell survival—by inducing antioxidant genes, inhibiting apoptosis, and managing reactive ROS—Nrf2 is a promising target for cancer treatment [34]. Fan et al. [66] reported that the involvement of Rh2 in the Nrf2 signaling pathway enhances the ability of cardiomyocytes to combat oxidative stress, leading to a reduction in infarct areas and improved cardiac function.

The antitumor activity of Rh2 is evident in its regulation of protein phosphorylation, which significantly affects signaling pathways. Phosphorylation plays a complex and vital role in cancer, serving as a key focus in cancer research and drug development. By targeting specific phosphorylation events, Rh2 influences tumor suppressor genes and oncogenes. Abnormal phosphorylation activities are likely to lead to sustained activation of the above biological pathways, which may promote tumor growth, invasion, and metastasis. According to the findings of Hou et al. [67], Rh2 was shown to block the phosphorylation of mitogen-activated protein kinase (MAPK) kinase 1 (also known as MEK1), p38 MAPK, STAT3, and NF- κ B p65, demonstrating its anticancer effect on senescent breast cells. For example, in the Keap1/Nrf2 signaling pathway, Rh2 phosphorylates Nrf2, facilitating its dissociation from Keap1 and promoting the expression of various downstream antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase [68]. Experimental evidence sug-

gests that Rh2 protects against trimethyltin-induced neuronal damage and oxidative stress in mice by stimulating the Keap1/Nrf2 signaling pathway and increasing antioxidant enzyme activity [69,70].

3.5 Regulating the TNF- α Signaling Pathway

TNF is a cytokine with diverse biological effects that serves as a typical inflammatory mediator. It is primarily produced by activated mononuclear macrophages and T lymphocytes. In 1985, the factor produced by mononuclear macrophages was designated TNF- α , whereas the lymphotoxin produced by T lymphocytes was referred to as TNF- β [71].

The biological activity of TNF- α accounts for 70–95% of total TNF activity; therefore, the term TNF commonly refers to TNF- α . The TNF receptor (TNFR) primarily promotes cell growth, differentiation, apoptosis, and the induction of inflammation. To date, two types of TNFR have been identified: TNFR1 and TNFR2. Both are transmembrane proteins characterized by similar extracellular domain structures, yet they exhibit distinct intracellular architectures. Notably, only TNFR1 contains a death domain (DD) within its intracellular region, which enables the receptor to induce apoptosis [72]. Initially, TNF- α binds to the extracellular domain of TNFR1, resulting in the formation of a trimeric structure. This aggregation of the intracellular DD subsequently recruits downstream signaling proteins, including TNFR-associated DD protein, TNFR-associated factor 2, receptor-interacting serine/threonine-protein kinase, and Fas-associated DD protein. These proteins can assemble into a complex that activates various downstream effector molecules and death receptors. By contrast, TNFR2 lacks a DD but is capable of activating pathways such as NF- κ B, MAPK, and c-Jun N-terminal kinase (JNK) [73,74]. Studies have shown that ginsenoside Rh2 specifically inhibits the activation of the NF- κ B and JNK signaling pathways in TNF- α -induced human astrocytes, and synergistically affects the inflammatory response via the TNF- α pathway [75,76].

Estrogen receptor beta (ER β) is a nuclear receptor that is part of the steroid hormone receptor family and plays significant physiological functions in the human body. Recent studies have indicated that the overexpression of ER β can influence intracellular TNF- α levels [77]. Consequently, ER β may serve as a target for ginsenoside Rh2 in the regulation of TNF- α expression, as shown in Fig. 4. Peng et al. [22] investigated the effect of ginsenoside Rh2 on TNF- α expression while inhibiting ER β protein using an ER β inhibitor. Their findings revealed that the inhibition of ER β effectively reversed the TNF- α overexpression induced by ginsenoside Rh2, thereby confirming the targeted relationship between ER β and TNF- α [22]. Simultaneously, ginsenoside Rh2 inhibits the proliferation of NSCLC H1299 cells by inducing ER β stress-dependent apoptosis [3]. Additionally, Huang et al. [78] determined the levels of TNF- α

in the A549 lung cancer cell line and MCF-7 human breast cancer cell line through *in vitro* experiments, revealing that the expression of TNF- α was significantly upregulated in cells treated with ginsenoside Rh2. Leukemia is also classified as a malignant tumor, with HL-60 representing a promyelocytic leukemia cell line [79]. Numerous studies have elucidated that the caspase family of proteins plays a crucial role in both the initiation and execution of apoptosis, and is a key target of Rh2 [39,80]. Furthermore, Rh2 induces the degradation and apoptosis of promyelocytic leukemia-retinoic acid receptor A in human leukemia cell lines via the TNF- α /caspase-8 pathway [81].

3.6 Inhibiting the IAPs/annexin A2/NF- κ B Signaling Pathway

Although TNF induces the transcription of NF- κ B, several studies have consistently demonstrated that Rh2 can suppress or reduce the activity of the NF- κ B signaling pathway [82] and inhibit apoptosis by suppressing the activation of caspase-8 [83]. Abnormal activation of the NF- κ B signaling pathway is strongly linked to the onset, advancement, and progression of cancer in humans [84,85]. NF- κ B plays a crucial role in regulating cell growth and proliferation, influencing various biological functions [86] such as immune reactions, inflammatory responses, stress responses, and apoptosis. Its activity is regulated by several factors, including the membrane protein ANXA2, IAPs, survival factors, and the interleukins IL-2 and IL-6 [87,88].

Studies have identified annexin A2 as a potential target for Rh2-mediated anticancer activity [62]. The compound 20(S)-Rh2, an isomer of Rh2, promotes the activation of caspase-3 and caspase-9 in cells after treatment. In the context of NF- κ B signaling, annexin A2 functions as a scaffold protein that facilitates the nuclear translocation of NF- κ B p50/p65 heterodimers and enhances their transcriptional activity. Mechanistic studies using co-immunoprecipitation and pull-down assays have demonstrated that the direct binding of Rh2 to annexin A2 disrupts its association with the p50 subunit, thereby retaining NF- κ B in the cytoplasm and inhibiting its DNA-binding activity [25,76]. This inhibition leads to the reduced expression of NF- κ B target genes, particularly IAPs, which are key regulators of cell survival [25,83]. The downregulation of IAPs sensitizes cancer cells to apoptosis and contributes to the antitumor effects of Rh2. Furthermore, Rh2 exhibits anti-inflammatory activity by targeting annexin A2, which suppresses the production of NF- κ B-dependent inflammatory mediators, such as cytokines and adhesion molecules [61]. Thus, annexin A2 serves as a critical direct molecular link through which Rh2 inhibits both the survival and inflammatory arms of the NF- κ B pathway [25], whereas the overall inhibition of this pathway by Rh2 likely results from a combination of such direct target engagement and indirect cellular responses. Atopic dermatitis is mediated by cytokines secreted from keratinocytes and T helper 2 (Th2)-polarized T cells. Furthermore, it has been demonstrated that Rh2

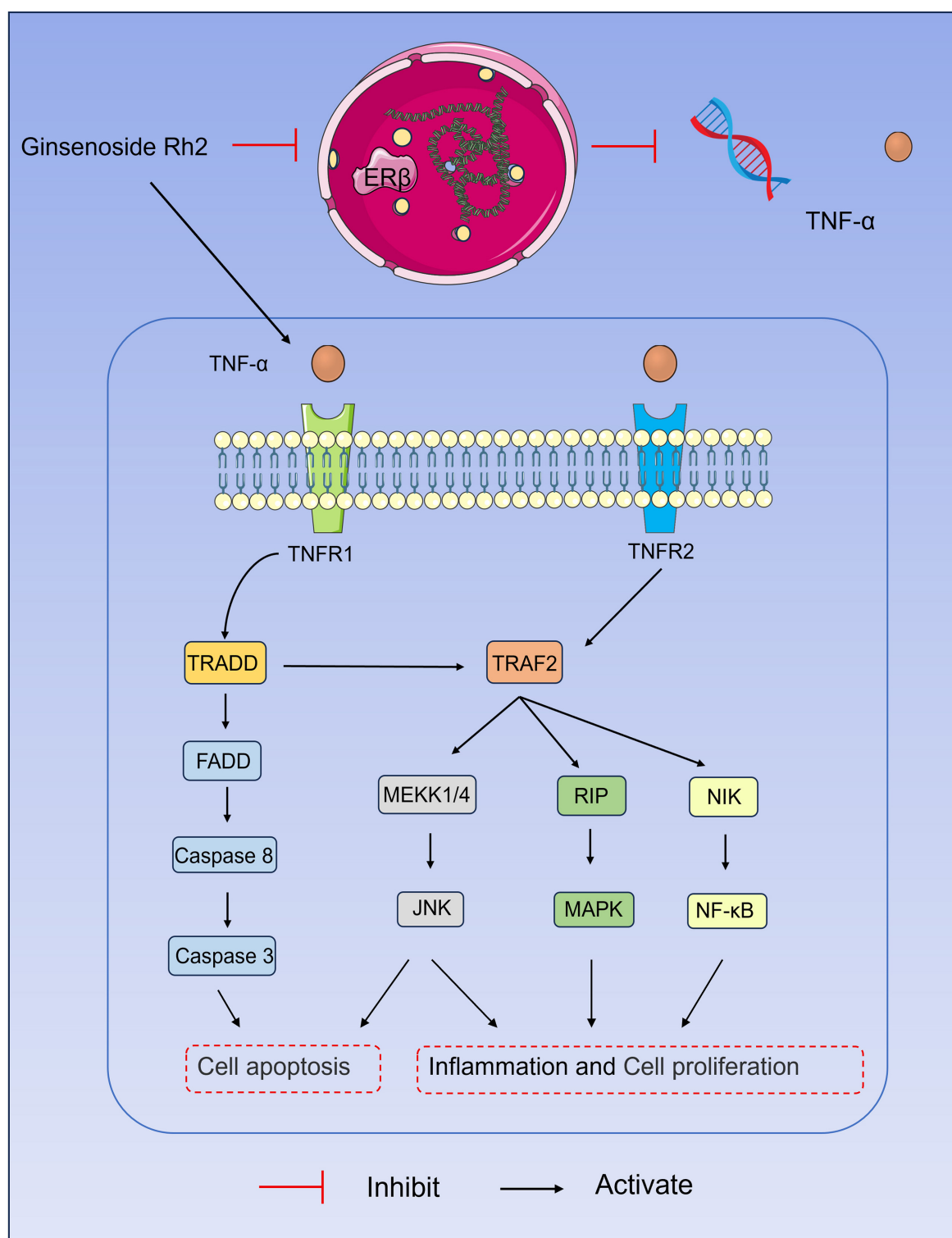


Fig. 4. Ginsenoside Rh2 inhibits ER β , leading to the downregulation of TNF- α expression, and activates the binding of TNF- α to its receptor TNFR1, thereby inducing apoptosis through activation of the downstream caspase family. The picture is drawn by PowerPoint. TNFR, TNF receptor; FADD, Fas-associated death domain protein; JNK, c-Jun N-terminal kinase; RIP, receptor-interacting serine/threonine-protein kinase; MAPK, mitogen-activated protein kinase; NIK, NF- κ B-inducing kinase.

inhibits the production of thymic stromal lymphopoietin in keratinocytes. This action, mediated by inhibition of NF- κ B signaling, allows Rh2 to modulate Th2 cell differentiation and activity [89].

3.7 Inducing Apoptosis and Autophagy

Apoptosis, one of the best-characterized forms of programmed cell death, results from a highly complex cascade of cellular events that lead to chromatin condensation, DNA

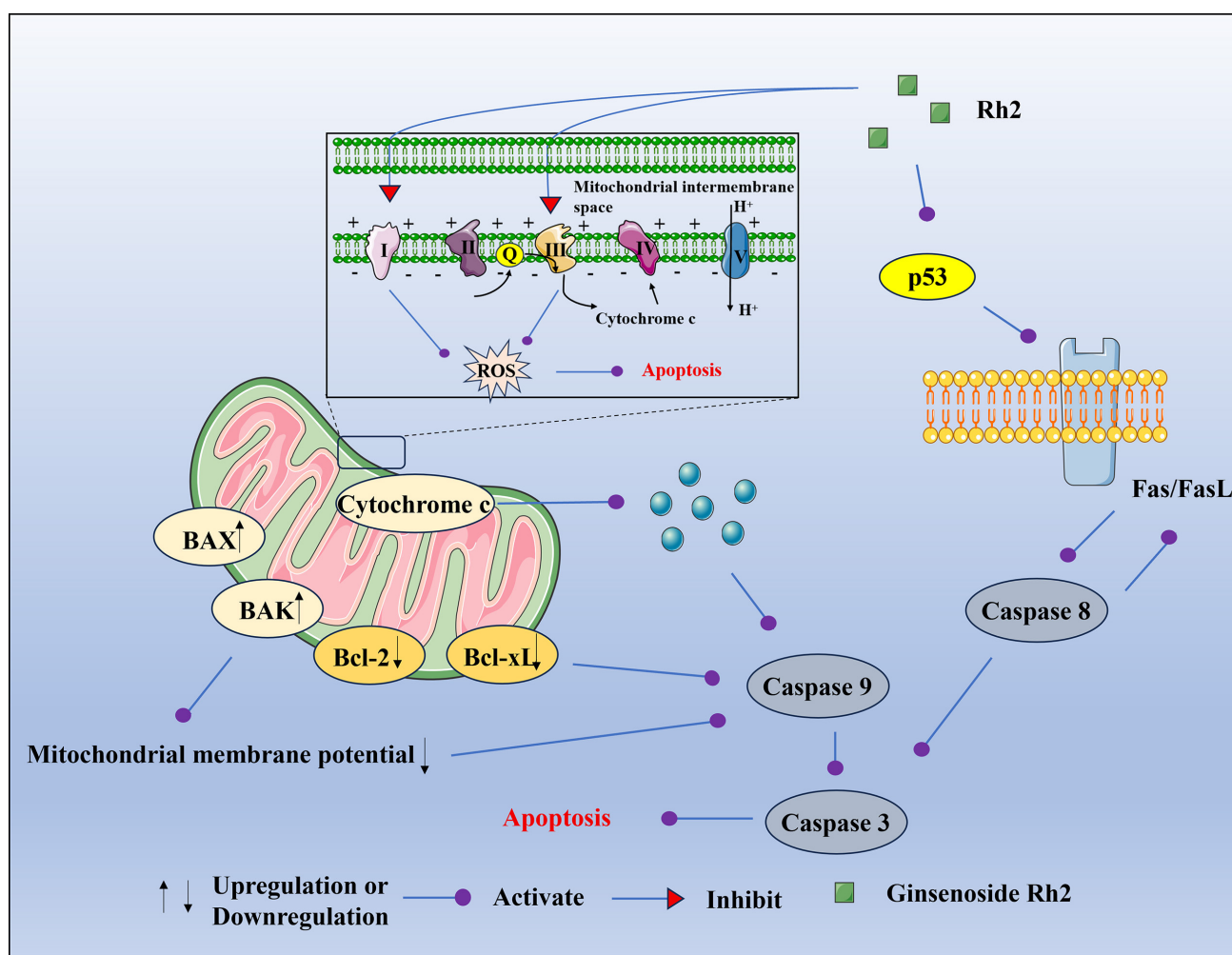


Fig. 5. The mechanism of ginsenoside Rh2 in regulating mitochondria and inducing apoptosis. The picture is drawn by PowerPoint. BAX, Bcl-2-associated X protein; BAK, Bcl-2 homologous antagonist/killer.

fragmentation, cytoplasmic membrane blebbing, and cell shrinkage [90]. Research indicates that ginsenoside Rh2 can significantly induce apoptosis in various cancer cell lines, including A431 human epidermoid carcinoma, A549 human lung cancer, A375-S2 human malignant melanoma, and HepG2 HCC [2,91,92]. Rh2 regulates the activation of two key proteases, caspase-8 and caspase-9, which are crucial for executing apoptosis. This regulation subsequently initiates hydrolysis and signaling cascades involving other caspases such as caspases-3, caspase-6, and caspase-7, ultimately leading to cell apoptosis, as shown in Fig. 5 [93].

Numerous reports have indicated that Rh2-induced apoptosis is associated with the activation of death receptors or related ligands, such as Fas/Fas ligand and death receptor 4 (also known as tumor necrosis factor-related apoptosis-inducing ligand [TRAIL] receptor 1). In TE-13 esophageal cancer cells, 20(S)-Rh2 has been shown to upregulate the transcription and protein expression of the death receptor Fas by activating caspase-8 [94]. Furthermore, in HepG2 HCC cells, the combination of 20(S)-Rh2 and TRAIL has been found to reduce cell viability and enhance caspase-

induced apoptosis [95]. The p53 gene product serves as a crucial tumor suppressor, and accumulating evidence suggests that p53 is a primary mediator of Rh2-induced apoptosis in cancer cells [96]. In HeLa cervical cancer cells, Rh2 treatment enhances p53 expression, leading to a significant increase in Fas expression and caspase-8 activity, thereby promoting apoptosis [97]. Furthermore, the Bcl-2 family of proteins is a crucial target influencing apoptosis. Rh2 induces dose-dependent apoptosis in U20S human osteosarcoma cells by upregulating Bcl-2-associated X protein (Bax) and reducing Bcl-2, caspase-3, and caspase-9 levels [73]. Furthermore, Rh2-induced intrinsic apoptosis is primarily driven by changes in mitochondrial membrane potential. Rh2 treatment of esophageal cancer cells triggers an increase in the anti-apoptotic Bcl-2 family of proteins, a reduction in the expression of Bax and Bcl-2 homologous antagonist/killer (Bak), and a decrease in mitochondrial membrane potential [94]. However, among different breast cancer cell lines, MCF-7 and MDA-MB-231, Rh2 exhibits a more pronounced apoptotic effect on MCF-7 cells, with a significantly higher increase in the Bax/Bcl-2

ratio and greater changes in mitochondrial membrane potential compared to MDA-MB-231 cells [67]. This indicates that Rh2 has varying apoptotic effects on different cancer cell lines. Investigating the therapeutic effects of ginsenoside Rh2 on prostate cancer, Wu et al. [28] discovered that Rh2 significantly reduced the survival rate of DU145 cells and increased cell apoptosis by upregulating the expression of PPAR- δ . In addition to apoptosis, Rh2 reportedly induces autophagy in certain cancer cell lines. For example, in K562 chronic myeloid leukemia cells, Rh2 treatment reduces caspase-3 activation and induces cellular autophagy through the mitochondrial signaling pathway [6]. Similarly, in doxorubicin-treated breast cancer cells, Rh2 modulates mitochondrial autophagy to alleviate chemotherapy-induced senescence while potentiating antitumor effects [24]. These findings suggest that autophagy may represent an additional cell death mechanism contributing to Rh2's antitumor activity. However, whether Rh2 triggers other forms of programmed cell death, such as pyroptosis or necroptosis, remains unexplored and requires further investigation.

3.8 Regulating Mitochondria

Mitochondria are complex organelles that play a crucial role in cancer development, growth, survival, and metastasis. Beyond their function in energy production, various aspects of mitochondrial biology actively contribute to tumorigenesis, including mitochondrial mass dynamics, regulation of cell death, redox homeostasis, and metabolic regulation and signaling [98,99]. Rh2 regulates ROS levels and mitochondrial autophagy. Because mitochondria are the primary source of ROS, generating more than 90% of total ROS in eukaryotic cells, they are regarded as critical organelles involved in the regulation of oxidative stress [100,101]. Excessive ROS production can lead to oxidative stress and subsequent damage to mitochondria [75]. Rh2 directly targets multiple mitochondrial components, including electron transport chain (ETC) complexes, pyruvate dehydrogenase kinase (PDK), and VDAC1, leading to impaired energy metabolism, mitochondrial ROS accumulation, and cytochrome c release. These direct effects initiate mitochondrial dysfunction and apoptosis. However, subsequent cellular outcomes—such as activation of caspase cascades, changes in Bcl-2 family protein expression, and cell cycle arrest—may be amplified through indirect mechanisms including ROS-mediated signaling, feedback regulation of mitochondrial biogenesis, and crosstalk with other cell death pathways [10,90]. Understanding how these direct mitochondrial targets integrate with broader cellular networks will be important for fully elucidating Rh2's antitumor mechanism.

Research has demonstrated that ginsenoside Rh2 alleviates oxidative stress-induced senescence in normal mammary epithelial cells and inhibits their associated breast cancer growth by regulating ROS levels and mitochon-

drial autophagy [24]. Additionally, Rh2 can induce apoptosis by promoting the accumulation of mtROS in human leukemic Jurkat, HepG2, and Hep3B cells [102,103,104]. Rh2 triggers significant ROS production in HepG2 HCC cells, leading to early lysosomal membrane permeabilization, cathepsin B release into the cytosol, and subsequent mitochondrial damage [103]. Studies have demonstrated that Rh2 preserves pig oocyte quality against aging and oxidative stress by enhancing mitochondrial activity and function [105]. Rh2 exhibits antioxidant effects in ultraviolet-damaged human dermal fibroblasts by inhibiting mitochondrial autophagy (mitophagy) and restoring mitochondrial membrane potential and ATP production [106]. PTEN-induced kinase 1 (PINK1) and Parkin are essential proteins for maintaining mitochondrial integrity, working together to regulate mitochondrial quality control and autophagy. PINK1, a mitochondrial membrane-bound kinase, detects dysfunction, signaling the E3 ubiquitin ligase Parkin to label damaged mitochondria for degradation. Rh2 modulates the expression of mitochondrial Bcl-2 and Bax, while simultaneously impeding cancer cell progression by elevating the levels of PINK1 and Parkin, and decreasing the concentrations of peroxisome proliferator-activated receptor gamma coactivator 1-alpha, which significantly promotes mitochondrial autophagy [24]. Beyond its effects on mitochondrial regulatory proteins, Rh2 directly interacts with specific mitochondrial components to exert its antitumor activity. One such target is the ETC complex. Studies have demonstrated that Rh2 directly inhibits the activity of ETC complexes without downregulating their protein expression, leading to mitochondrial functional impairment, decreased ATP production, and accumulation of mtROS [10,90]. This direct inhibition of ETC complexes triggers the intrinsic apoptotic pathway and sensitizes cancer cells to cell death. Another direct mitochondrial target is PDK, a key enzyme localized in the mitochondrial matrix that regulates the switch between glycolysis and oxidative phosphorylation (OXPHOS).

Rh2 promotes apoptosis by inducing mitochondrial dysfunction and disrupting the membrane potential, achieved through mechanisms such as targeting the ETC complex, increasing ROS, activating membrane receptors, and modulating membrane potential. Mitochondria synthesize ATP primarily through OXPHOS, which involves the ETC complex localized on the inner mitochondrial membrane [107]. Rh2 regulates mitochondrial dysfunction, leading to a rapid decrease in mitochondrial membrane potential by inhibiting both mitochondrial OXPHOS and glycolysis. This inhibition reduces cellular ATP production, consequently leading to apoptosis in cancer cells [102]. Importantly, studies have shown that the detrimental effects of Rh2 on OXPHOS are not attributable to the downregulation of ETC protein expression. Rather, Rh2 directly inhibits the activity of ETC complexes, leading to impaired mitochondrial function. PDK, which is primarily localized in the mitochondrial matrix, serves as a key regulatory factor in cel-

lular energy metabolism and is functionally associated with the ETC on the inner mitochondrial membrane. By directly targeting mitochondrial PDK, Rh2 enhances mitochondrial OXPHOS, increases ROS accumulation, and promotes the normal apoptotic process in tumor cells. Accumulating evidence indicates that Rh2 can directly interact with mitochondria and modulate cytochrome-related pathways in melanoma [90]. In general, the mitochondrial membrane potential in various cancer cells is regulated by several key genes, including Bcl-2, Bcl-xL, and Bax [108], whose interactions play a crucial role in determining cell survival and apoptosis.

Cytochrome c is a class of iron-rich proteins that play a crucial role in ETC during cellular energy metabolism. It is mainly distributed on the inner membrane of mitochondria and serves as a central factor connecting the components of the ETC, ensuring efficient conversion and utilization of cellular energy [109]. The backbone of 20(S)-Rh2, characterized by a dammarane structure, has been shown to induce apoptosis in various cancer cell lines by activating apoptotic pathways facilitated by mitochondria or membrane death receptors [90,110]. In cervical cancer cell lines, the upregulation of VDAC1 by ginsenoside Rh2 triggers the translocation of mitochondrial Bax, promoting the release of cytochrome c and initiating mitochondria-dependent apoptosis in HeLa cells, confirming VDAC1 as a functional target of Rh2 [90]. These findings demonstrate that Rh2 directly targets multiple mitochondrial proteins—including ETC complexes, PDK, and VDAC1—to disrupt mitochondrial function and promote cancer cell apoptosis. Apoptosis can also be induced through the mitochondrial pathway when the pro-apoptotic protein Bax migrates to the mitochondrial membrane, causing depolarization, the release of pro-apoptotic factors, and subsequent caspase-9 activation. Ginsenoside Rh2 induces apoptosis in leukemia cell lines by upregulating Bax and Bak, which triggers the release of cytochrome c from the mitochondria into the cytoplasm. This mitochondrial event initiates a cascade involving the cleavage of caspase-8 and caspase-9, ultimately resulting in caspase-3 activation [93,110]. This apoptotic process often causes corresponding cell cycle arrest. *In vitro* experiments have demonstrated that increasing doses of Rh2 induce apoptosis in rapidly proliferating SGC-7901SP gastric cancer cells by upregulating mitochondrial Bax and down-regulating Bcl-2. This dose-dependent modulation triggers cell cycle arrest at the G1/G0 phase, which progressively inhibits tumor cell growth, as shown in Fig. 5 [111].

4. Conclusion and Prospects

The identification of direct molecular targets of Rh2 (including AXL, annexin A2, VDAC1, PDK, and ETC complexes) provides a mechanistic basis for its anticancer activity and opens new avenues for combination therapies. Given its multi-targeting properties, Rh2 holds significant potential as an adjuvant to enhance the efficacy

of existing cancer therapies while mitigating adverse effects, a concept increasingly supported by emerging evidence. Rh2 synergizes with the mTOR inhibitor SMI-4a to enhance autophagic cell death in melanoma [27], sensitizes HCC cells to TRAIL-induced apoptosis [95], and alleviates doxorubicin-induced senescence while potentiating its anticancer effects on breast cancer [24,67]. In NSCLC, Rh2 enhances the efficacy of miR-28-5p inhibitors by activating the STK4 tumor suppressor and inhibiting Wnt/ β -catenin signaling [2].

Despite these promising findings, there are still several issues that need to be addressed before Rh2 can be applied in clinical practice. First, the structural optimization of Rh2 deserves more attention. Rh2 has low natural abundance and poor water solubility, which limit its bioavailability. Some studies have attempted to modify its structure, such as changing glycosylation patterns, introducing sulfation, or developing derivatives like Rh2E2, and these modifications have shown improved solubility and metabolic stability [5]. However, systematic investigation into the structure–activity relationship is required to facilitate the rational design of Rh2 analogs with improved pharmacological properties. Second, comprehensive toxicity data for Rh2 remain limited. While generally considered safer than conventional chemotherapy, most current studies prioritize efficacy, leaving a gap in systematic assessments regarding its off-target effects, organ-specific toxicity, and long-term safety. Future research should address these aspects and establish reliable methods to evaluate its safety profile. Third, more novel molecular targets of Rh2 remain to be discovered. Current research has identified several direct targets, such as AXL and annexin A2; however, network pharmacology analysis predicts that Rh2 may interact with more than 200 proteins [2]. With the development of technologies like chemical proteomics, CRISPR screening, and computer-aided drug design, it is possible to identify more targets and gain a deeper understanding of Rh2's mechanism of action.

These findings suggest that Rh2 could serve as a broad-spectrum adjuvant to improve the efficacy of chemotherapy, targeted therapy, and immunotherapy. Its ability to modulate multiple direct targets may help overcome drug resistance—a major challenge in current cancer treatment. Future studies should focus on optimizing combination regimens, exploring their role in overcoming resistance to checkpoint and tyrosine kinase inhibitors, and developing targeted delivery methods that maximize synergistic effects while minimizing toxicity. Furthermore, the pharmacological effects of the two Rh2 configurations can be altered via chemical modification. For example, sulfating the R-type structure significantly improves its water solubility. Nonetheless, challenges remain, particularly the low natural abundance of Rh2, which complicates extraction processes. Developing synthetic chemical modifications could expand its presence in the food and medical sectors, significantly improving global health outcomes.

Author Contributions

YW: Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Conceptualization. YLiang: Writing – original draft, Visualization, Conceptualization. YH, CS, YC, WX, QZ, SY, YLong, CJ: Visualization, Investigation, Supervision. CD: Conceptualization and design of the review framework, funding acquisition. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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