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Review

The experimental significance of isorhamnetin as an effective therapeutic option for cancer: A comprehensive analysis

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ABSTRACT

Isorhamnetin ($C_{16}H_{12}O_7$), a 3′-O-methylated derivative of quercetin from the class of flavonoids, is predominantly present in the leaves and fruits of several plants, many of which have traditionally been employed as remedies due to its diverse therapeutic activities. The objective of this in-depth analysis is to concentrate on Isorhamnetin by addressing its molecular insights as an effective anticancer compound and its synergistic activity with other anti-cancer drugs. The main contributors to Isorhamnetin's anti-malignant activities at the molecular level have been identified as alterations of a variety of signal transduction processes and transcriptional agents. These include ROS-mediated cell cycle arrest and apoptosis, inhibition of mTOR and P13K pathway, suppression of MEK1, PI3K, NF-κB, and Akt/ERK pathways, and inhibition of Hypoxia Inducible Factor (HIF)-1α expression. A significant number of in vitro and in vivo research studies have confirmed that it destroys cancerous cells by arresting cell cycle at the G2/M phase and S-phase, down-regulating COX-2 protein expression, PI3K, Akt, mTOR, MEK1, ERKs, and PI3K signaling pathways, and up-regulating apoptosis-induced genes (Casp3, Casp9, and Apaf1), Bax, Caspase-3, P53 gene expression and mitochondrial-dependent apoptosis pathway. Its ability to suppress malignant cells, evidence of synergistic effects, and design of drugs based on nanomedicine are also well supported to treat cancer patients effectively. Together, our findings establish a crucial foundation for understanding Isorhamnetin's underlying anti-cancer mechanism in cancer cells and reinforce the case for the requirement to assess more exact molecular signaling pathways relating to specific cancer and in vivo anti-cancer activities.

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1. Introduction

Cancer originates from the dysregulated proliferation of aberrant cells and concurrent genomic modifications, which induce oncogenic traits in otherwise healthy cells [1–3]. Human understanding of cancer's biological features is constantly evolving as a result of developments in cancer research. Cancer is a disease of the genome [4]. A multitude of cancer types exist, including bladder cancer, breast cancer, colorectal cancer, tumors of the nervous system, and lung cancer—their prevalence, fatality rates, as well as some risk factors. Bladder cancer is extensive, with urothelial cancer being the most common type [5–7]. Breast cancer is heterogeneous and the second most prevalent cause of cancer mortality among women in the Western hemisphere. The 2nd most frequent cancer follows the adenoma-carcinoma sequence in the world, colorectal cancer. Nervous system tumors have many morphological subtypes and are more common in males. In the United States, malignancy of the lung is the leading cause of cancer death for both men and women, with the use of tobacco serving as the main risk factor. Molecular and tumor biology have significantly shifted cancer therapy paradigms [8–10]. Traditional therapies include chemotherapy, surgery, and radiation. Immunotherapy using inhibitors of immune checkpoints has led to the creation of oncolytic viral treatment, which employs genetically produced or naturally occurring viruses to attack cancer cells. Radiotherapy is also essential to cancer treatment, but its usage rates vary between countries [11,12]. Due to the significant mortality rate and harsh side effects of traditional cancer treatments like radiation and chemotherapy, many patients are exploring alternative and complementary treatment methods. Currently, there is a pressing need to discover effective chemotherapy options that do not produce toxic effects [13]. Many modern medications are derived from natural sources, effectively inhibiting cancer cell growth [14–16]. Plant-derived chemicals have led to therapeutically relevant anti-cancer medicines, such as vinca alkaloids and paclitaxel. Natural substances, such as curcumin, indol-3-carbinol omega-3 fatty acids, isorhamnetin, and quercetin, can reduce cancer cell growth, survival, and resistance to chemotherapy drugs [17]. Flavonoids are a class of chemicals that contain a compound called flavone and have been used in Chinese conventional medicine. Isorhamnetin, a type of flavonoid, is extracted and refined from medicinal herbs such as *Persicaria thunbergia* H. and *Elaeagnus rhamnoides* (L.) A. Nelson. It is also known as 3-methoxy 3,4,5, 7-tetrahydroxyflavone or [18]. Active ingredients that protect against oxidative damage reduce atherosclerosis, inhibit platelet aggregation, and induce necrosis in human carcinoma have been identified [19,20].

Isorhamnetin (ISO), a compound structurally similar to flavones, has been studied for its potential clinical pharmacology in cancer treatment due to its cytotoxic effects against human cancer cells [21,22]. Isorhamnetin is a compound found in several plants' leaves, flowers, and fruits, including *Hippophae rhamnoides L.* and *Ginkgo biloba L.* Several studies have shown that ISO significantly affects the modulation of the immune system, reduces inflammation, and protects against cardiovascular and cerebrovascular diseases [23–25]. ISO has recently gained recognition for its ability to suppress tumors in various human cancers such as colorectal, skin, lung, and breast [26–30]. It exerts anti-tumor effects by inhibiting cell migration and proliferation and promoting apoptosis. Despite extensive research on the cytostatic and pro-apoptotic properties of ISO, its potential in gastric cancer therapy and the molecular mechanisms involved in inducing apoptosis have yet to be fully explored [31–33]. Apoptosis is essential for controlling cell growth and preventing diseases, particularly cancer. Numerous studies have revealed that ISO can inhibit the growth and invasion of cancer cells by activating apoptosis, mainly through the PPAR-γ, mitochondria-cytochrome C-caspase-9, and ROS-mediated CaMKII/Drp1 pathways. ISO can make cancer cells more radiation-sensitive through signaling pathways and encourage apoptosis. Overall, ISO has exhibited significant pro-apoptotic effects in multiple cancer therapies. Furthermore, ISO can also stop the proliferation of human bladder cancer cells by inducing cell cycle arrest during the G2/M phase and promoting apoptosis [34,35]. Additionally, it triggers the activation of caspase-8, caspase-9, and caspase-3, resulting in the breakdown of PARP. Isorhamnetin also prompts dysfunction in mitochondria and amplifies the ratio of Bax to Bcl-2 expression, causing the release of cytochrome C into the cytoplasm. Furthermore, isorhamnetin induces a halt in the cycle at the G2/M phase and promotes apoptosis through the upregulation of the AMPL signaling pathway and excessive generation of reactive oxygen species (ROS). Inhibition of the AMPK signaling pathway mitigates the apoptotic effects triggered by isorhamnetin, and impeding ROS production enables cells to evade G2/M arrest and apoptosis [18,36,37].

As we explore the realm of science, our review study reveals the potential of Isorhamnetin, displaying it as a promising intervention in the battle against the persistent and devastating impact of cancer. The present analysis reveals the impressive individual capabilities of the subject under examination and its considerable capacity for synergistic integration, effectively coordinating various therapeutic elements to produce harmonious melodies of enhanced efficacy that go beyond the mere cumulative impact of their constituent components. Moreover, our work positions Isorhamnetin within the field of nanomedicine, a cutting-edge area that offers the potential to enhance its therapeutic efficacy through deliberate drug design strategies. As we define the parameters of Isorhamnetin techniques in the field of nanomedicine, we establish the groundwork for a new epoch in the realm of cancer therapy. This age is characterized by meticulousness, efficacy, and an unyielding dedication to eliminating this powerful opponent. Our research stands out in scientific investigation due to its comprehensive examination, steadfast dedication to unraveling the intricate molecular details, and forward-thinking approach toward converting Isorhamnetin from a mysterious compound to a highly regarded anticancer agent. In pursuing academic inquiry, the subsequent content serves as evidence of our firm conviction that Isorhamnetin holds potential as a leading agent in the fight against cancer. It symbolizes a source of optimism that guides us toward a future where the influence of this disease is reduced while our unwavering commitment to this formidable task remains steadfast.

2. Biochemical and pharmacological profiling of isorhamnetin

Over the past few years, there has been a notable rise in the utilization of plant-derived medication systems within the therapy field. Plants contain around 4000 flavonoids, many of which possess therapeutic attributes [38]. Isorhamnetin, a phytochemical, can be exhibited in multiple parts of plants known as the flowers, leaves, and fruits, including *Ginkgo biloba L.*, *Hippophae rhamnoides L.*, and many more plant species. The fruit produced by *Hippophae rhamnoides* has traditionally been known for its ability to alleviate cough and phlegm, promote blood circulation, eliminate blood stasis, invigorate the spleen, and aid digestion. Ginkgo biloba leaves are traditionally recognized for relieving pain, alleviating asthma symptoms, reducing lipid levels, clearing lung congestion, and improving blood circulation. Isorhamnetin is considered one of the vital active constituents in *Hippophae rhamnose's* fruiting bodies and Ginkgo biloba's leaf clusters. Isorhamnetin demonstrates a broad spectrum of pharmacological impacts, such as anti-inflammatory properties, anti-tumor activity, antioxidant action, antimicrobial capabilities, and antiviral potential [39]. Studies have demonstrated that isorhamnetin exhibits diverse pharmacological properties concerning various types of tumors, cardiovascular diseases [40], and potential prevention of neurodegenerative disorders like Alzheimer's disease [41].

Additionally, it displays pharmacodynamic effects against pulmonary fibrosis [42] and hyperuricemia [43]. Isorhamnetin, also referred to as 3-methyl quercetin, is a flavonoid compound with a structural backbone called 3-hydroxy-2-(3,4,5-tri hydroxyphenyl) chromen-4-one (Fig. 1). It has a molecular weight of 316.26 g/mol.

The small intestine is where isorhamnetin is largely absorbed owing

to active transport processes and passive diffusion. However, because it is poorly soluble in water, it is difficult to drink and has a low bioavailability when taken orally [44]. Researchers have investigated several methods to increase the bioavailability of isorhamnetin to address this problem, including delivery systems, nanoencapsulation, and complexation with phospholipids. These methods have shown promise in improving the bioavailability and absorption of isorhamnetin, increasing its therapeutic potential [45]. Since it is a naturally occurring substance in many fruits and vegetables, isorhamnetin is generally considered safe when ingested in moderation from dietary sources. Isorhamnetin has been generally recognized as safe (GRAS) for use in foods and drinks by the U.S. Food and Drug Administration (FDA). However, excessive consumption of isorhamnetin in supplement form could have negative consequences, similar to many other bioactive substances. High-dose isorhamnetin supplementation has been linked to several harmful side effects. High dosages of isorhamnetin have been associated with gastrointestinal disturbances, such as stomach upset, nausea, diarrhea, or abdominal pain [46]. Although uncommon, some people may develop allergic responses to isorhamnetin, which are skin rashes, itching, or breathing problems [47]. Isorhamnetin may interact with some medicines, possibly influencing how well they work and how quickly they are metabolized. In particular, it can disrupt cytochrome P450 enzymes, which may result in altered drug metabolism and possible drug interactions [48]. Interestingly, isorhamnetin can have pro-oxidant characteristics at high concentrations, which can cause cells to experience oxidative stress and the production of reactive oxygen species (ROS). Under specific circumstances, this pro-oxidant action has prompted questions about its safety [49]. It is important to emphasize that these possible adverse effects may differ across individuals based on their health state and sensitivities. They are more likely to occur with isorhamnetin consumption at greater doses. Generally, isorhamnetin is well-tolerated and unlikely to have significant adverse effects when taken in the prescribed amounts from dietary sources. Additionally, the fact that it is widely present in plant-based foods implies that it is safe when consumed as part of a balanced diet. However, the safety margin can vary from person to person, so it's important to use caution, especially when using supplements with higher amounts of isorhamnetin.

3. Cellular and molecular mechanisms of isorhamnetin in impeding selective carcinoma

3.1. In-Vivo evidence

According to study, the inhibition of autophagy/mitophagy by CQ selectively enhances IH-induced mitochondrial fission and apoptosis in TNBC cells but not in estrogen-dependent breast cancer cells. The combination of CQ/IH was a marked inhibitor tumor growth, inducing apoptosis in the TNBC xenograft mouse model in association with the activation of CaMKII and Drp1 (S616) [24]. Another study reported anti–skin cancer effects of isorhamnetin, which inhibited epidermal growth factor (EGF)-induced neoplastic cell transformation. It also suppressed anchorage-dependent and -independent growth of A431 human epithelial carcinoma cells. Isorhamnetin attenuated EGF-induced COX-2 expression in JB6 and A431 cells. In an in vivo mouse xenograft using A431 cells, isorhamnetin reduced tumor growth and COX-2 expression. The EGF-induced phosphorylation of extracellular signal-regulated kinases, p90 and p70 ribosomal S6 kinases, and Akt was suppressed by isorhamnetin [29]. Isorhamnetin significantly reduced inflammatory cell infiltration and pro-inflammatory gene expression in rats. Isorhamnetin pretreatment inhibited inducible nitric oxide synthase (iNOS) expression and NO release in LPS-stimulated cells [50]. Isorhamnetin is very critical in Tsoong because Tsoong can down-regulate Hsp70 genes and promote apoptosis of colon cancer cells by inhibiting Hsp70 largely due to the efficacy of Isorhamnetin [51].

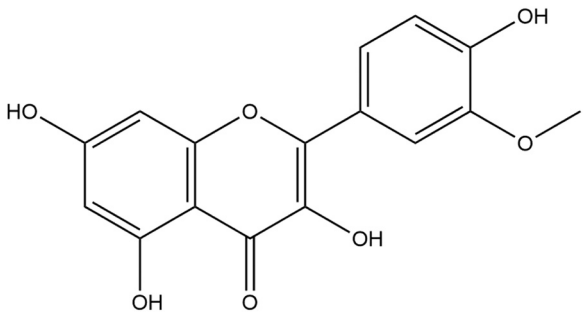

Fig. 1. : Chemical Structure of Isorhamnetin.

3.2. In-Vitro evidence

Isorhamnetin is derived from the flavonoid source found in several different plant species' leaves, flowers, and fruits, including *Ginkgo biloba L.* and *Hippophae rhamnoides L* [39]. In addition to its potential to prevent neurological illnesses like Alzheimer's, isorhamnetin has been demonstrated to have potential therapeutic effects on cardiovascular diseases and multifarious human cancers [40,41,52]. Isorhamnetin can influence signal pathways, tumor suppressor genes, and proto-oncogenes, in addition to preventing the proliferation of tumor cells and inducing their death through apoptosis [52]. The anti-tumor benefits of isorhamnetin and its mechanism of action are outlined in Table 1.

To begin with, the mitogen-activated protein kinases (MAPKs), a family of serine/threonine protein kinases that can effectively regulate the parallel signaling pathways in cells, whereas P38, JNK, RAS, MEK, and ERK are all the downstream factors. RAS is a protein that works as an upstream regulator of ERK, which plays a significant role in multiple cellular activities known as cell differentiation and proliferation, apoptosis, and signal transmission from surface receptors to the cell's nucleus. Isorhamnetin has been demonstrated to induce apoptosis via several mechanisms, including G1 cell cycle arrest, reduced the ERK and Akt phosphorylation and the activation of nuclear antigen Ki67 proliferation, decreased the expression of Bcl-2, enhanced the Bax expression, and promoted Caspase 3 cleavage [53]. Isorhamnetin slows the expansion of breast cancer cells by regulating the Akt and MEK signal transduction pathways [54]. The research work by Wang and his colleagues has reported that via inhibiting MEK, ERK, and Ras/MAPK signaling pathways, isorhamnetin possessed potential anticancer activity by regulating cell differentiation and proliferation, apoptosis [55]. Through an in vitro cell proliferation assay, Jiang et al. found that isorhamnetin prevented HepG-2 cells from approaching the S phase of DNA synthesis [56].

Similarly, the mutation that causes ataxia-telangiectasia (ATM), which is a kinase that becomes active in response to the presence of a cellular damage signal, triggers cell cycle arrest by activating the checkpoint effector kinase CHK2 [57]. Isorhamnetin's ability to suppress HeLa cell growth by arresting cells in the G2 / M phase of the cell cycle is directly linked to the activation of the ATM-CHK2 pathway and the loss of microtubule function [58]. Isorhamnetin prevents the growth of new lung cancer colonies, the apoptosis induction in A549 cells, and the proliferation of human lung cancer cells. In addition, Mitochondrial-dependent mechanisms may be involved in apoptosis induction. Isorhamnetin causes apoptosis in A549 cells by reducing the potential of the mitochondrial membrane, which allows for the release and high expression of caspase and Cytochrome c [59,60]. Isorhamnetin also plays a significant anti-tumor function due to its ability to induce apoptosis by down-regulating carcinogenic genes and up-regulating apoptosis-related genes [60].

It also promotes the upregulation of apoptotic genes, which are in charge of starting and carrying out the programmed cell death process, to perform its anti-tumor actions. Isorhamnetin is essential in preventing tumor growth and spread by controlling these genes' expression [61]. It

Table 1
Tabular representation of anticancer activities of Isorhamnetin in both in vitro and in vivo research studies.

In-Vivo

Name of the Compound	Research Model	Estimated Dose	Duration of Treatment	Targeted Signaling Pathways	Mechanistic Details	Research Findings	Reference Articles
Isorhamnetin	Sprague-Dawley rats	30 or 100 μM	12 h	NF- κB, AP-1, JNK, Akt and IKKα/β pathways	↑Phosphorylation of ERK, p38, and JNK, ↓Activation of NF- κB, AP-1, ↓Phosphorylation of JNK, ↑Activation of MAPKs	Suppression of acute inflammation	[50]
Isorhamnetin	A431 xenograft tumors in nude mice	1 or 5 mg/kg	4 weeks	COX-2 protein	↓COX-2 protein expression	Suppress the A431 xenograft tumor progression	[29]
Isorhamnetin	Kunming mice-induced colon cancer	5, 10, and 20 g/kg	6 weeks	Apoptosis-induced genes (Casp3 and Casp9, Apaf1), Hsp70 genes (Hspa1a, Hspa1b and Hspa8)	↑Apoptosis-induced genes (Apaf1, Casp3 and Casp9) expression, ↓Hsp70 genes (Hspa1a, Hspa1b and Hspa8) expression	Potentially induced apoptosis and inhibited colon cancer proliferation	[51]
Isorhamnetin	C57BL/6 mice inoculated with 0.2 ml/each of Lewis cells	50 mg/kg	7 days	Apoptosis-induced genes, PCNA, CyclinD1, Bcl-2, cyclinD1 and PCNA genes	↑Expression of PCNA, cyclinD1 genes, ↓Bcl-2, cyclinD1 and PCNA gene expression level	Induced apoptosis and antiproliferative activity of lung tumors	[69]
Isorhamnetin	xenograft mouse	20 mg/kg	80 days	Mitochondrial-dependent apoptosis pathway	↑Activation of Mitochondrial dependent apoptosis pathway	Promotion of apoptosis	[24]

In-Vitro

Name of the Compound	**Research Model**	**Estimated Dose**	**Duration of Treatment**	**Targeted Signaling Pathways**	**Mechanistic Details**	**Research Findings**	**Reference Articles**
Isorhamnetin	JB6 and A431 skin cancer cells	10 mmol/L	12 h	COX-2, MEK1, P13-K, and ERKs signaling pathways	↓COX-2 protein expression, ↓ERKs, P13-K, and MEK1 signaling pathways	Effectively suppress the skin cancer progression	[29]
Isorhamnetin	HT-29 and HCT116 colon cancer cell lines	0, 10, 20, 40 and 80 μmol/l	3 days	PI3K-Akt-mTOR pathway, Cell cycle at G2/M phase	↑Cell cycle arrest at the G2/M phase, ↓PI3K-Akt-mTOR pathway	Slowed the G2/M phase and inhibited the PI3KAktmTOR pathway.	[70]
Isorhamnetin	Human Breast Cancer MDA-MB-231 call line	40 μM	12 h	P38, STAT3 signaling pathways, matrix Metalloproteinase-2 (MMP-2), MMP-9	↓MMP-2 and MMp-9 expression, ↓Phosphorylation of p38 and STAT3	Suppressed the activity and expression of MMP-2 and MMP-9, Impaired the phosphorylation of STAT3 and p38 pathways	[71]
Isorhamnetin	HCT116 and HT29 human colorectal cancer cell lines	30 or 60 μM	6 h or 3 h	Hypoxia inducible factor-1α (HIF-1α)	↓HIF-1α expression	Effective inhibition of HIF-1α expression	[72]
Isorhamnetin	Pancreatic adenocarcinoma cell line PANC-1	0, 20, 40 and 80 μM	48 h	Cyclin A, ERK, and MEK in the Ras/MAK pathway, Cell cycle at S-phase	↓ERK and MEK phosphorylation level, ↑Cell cycle arrest at S-phase	Arrest the cell cycle S-phase, Reduced the phosphorylation levels of MEK and ERK, Induced apoptosis	[73]
Isorhamnetin	HCT116 and SW480 colon cancer cell lines	5, 10, and 20 g/kg	48 and 72 h	Cell cycle at G1 phase	↓The proportion of cells in the G1 phase, ↑Apoptosis	Inhibited cell progression in a dose-dependent manner	[51]
Isorhamnetin	Bladder cancer T24 cell lines (T24, 5637, and 2531 J)	127.86 μM and 145.75 μM	48 h	Cell cycle at G2/M phase, Apoptosis, Wee1 and cyclin B1, p21WAF1/CIP1, and adenosine 5′monophosphate-activated protein kinase (AMPK)	↑Cell cycle arrest at the G2/M phase, ↑Apoptosis, ↓Wee1 and cyclin B1, ↑p21WAF1/CIP1 expression, ↓AMPK expression	Effectively suppressed the progression of bladder cancer cell lines by regulating G2/M phase arrest and apoptosis	[36]
Isorhamnetin	Female cervical cancer cell line (HeLa cells)	100.03 μmol/l, 304.15 μmol/l, and 54.79 μmol/l	24 h, 48 h, and 72 h	Cyclin B1, Apoptosis, and Cell cycle arrest at the G2/M phase	↑Cell cycle arrest at the G2/M phase, ↓Cyclin B1 protein expression, ↑Apoptosis	Inhibited the proliferation of the HeLa Cell line	[74]
Isorhamnetin	Lung cancer A549 cell line	16 μM	12 h	Cytochrome C and caspase, Mitochondria dependent apoptosis, Autophagosomes, and light chain 3-II protein	↑Cytochrome C and caspase release, ↑Mitochondria dependent apoptosis, ↑Autophagosomes, and light chain 3-II protein expression	Significantly suppressed colony formation and cell proliferation	[26]

(*continued on next page*)

Table 1 (*continued*)

In-Vivo

Name of the Compound	Research Model	Estimated Dose	Duration of Treatment	Targeted Signaling Pathways	Mechanistic Details	Research Findings	Reference Articles
Isorhamnetin	Human gastric cancer MKN45 cell line	0, 10, 25, and 50 μM	12, 24, and 48 h	Peroxisome proliferator-activated receptor γ (PPAR- γ), Apoptosis	↑PPAR- γ activity, ↑Apoptosis	Inhibited gastric cancer invasion and proliferation	[75]
Isorhamnetin	Androgen-dependent prostate 97 LNCaP cell line	5, 10 and 20 μM	48 h	P13K-Akt-mTOR pathway, MMP-2 and MMP-9 pathway, Mitochondrion-dependent intrinsic apoptotic pathway	↓ MMP-2 and MMP-9 pathway, ↓P13K-Akt-mTOR pathway, ↑Mitochondrion -dependent intrinsic apoptotic	Effectively suppressed prostate cancer cell proliferation and metastasis	[76]
Isorhamnetin	AGS-1 and HGC-27 gastric cancer cell lines	20 μM	72 h	Caspase-3 cascade, Mitochondria-associated Bax/Bcl-2, Cytosolic cytochrome c, Mitochondria-dependent apoptotic pathway	↑Caspase-3 cascade, ↑Bax/Bcl-2 and Cytosolic cytochrome c, ↑Mitochondria-dependent apoptotic pathway	Effectively suppressed the human gastric cancer cell proliferation	[33]
Isorhamnetin	Esophageal squamous carcinoma cell line Eca-109	0–80 μg/ml	48 h	Cell cycle at G2/M phase, Stimulation of apoptosis	↑ Cell cycle arrest at G2/M phase, ↑Cytostatic dependent apoptosis	Inhibited cancer cell proliferation and induced apoptosis	[77]
Isorhamnetin	Melanoma Cell line B16F10	0–100 μmol/L	0, 12, and 24 h	Translocation of NF-κB pathways, Phosphorylation of Akt pathway	↓Phosphorylation of Akt, ↓Translocation of NF-κB	Induced apoptosis and inhibited cancer cell progression	[18]
Isorhamnetin	Leukemia RAW264.7 cell line	200 ng/ml	30 min	JNK and p38 pathways, Heme-Oxygenase-1	↓JNK and p38 expression, ↑Heme-Oxygenase-1	Inhibited cells proliferation	[78]
Isorhamnetin	A549 non-small cell lung cancer cell line	2.5, 5, and 10 μM	48 h	AKT/ERK1/2 signaling pathways, Matrix metalloproteinase (MMP)-2 and MMP-9, N-cadherin, and E-cadherin.	↓AKT/ERK1/2 signaling, ↓MMP-2 and MMP-9, ↓N-cadherin expression, ↑E-cadherin expression	Effectively suppressed the migration and invasion of non-small cell lung cancer cells	[31]
Isorhamnetin	Colon cancer HT29 cell line	40 mmol/L	24 h	Oncogenic c-Src, b-catenin, C-terminal Src kinase (CSK)	↓Oncogenic c-Src activation, ↑C-terminal Src kinase (CSK) expression ↓b-catenin nuclear translocation	Significant inhibition of oncogenic Src activity	[79]
Isorhamnetin	oral squamous cell carcinoma (OSCC) cell lines (HSC-3 and HSC-4)	40, 60, and 80 μM	24 h, 48 h, and 72 h	Cell cycle at G2/M phase, CDC2 and Cyclin B2, ROS, ERK pathway	↑Cell cycle arrest at the G2/M phase, ↓Cyclin B1 and CDC2 protein expression, ↑ERK phosphorylation, ↑ROS level	Significantly triggered proptosis	[80]
Isorhamnetin	Lung carcinoma A549 cell line	10–320 μg/ml	48 h	Apoptosis genes Bax, Caspase-3, P53, and Bcl-2, cyclinD1 and PCNA genes	↑Bax, Caspase-3, P53 gene expression, ↓Bcl-2, cyclinD1 and PCNA gene expression level	Induced apoptosis and antiproliferative activity of lung cancer cells	[69]
Isorhamnetin	Cervical cancer of Hela cell	20 μg /ml	——	Cell cycle at G2 / M phase	↓ Bcl-2 gene, ↑ Bax gene	Suppression of cell proliferation and induction of apoptosis	[81]
Isorhamnetin	Hela cell line of cervical cancer	1,10,100,1000 μmol/l	24 h, 48 h, and 72 h	Cell cycle at G2/M phase	↑Activation of ATM-Chk2 pathway	Inhibition of proliferation	[74]
Isorhamnetin	Colon cancer of Caco2 HCT-116 cell and HT-29 cell	———	———	———	———	Suppressed the proliferation of cancer cells and induced apoptosis	[82]
Isorhamnetin	Different Breast cancer cell lines like as MCF7, BT474, T47D, BT-549, MDA-MB-468, and MDA-MB-231	0, 10 μM	72 h	MEK and Akt/mTOR pathway	↓Signal-regulated kinase phosphate cascade reaction among the MEK and Akt/mTOR signaling pathways	Inhibited the proliferation of cancer cells and induced apoptosis	[30]
Isorhamnetin	Breast cancer TNBC cells	2.5, 5, 10, 15 μM	48 h	Mitochondrial-dependent apoptosis pathway	↑Upregulation of mitochondrial-dependent apoptosis pathway	Promotion of apoptosis	[24]
Isorhamnetin	Nasopharyngeal cancer CNE-2	10, 20, 40, 80 mg/L	———	———	———	Suppression of cell proliferation	[83]
Isorhamnetin	Gastric cancer SGC-7901	0.4×10^{-4}, 0.8×10^{-4}, 1.2×10^{-4}, 2.4×10^{-4} mol /L	———	———	———	Inhibition of proliferation	[84]

Synergistic Effects of Isorhamnetin and Related Drugs for the Treatment of Different Cancers

(*continued on next page*)

Table 1 (*continued*)

In-Vivo							
Name of the Compound	Research Model	Estimated Dose	Duration of Treatment	Targeted Signaling Pathways	Mechanistic Details	Research Findings	Reference Articles
Name of the Compound	**Research Model**	**Estimated Dose**	**Duration of Treatment**	**Targeted Signaling Pathways**	**Mechanistic Details**	**Research Findings**	**Reference Articles**
Isorhamnetin with capecitabine	Female mice model with gastric tumor	1 mg/kg body weight	1 week	NF-κB pathway	↓NF-κB activation	Possessed significant anti-tumor effects	[85]
Isorhamnetin with cisplatin and carboplatin	A-549 lung cancer cells	25 μM, 0.5 μM, and 0.5 μM	24 h	Cell migration, Apoptosis, and Cell cycle at the G2/M phase	↓Cancer cell migration, ↑Cell cycle arrest at the G2/M phase, ↑Apoptosis	Arrest cancer cell cycle at the G2/M phase, suppress cancer cell migration and induce apoptosis	[86]
Isorhamnetin with Quercetin	MCF-7 breast cancer cell line	100 μM	48 h	ROS-dependent apoptosis pathway, Cell cycle at S-phase	↑Cell cycle arrest at S-phase, ↑ROS-dependent apoptosis pathway	Effectively suppressed the proliferation of human breast cancer MCF-7 cell line	[87]
Isorhamnetin with Genkwanin and Acacetin	Breast cancer MDA-MB-231 cell line	55.51 μM, 58.54 μM, and 82.75 μM	_	Cell cycle at G2/M phase, PI3Kγ-p110, phospho-PI3K, phospho-AKT, phospho-mTOR, phospho-p70S6K, and phospho-ULK pathways	↓AKT/mTOR/P13K/p70S6K/ULK signaling pathways, ↑Cell cycle arrest at the G2/M phase	Effectively inhibited the proliferation of breast cancer cells and induced apoptosis	[88]
Isorhamnetin with capecitabine	Gastric cancer cell lines AGS, SNU-5, and SNU-16	10 μM	1 h	NF-κB pathway	↓NF-κB activation	Effectively suppressed cancer cell growth	[85]

was discovered that the inhibition of topoisomerase II, a crucial enzyme involved in DNA replication and repair processes, was responsible for this adverse effect on DNA integrity [62]. Isorhamnetin has been found to induce DNA damage, which raises the possibility of a possible mechanism by which it can aid in the development of cancer. Topoisomerase II suppression can impair DNA's capacity to operate normally, resulting in genetic anomalies and even encouraging carcinogenesis. These findings highlight the value of future research into the consequences of isorhamnetin-induced DNA damage and its potential effects on cellular health and the emergence of cancer. Future studies may dive more deeply into the specific molecular pathways behind the DNA-damaging effects of isorhamnetin and investigate possible countermeasures or mitigation techniques. To ensure the safety of its usage and to create suitable preventative measures to reduce any potential dangers, it is essential to comprehend fully the carcinogenic pathways connected to isorhamnetin. The anti-inflammatory properties of isorhamnetin are recognized in various conditions, such as osteoarthritis and periodontitis. These outcomes result from its capacity to reduce inflammatory responses within the body. Isorhamnetin's anti-inflammatory properties also protect against other diseases, such as acute lung injury, tuberculosis, and kidney damage. Studies have shown that it may benefit renal health and prevent critical lung damage and tuberculosis-related inflammation [63–66]. In several investigations, Isorhamnetin has been demonstrated to protect against acute lung damage caused by LPS [63,64]. Isorhamnetin exhibits therapeutic potential in treating osteoarthritis, a degenerative joint disease. Multiple research studies have reported that isorhamnetin has anti-inflammatory characteristics and protects cartilage cells from damage when subjected to IL1β stimulation. The anti-inflammatory characteristics of isorhamnetin help reduce inflammation by decreasing the synthesis of pro-inflammatory molecules and mitigating the detrimental impact on cartilage tissue. [67]. By regulating reactive oxygen species levels (ROS), isorhamnetin prevents RANKL's induction of osteoclasts and protects chondrocytes from ROS damage [68]. Additionally, it has anti-inflammatory properties by inhibiting the NF-B signaling pathway, thereby reducing the release of inflammatory molecules and the production of ROS [65].

Isorhamnetin predominantly inhibits the NF-κB pathway to exhibit its anti-inflammatory actions. It prevents NF-κB from being activated and translocated, obstructing the subsequent signaling processes that produce and release numerous inflammatory molecules. This inhibition of NF-κB serves as the primary mechanism by which isorhamnetin mitigates inflammation. Isorhamnetin can prevent drug-resistant formation in human lung cancer cell lines (PC9-IR) by lowering the amount of Akt473 phosphorylation [89]. The anticancer action of isorhamnetin was also associated with the activation of autophagy, as found by Liu and colleagues in their research [90]. Scientific evidence has demonstrated the inhibitory effect of isorhamnetin on the progression of human lung cancer cells, specifically the A549 cell line. Isorhamnetin has shown promise in limiting A549 cell growth and preventing the formation of colonies.

Additionally, it has been shown that isorhamnetin causes A549 cells to undergo apoptosis or programmed cell death. According to these results, isorhamnetin inhibits lung cancer cell growth, prevents the development of cell clusters, and causes programmed cell death in lung cancer cells, especially in A549 cells. Isorhamnetin induces apoptosis in A549 cells by lowering the mitochondrial membrane, leading to the liberation and initiation of cytochrome c and caspase [26,61]. Additionally, isorhamnetin can suppress HeLa cell expansion by reducing telomerase activity [91]. Isorhamnetin can also prevent the proliferation of HeLa cells, a well-known cervical cancer cell line, from growing. The suppression of telomerase activity is a component of the process causing this inhibition. Isorhamnetin interferes with HeLa cells' capacity to preserve their telomeres by blocking telomerase activity, which impairs cell growth and proliferation [63]. The cytotoxic effect is a crucial mechanism exhibited by anti-tumor drugs. According to research by Dong et al., Isorhamnetin exhibits cytotoxicity toward H9C2 cardiomyocytes when given at 80 mol/L [92]. When isorhamnetin was applied to rat primary hepatocytes for 24 hours at concentrations of 30, 100, and 300 mol/L, the aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and alanine transaminase (ALT) levels increased in the culture medium. This finding shows that isorhamnetin could be able to trigger hepatocyte damage [93]. Researchers used human hepatoma cells known as HepG2 for experimental purposes to search for the underlying potentially carcinogenic effects. Based on the research, it was found that isorhamnetin induced DNA damage in HepG2 cells.

Furthermore, cytotoxicity is a vital part of the anti-tumor medication mechanism of action. According to the findings of research carried out by Dong et al., isorhamnetin displayed cytotoxicity when it was exposed to H9C2 cardiomyocytes at a concentration of 80 mol/L [92]. After

24 hours of incubation with isorhamnetin (30, 100, 300 mol/L) in rat primary hepatocytes, the contents of AST (aspartate aminotransferase), ALT (alanine transaminase), and LDH (Lactate dehydrogenase) in the culture medium were elevated, suggesting that isorhamnetin may have caused hepatocyte injury [93]. To evaluate the possible mechanism of carcinogenesis, human hepatoma cell lines derived from the HepG2 line were used. Isorhamnetin was found to be damaging to DNA, and the mechanism that led to this impact was found to be associated with the suppression of the function of topoisomerase II [94]. Among the many mechanisms by which isorhamnetin exerts its anti-cancer effects are the reduction of the Bcl-2 gene expression, increased transcription of the Bax gene, the suppression of telomere activity, the reduction in expression of related proteins to restrict the cell cycle, the suppression of cancer cells proliferation, and the induction of apoptosis in cancer tissue.

Isorhamnetin exhibits antioxidant properties through effective neutralization of free radicals like DPPH(2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid)). Isorhamnetin's antioxidant activity has also been highlighted by in vitro experiments that show it can prevent lipid peroxidation in liver mitochondria [95]. Additionally, isorhamnetin shows potential in protecting human RPE (retinal pigment epithelial) cells against the detrimental effects of oxidative stress. It is an important antioxidant that might help prevent age-related macular degeneration [96]. Additionally, isorhamnetin has shown that it has antioxidant properties by protecting against linoleic acid peroxide brought on by Gu2+ and H2O2 [97]. The findings suggest that the antioxidant properties of isorhamnetin are accountable for its anti-cancer effects. This suggests that isorhamnetin's potential as a powerful cancer treatment depends critically on its capacity to mitigate oxidative stress. Kong et al. conducted research investigating the potential inhibitory impact of isorhamnetin in 3-O-D-glucopyranoside on oxidative stress, examining its effects on isolated cells and cell systems. The results of their study suggest that isorhamnetin possesses significant potential for natural bioactive antioxidants and would be a good candidate for further research in this area. Isorhamnetin was found to have strong antiviral activities in an important investigation by Ahmed et al. [98]. Isorhamnetin has shown great efficiency when given to the mice model infected with the Influenza A virus. It demonstrated its capacity to prevent viral multiplication by producing a substantial 50 % decrease in lung virus titer. Moreover, the mice given isorhamnetin had a significant 25 % reduction in weight loss, indicating that it could potentially lessen the infection's severe effects. Isorhamnetin has the potential to become the main ingredient in the creation of anti-virulence medications that target S. aureus infections. This shows that isorhamnetin has unique qualities that can successfully combat S. aureus's virulence mechanisms. Bhattacharya et al. conducted a study on the antibacterial mechanism of polyphenols, revealing that isorhamnetin exhibits a unique capability to penetrate bacterial cell membranes by inducing oxidative stress[99]. This fascinating observation raises the possibility that isorhamnetin may operate as an antibacterial agent by interfering with the structure of bacterial cells. Isorhamnetin has been proven to have a wide range of antibacterial properties. It is useful in the treatment of a variety of bacterial and fungal illnesses due to its remarkable antibacterial capabilities. Isorhamnetin can be used as a treatment alternative to block the growth and spread of a variety of harmful bacteria by utilizing its antimicrobial characteristics Tatjana, et. al. showed that their potential for avoiding contamination in various food items produced by a variety of bacteria, the inhibitory properties of isorhamnetin are particularly noteworthy. Notably, foodborne infections and food deterioration are known to be caused by microbes such as *Bacillus spp.*, *Staphylococcus spp.*, *Pseudomonas fluorescens*, *Salmonella spp.*, and *Clostridium botulinum*. Isorhamnetin is a strong contender for guaranteeing food safety and quality due to its capacity to suppress the development and activity of these bacteria.

4. Metabolic alteration of cancer cells considering ROS-mediated pathways by isorhamnetin

Isorhamnetin is a flavonoid compound with many curative properties such as anti-cancer, neuroprotective, and anti-inflammatory [100]. According to studies, Isorhamnetin can induce cell cycle arrest and apoptosis in many cancer cell lines, such as lung, breast, prostate, and colon cell lines. Apoptosis is a programmed cell death process that eliminates the cells from the organism that should no longer be a part of the organism [101]. Pre-cancerous cells, infected cells, and others are removed through the apoptosis process, which keeps the balance of cells in the human body. Consequently, this is necessary for the proper growth of cells, the development of the cell cycle, and the regular activities and functions of cells. A survival mechanism in stem cells called cell cycle arrest protects the cellular integrity of actively dividing stem cells. Similar to other dividing cells, stem cells experience arrest, during which they attempt to fix any mistakes made during the previous division [102]. Tight control over the spatiotemporal expression of mitogens and tumor suppressor proteins maintains a balance between cell cycle and proliferation. Reactive Oxygen Species (ROS) are highly reactive oxygen-containing molecules by-products of regular metabolic activity [103]. However, when ROS production exceeds normal levels, it may cause oxidative stress, mitochondrial malfunction, and cellular apoptosis [104]. The formation of ROS is involved in the mechanism of isorhamnetin anti-cancer effects. ROS are applied to control various biological processes, including cell cycle progression and apoptosis [105]. Isorhamnetin can increase the production of ROS [106], which drives a process such as cell cycle arrest and apoptosis. ROS inhibitor known as N-acetyl cysteine (NAC) reduced isorhamnetin-induced mitochondrial dysfunction when added to it [106].

Additionally, isorhamnetin-mediated G2/M arrest and apoptosis were significantly reduced when ROS formation was stopped with NAC [106]. Isorhamnetin-induced ROS generation may cause DNA damage and stimulate the DNA damage response pathway that triggers cell cycle arrest by inducing the checkpoints pathways [107]. In addition, Isorhamnetin may induce apoptosis by stimulating caspase-independent and caspase-dependent pathways [108]. Caspases are protein-cleaving enzymes that are used to carry out apoptosis. Isorhamnetin triggers (G2/M) phase cell arrest and apoptosis [107]. This process is linked to the reduced expression of multiplying cell nuclear antigens and cyclin A and cyclin B [106]. However, it enhanced the expression of the Cdk inhibitor p21 WAF1/CIP1 and p21 complexed with Cdk2/Cdc2 (Fig. 2).

Additionally, pretreatment with isorhamnetin selectively reduced the expression of FAS/FASL [106]. Both receptor-mediated (extrinsic) and mitochondrial (intrinsic) pathways may trigger apoptosis [109]. Isorhamnetin lowered the activation of the extrinsic apoptotic pathway. As shown by its absence in suppressing tBid, caspase-8 deactivation, and unaltered TNFR1 and Fas levels [123], it did not inhibit the death receptor-dependent pathways. Still, it inhibits mitochondria-dependent or intrinsic apoptotic pathways. This is shown by preserving mitochondrial membrane potential, deactivation of caspase-9, and modulation of a variety of genes such as Bcl-2 family genes [110].

Moreover, angiogenesis is a significant process for cancer progression in which the new blood vessels grow from the endothelium of an already-existing vasculature. The induction process of angiogenesis is characterized by the degradation of the vascular basement membrane, endothelial cell migration, proliferation, and tube formation [111]. Several studies revealed that isorhamnetin inhibits bFGF-induced proliferation. To elucidate the anti-angiogenic activity of isorhamnetin, a study revealed bFGF-induced proliferation and tube formation of HUVECs in vitro. Endothelial cell migration is a critical event for angiogenesis.

To examine whether isorhamnetin has in vitro angiogenic activity, a bFGF-induced migration assay was carried out and confirmed that isorhamnetin inhibits bFGF-induced migration [111]. A Lewis lung cancer mouse model was developed in different research, and isorhamnetin's

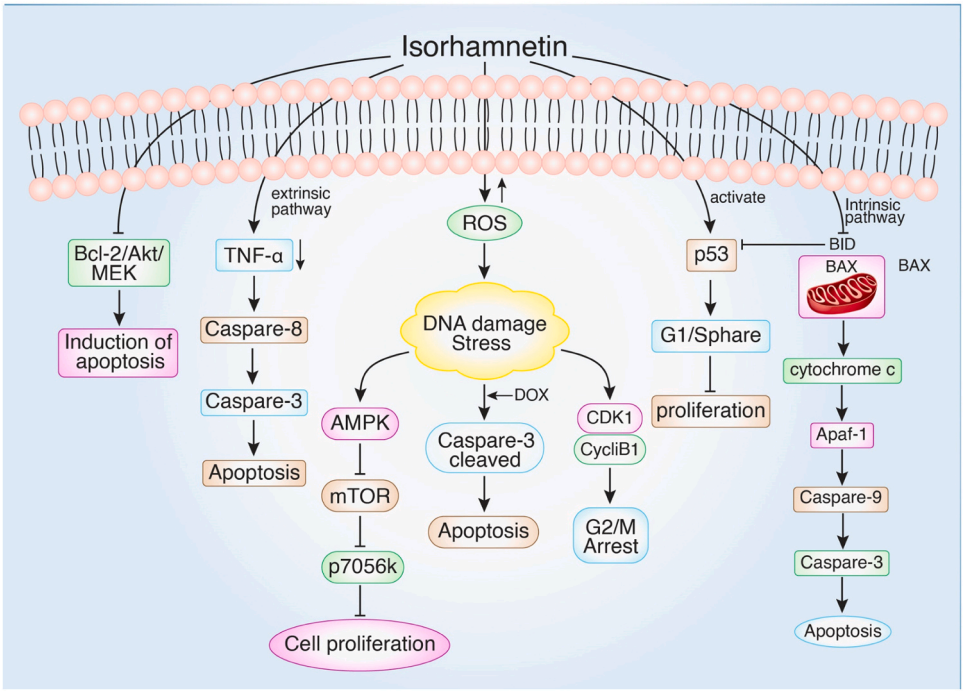

Fig. 2. Schematic representation of reactive oxygen (ROS) mediated cell cycle arrest and apoptosis by isorhamnetin. The anti-cancer effect of isorhamnetin involves the generation of reactive oxygen species (ROS). Isorhamnetin can increase ROS production, leading to cell cycle arrest and apoptosis. Additionally, isorhamnetin-mediated G2/M arrest and apoptosis were significantly reduced when ROS formation was stopped with NAC. Isorhamnetin lowers activation of the extrinsic apoptotic pathway and inhibits the mitochondria-dependent or intrinsic apoptotic pathway—abbreviation: NAC, N-acetyl cysteine.

impact on the expression of the proteins vascular endothelial growth factor (VEGF), endostatin, and matrix metalloproteinase-2 (MMP-2) was assessed to examine potential functional processes (Fig. 3). They concluded that isorhamnetin slows the growth of tumors, potentially as a result of upregulating endostatin and downregulating VEGF or MMP-2 [112].

5. Isorhamnetin in blocking the PI3K-Akt-mTOR networks

5.1. PI3K/Akt/mTOR as a part of a big network

The phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway controls a wide range of cellular activities, including survival, proliferation, growth, metabolism, angiogenesis, and metastasis. It is overactive in several cancer types. The PI3K/Akt/mTOR system transmits signals from numerous downstream effectors, such as GSK-3, FOXO, and MDM2, which are also controlled by multiple compensatory signaling networks, to several upstream

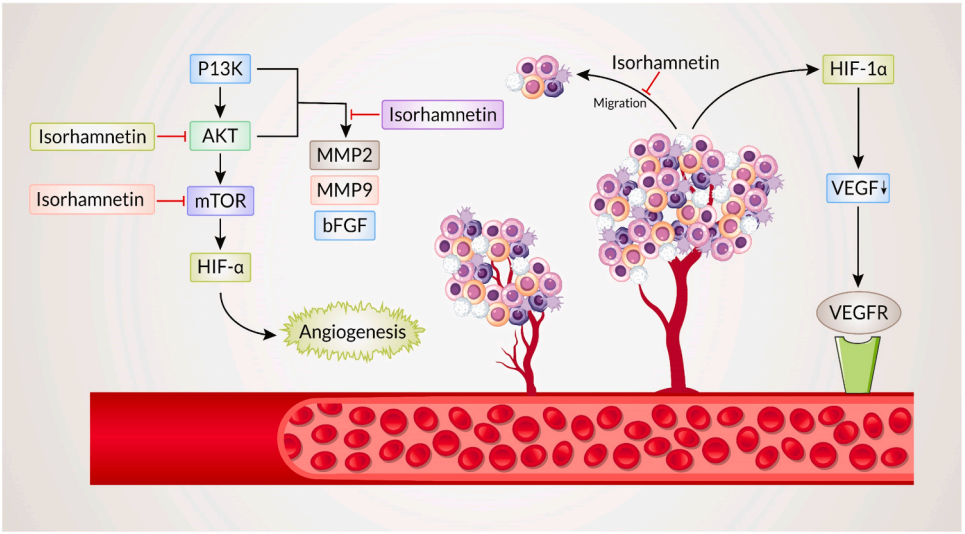

Fig. 3. : Anti-angiogenic activities of isorhamnetin. This figure shows the anti-angiogenetic activities of isorhamnetin, including cell migration, proliferation, and tube formation. Isorhamnetin inhibits the bFGF-induced proliferation and downregulates the expression of VEGF. Here, bFGF is the essential fibroblast growth factor, and VEGF is the vascular endothelial growth factor.

regulatory proteins, such as PTEN, PI3K, and RTKs. The rigorous regulation of upstream regulators and downstream effectors by feedback mechanisms further complicates the signaling pathway [113]. The phosphatidylinositol 3-kinase (PI3K) can be bound to and activated by either the protein IRS-1 or the activated receptor tyrosine kinase. As an alternative, PI3K can be activated by attaching to the GTP-bound form of the membrane-bound protein Ras—the catalytic activity of active PI3K results in the production of membrane-bound PIP3. The second messenger, PIP3, triggers the serine-threonine kinase Akt. Active Akt phosphorylates many proteins, inhibiting apoptosis and promoting translation and proliferation (Fig. 4).

PI3K phosphorylation triggers Akt activation, which regulates several signaling pathways downstream, including mTOR. The P13K/Akt/mTOR signaling pathway may be constitutively activated by a few chemicals, including SHH (Sonic Hedgehog Signaling Molecule), EGF (Epidermal Growth Factor), IGF-1, Insulin, and CAM. PTEN (Phosphatase and Tensin homolog), GSK3B (Glycogen Synthase Kinase - 3 beta), and HB9 (Homeobox-9), on the other hand, hinder the pathway. IGF-1 and IGF1R work together to recruit IRS-1 and class I PI3Ks, which they subsequently use to help turn PIP2 into PIP3. Additionally, TBK1 can activate mTORC1 and mTORC2, and mTORC2 can alter Akt activity by influencing Akt phosphorylation, which affects mTORC1 downstream via TSC1/2. Class I PI3Ks can be started by BCRs via B cell adapters and GPCRs. On the other hand, type I PI3Ks can be activated by ligands paired with RTKs (EGFR, VEGFR, and FGFR) via RAS. Class I PI3Ks are activated by the phosphorylation of the FGFR substrate FRS2, which also involves GRB2, SOS, and GAB1. TCRs can also trigger Class II PI3Ks in addition to EGFR. Amino acids activate Class III PI3Ks, whereas total activated PI3K phosphorylates the third carbon of the PIP2 inositol head and changes it into PIP3, activating Akt through PDK1 and RAC. PTEN can prevent this transformation process [114].

5.2. PI3K/Akt/mTOR explain as a complete pathway of cell cycle

The P13K/Akt/mTOR is a molecular signaling pathway that is highly significant for regulating the cell cycle and metabolism in the human body. The pathway is overactive in several malignancies, including Hepatocellular carcinoma (HCC), which reduces apoptosis and promotes cellular proliferation [115]. Dysregulation of the P13K/Akt/mTOR pathway has already been shown to create a permissive oncogenic environment in a range of altered cells and human cancers. Human malignant progression and a lousy prognosis are associated with a high prevalence of mutations in this pathway's constituent parts, including PTEN, TSC (Tuberous sclerosis complex), and PI3K. Recently, it was shown that a mTOR mutation (L2431P) within an autoinhibitory domain caused mTOR to be activated (Fig. 5). It's interesting to note that P13K/Akt/mTOR-dependent tumor cells are more susceptible to their inhibitors than normal cells are. As a result, the P13K/Akt/mTOR pathway has been specifically targeted as a novel and effective cancer treatment method [116]. Hence, the route must be blocked to stop the unchecked proliferation to correct such defects. The flavonoids can either stimulate or inhibit these receptors when they bind to them, which then causes the receptors' effects to be mediated by changes in gene expression or phosphorylation [117]. Isorhamnetin, like flavonoids, can act as a potent inhibitor in all these pathways to help with this. A multitude of regulatory regions and receptors control the

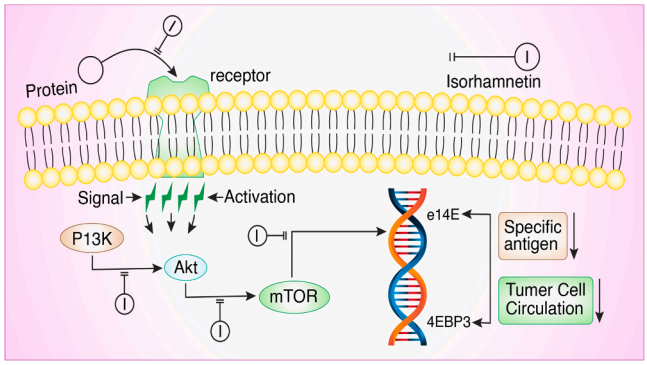

Fig. 5. : The inhibitory mechanism of the pathway using Isorhamnetin. In this mechanism, isorhamnetin flavonoids act on different receptors and take control of them, forcing them to cease and ultimately preventing the process from continuing. Later, the targeted molecule is blocked to adjoin, inhibiting the pathway as a whole.

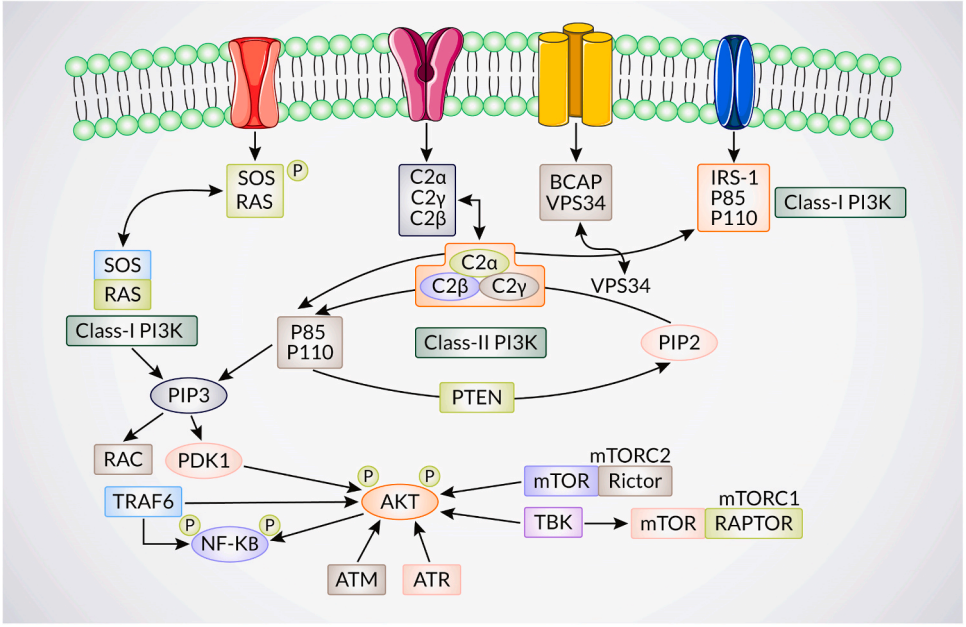

Fig. 4. : The complex network of PI3K/AKT/mTOR pathway (mostly simplified). In this network, different signaling molecules, including the SOS RAS, IRS1, VPS34, C2a, C2B, C2y, p85, p110, and many other ligands, diffuse through the cell membrane and activate the PI3K/AKT/mTOR in an upstream direction. They contain complex interactions between the molecules that regulate the pathway.

pathway. They are bound, which blocks the receptor, and are specifically used in cancer treatment. Multiple research studies have found that regular consumption of blueberries increases Akt phosphorylation, activation of the downstream mammalian target of rapamycin (mTOR) receptor, and the content of Arc/Arg3.1 (activity-regulated cytoskeletal-associated protein) in the hippocampus [118]. In this case, isorhamnetin flavonoids act on different receptors and take control of them, forcing them to cease and ultimately preventing the process from continuing. Later, the targeted molecule is blocked to adjoin, inhibiting the pathway as a whole.

6. Suppression of MEK1, PI3-K, NF-κB, and Akt/ERK pathways by isorhamnetin

Isorhamnetin showed its anticancer activity by inhibiting specific signaling pathways. These pathways include PI3-K (phosphatidylinositol-3-OH-kinase), MEK1, Akt/ERK, etc. An imbalance between anti-oncogenes and oncogenes designated that cancer is an uncontrolled proliferating illness. Cancer cells divide unusually fast, cell-cycle checkpoints are not recognized, and cause irregular stimulation of specific signaling pathways. In skin cancer, the phosphorylation of $p90^{RSK}$, $p70^{S6K}$, Akt, and ERKs is repressed by isorhamnetin. In addition, MEK 1 kinase activity was suppressed through direct binding by it, and since ERKs are MEK1 substrates, isorhamnetin inhibits MEK1 drives to prohibit EGF-induced ERK phosphorylation. Later, isorhamnetin hinders EGF-activated p^{90RSK} phosphorylation substates of ERKs [29]. In malignant melanoma skin cancer, after being treated with isorhamnetin on B16F10 cells, the Bax/Bcl-2 ratio was higher because the Bcl-2 level decreased, and Caspase-3 and Bax levels were high. This result confirmed that isorhamnetin might cause apoptosis in B16F10 cells because the pro-apoptotic protein is Bax and Caspase-3, whereas Bcl-2 is an anti-apoptotic protein [18].

Furthermore, the propagation of colorectal cancer cells was blocked by isorhamnetin, which blocked the G2/M cell cycle phase and put down PI3K-Akt-mTOR pathways [70].

Similarly, PANC-1 pancreatic adenocarcinoma cells were also suppressed by it through a mechanism such as arresting the cell-cycle S phase in which Ras/MAPK signaling pathways are downregulated [73]. It interrupts cell multiplying and metastasis in gall bladder cancer and induces apoptosis, constraining the G2/M phase by the PI3K/Akt signaling cascade's deactivation [119]. Similarly, in lung cancer, it stops epithelial to mesenchymal transition (EMT) markers expression, and this was demonstrated by decreasing vimentin, N-cadherin, and snail expression along with increased E-cadherin expression. Moreover, these inhibitions are intermediated by interfering with Akt/ERK1/2 signaling pathways [31]. It is shown to stifle cell spread and activate cell apoptosis and also prevent MEK/extracellular and Akt/mTOR signal-mediated phosphorylation cascades of kinase and impede epidermal growth by stimulation of Akt and MEK signaling pathways in breast cancer (Fig. 6) [120]. It inhibits invasion and cell spread in concentration-dependent ways through increasing mesenchymal to epithelial transition (MET) and constraining higher expressions of MMP9 and MMP2. Isorhamnetin is the PI3K/Akt/mTOR pathway barrier by lowering the expression of phosphorylated mTOR, Akt, and PI3K proteins in androgen-independent DU145 and PC3 cells and androgen-dependent LNCaP cancer cells [76]. It interrupts microtubule function and activates the ataxia telangiectasia mutated Chk2 pathway, consequently arresting the G2/M cell cycle phase in cervical cancer [74].In addition, isorhamnetin and capecitabine boost capecitabine's antitumor activity through negatively regulated NF-kB oncogenic genes in gastric cancer [85]. Cytoplasmic NF-kB and nuclear NF-kB were increased and decreased by the action of isorhamnetin [18].

7. Potential of isorhamnetin against obesity-induced cancer

A number of malignancies, including colorectal, post-menopausal breast, uterine, esophageal, kidney, and pancreatic cancers have been linked to excess body fat. Adipose tissue plays a major role in this connection because it secretes a variety of adipokines, cytokines, and hormones that may induce chronic inflammation, insulin resistance, and changes in the metabolism of sex hormones, all of which can lead to carcinogenesis [121,122]. Given this, studies have looked at the possibility of using natural substances such isorhamnetin to reduce the risk of cancer associated with obesity. Flavonoids like isorhamnetin, which are present in fruits, vegetables, and medicinal herbs, have shown encouraging anti-obesity properties that may help prevent cancer. Isorhamnetin works against obesity via a number of methods, all of which lower the risk of cancer. It has shown to impede adipogenesis, the process of fat cell formation, by suppressing the expression of important adipogenic transcription factors, including C/EBPα (CCAAT/enhancer-binding protein alpha) and PPARγ (peroxisome proliferator-activated receptor gamma) [123]. Isorhamnetin limits the

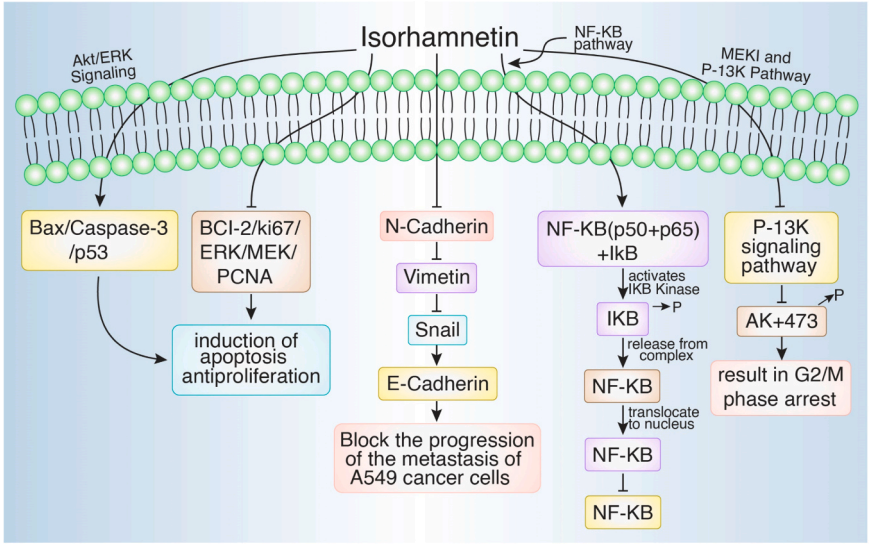

Fig. 6. : Isorhamnetin suppresses tumor cell growth, propagation, and development and stimulates apoptosis by regulating the expression of tumor-related proteins or genes such as Bax and Bcl2. It inhibits PI3-K pathways, phosphorylation of AKT (Ser473), and subsequent G2/M phase arrest. It also suppresses N-cadherin and vimentin expression and increases the expression of snail E-cadherin.

development of preadipocytes into mature adipocytes by blocking these factors, which in turn limits the storage of fat. Furthermore, isorhamnetin promotes fatty acid oxidation and lipolysis, the breakdown of lipids, which further lowers the amount of lipid in already-existing adipocytes and aids in weight reduction [124]. Moreover, the anti-inflammatory characteristics of isorhamnetin are important in preventing cancer. By increasing levels of pro-inflammatory cytokines including TNF-α (tumour necrosis factor-alpha), IL-6 (interleukin-6), and IL-1β (interleukin-1 beta), obesity-induced chronic inflammation produces an environment that is conducive to tumour growth [125]. Research indicates that isorhamnetin inhibits the generation of these cytokines, which in turn interferes with the inflammatory signalling pathways that promote tumour development and metastasis. Furthermore, isorhamnetin decreases hyperinsulinemia and increases insulin sensitivity, both of which are linked to obesity and aid in the growth and survival of cancer cells [126].

It has also been noted that isorhamnetin has direct anti-cancer actions. It does this by triggering the intrinsic and extrinsic apoptotic pathways, which causes cancer cells to undergo programmed cell death, or apoptosis. Isorhamnetin induces cancer cell death by upregulating the expression of pro-apoptotic proteins like Bax and downregulating the expression of anti-apoptotic proteins like Bcl-2 [126]. Furthermore, by inducing cell cycle arrest at different stages, isorhamnetin suppresses the growth of cancer cells. For example, it has been discovered to cause colorectal cancer cells to enter the G2/M phase arrest, which stops cell division and tumour development [127]. Its antioxidant qualities also shield cells from DNA damage brought on by oxidative stress, which is a major contributing factor to the development of cancer [128]. In overall observation, the anti-obesity effects of isorhamnetin are closely linked to its potential in reducing the risk of various cancers associated with excess body fat. By inhibiting adipogenesis, promoting lipolysis, reducing inflammation, and improving metabolic health, isorhamnetin not only aids in weight management but also creates a less favorable environment for cancer initiation and progression. Additionally, its direct anti-cancer activities enhance its profile as a multifunctional compound in cancer prevention strategies. Continued research into isorhamnetin's molecular mechanisms and clinical efficacy will be crucial in validating its therapeutic potential and translating these findings into practical health interventions.

8. Impacts of isorhamnetin in modulating the activity of the most frequent cancer biomarkers

Hypoxia Inducible factor-1 (HIF-1) accelerates the development and spread of cancer cells by playing a role as a transcription factor for numerous genes [129]. The HIF family consists of four subunits: HIF-2α, HIF-1α, HIF-3α, and HIF-1β subunits [130]. HIF-1α and HIF-2α are significant transcription factors for many gene expressions regarding low oxygen conditions and enhancement in many cancers controlled via oxygen concentrations of the cell. HIF-1 α is activated in hypoxia conditions and works as a transcription factor for many genes that are needed for propagation and metastasis of cancer cells [129]. At average oxygen levels, prolyl hydroxylase hydroxylates HIF-1α, and ubiquitin-dependent proteasomal pathways generally degrade it [129, 131]. However, in lower oxygen concentrations, the HIF-1 α protein increases its stability and consequently decreases PHD activity, leading to the translocation of HIF-1 α into the nucleus. In the nucleus, HIF-1α combines with HIF-1β to construct (HIF-1 β +HIF-1 α) complex. Hypoxia Response Elements (HREs) are then combined with this complex to make [HREs+(HIF-1 β +HIF-1 α]. The complex stimulates hypoxia response gene expression, which induces invasion, cell propagation, migration, angiogenesis, and survival (Fig. 7) [129,132].

Isorhamnetin is a flavonoid metabolite of quercetin and has many therapeutic characteristics, such as antiproliferative, antioxidant, and anti-inflammatory activity. Some studies confirmed that isorhamnetin's antioxidant activity is associated with its ability to treat colorectal cancer, and it also obstructs the Hypoxia Inducible Factor-1 (HIF-1) deposition in HCT116 and HT29 cells. In addition, it repressed HIF-1-dependent transcriptase genes such as glucose transporter 2, lactate dehydrogenase A, carbonic anhydrase-IX, and HIF-1-induced hypoxia response element reporter gene·H_2O_2-induced reactive oxygen species (ROS) production confirmed the isorhamnetin antioxidant effects, reducing the overexpression of HIF-1 in HEK293 cells. These results show that it suppresses ROS-mediated HIF-1α deposition and drives its anti-proliferative activity [72]. Therefore, in gastric cancer, PI3K was targeted by it and inhibited PI3K-AKT-mTOR pathways, consequently suppressing cell proliferation [133].

Epithelial-mesenchymal transition (EMT) is vital in tumor [134]. Tumor cells, through EMT, may develop better migratory and invasion potential. Thus, suppressing EMT is critical to reduce tumor metastasis. EMT also plays a critical role in tumor immunosuppressive and immune evasion [135,136]. The bidirectional regulation of EMT state and immune checkpoint inhibitors such as PD-1 expression may contribute to tumor immune escape. Yin-yang-1 (YY1), a transcription factor regulator, is aberrantly produced in many malignancies, where it affects numerous processes ranging from tumor cell invasion and metastasis to cell survival and proliferation [137–139]. YY1 may affect EMT directly and indirectly via modulating Snail transcription [140]. Several studies have shown that YY1 is also intimately associated with the remodeling of tumor immune microenvironment, and PD-L1 expression is controlled by YY1-mediated signal crosstalk. Such pathways include p53, STAT3, NF- κB, PI3K/AKT/mTOR, and COX-2. YY1 also adjusts the levels of cytokines and growth factors (e.g., IIL-6, IL-17, TGF- β, and IFN- γ) [141], consequently altering the therapeutic efficacy of tumor immune checkpoint medicine. Inhibiting YY1 expression might have many impacts on tumor cells, which can reduce the proliferation, migration, and EMT of tumor cells and boost the efficacy of tumor immunotherapy. So, inhibiting YY1 expression is a potentially useful technique for creating combination medicines with immune checkpoint inhibitors (ICISs).

An unusually elevated YY1 expression in tumor cells shows that a stable factor of YY1 exists in tumor cells. Thus, finding the stability factor of YY1 may be an effective strategy to lower YY1 levels in tumor cells. We first examined the protein that affected YY1 stability in the present investigation. We showed that YY1 can particularly bind to deubiquitinase USP7, which may govern the malignant evolution of hepatocellular carcinoma (HCC) by modulating the stability of YY1. We suggest that deubiquitination may be a major approach to stabilizing YY1. Subsequently, virtual screening and cell function tests were done to evaluate the USP7 inhibitors for controlling YY1 expression and

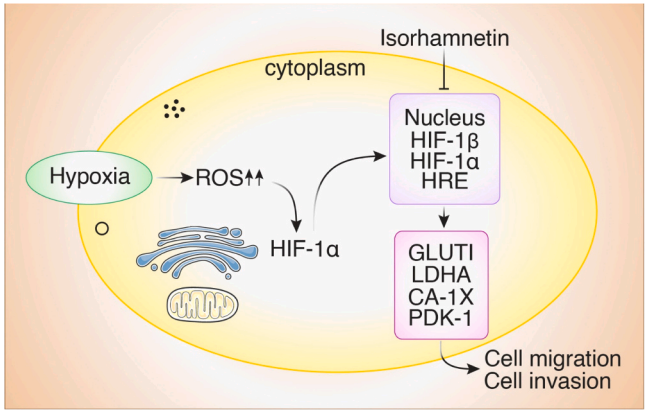

Fig. 7. : In hypoxia condition, HIF-1α binds with HIF-1 β to form (HIF-1 β +HIF-1 α) complex. This complex combines with HREs to create (HIF-1β +HIF-1α) +HREs complex that stimulates the hypoxia response gene, which induces cancer cell proliferation and metastasis. Reactive Oxygen Species -Dependent Hypoxia Inducible Factor (HIF)-1 α accumulation is suppressed by isorhamnetin.

reducing tumor growth. Isorhamnetin (ISO) may target USP9 and reduce YY1 expression by reducing USP7-mediated YY1 deubiquitination. Given that YY1 may modulate the impact of tumor immunotherapy, we further suggested a drug development approach that integrated the modulation of YY1 expression with ICIs [142]. Based on the above background, we designed dual-functional mesoporous silica nanoparticles loading with ISO and anti-PD-L1 monoclonal antibodies, which can target tumor cells, inhibit YY1-mediated tumor progression, and improve the killing effect of T-cells on tumors by inhibiting the PD-1/PD-L1 signaling pathway (Fig. 8).

In this study, FVB mice treated with AOM and DSS develop tumors that will proceed to adenoma and adenocarcinomas [143,144]. Dietary isorhamnetin decreased cell proliferation, inflammation, tumor burden, neutrophil infiltration, and mortality associated with the AOM/DSS therapy. SRC activation and β catenin nuclear localization generated by AOM/DSS were likewise decreased in the isorhamnetin-fed animals and HT29 colon cancer cells treated with isorhamnetin. Isorhamnetin enhanced the expression of C-terminal Src kinase (CSK), a negative regulator of Src. In HT29 cells, isorhamnetin-induced suppression of Src activity and nuclear localization of β catenin was reliant on CSK expression. Isorhamnetin did not influence the expression of E-cadherin, activation of GSK3, or activation of S6 kinase (Fig. 9). These data demonstrate the anti-inflammatory and anti-cancer effects of isorhamnetin are associated with suppressing oncogenic Src activity, which may phosphorylate β catenin at Y654, leading to its separation from the membrane and nuclear localization [79].

9. Synergistic effects of isorhamnetin and related drugs for different cancers

Synergistic effects are related to the interaction or cooperation of two active chemicals to produce combined effects more significant than the sum of their separate effects [145]. To increase the prognosis and efficacy of lung cancer therapies, novel anticancer drugs are necessary for the treatment of lung carcinoma. So, isorhamnetin, cisplatin, and carboplatin have been demonstrated to have anticancer efficacy in A-549 lung cancer cells. Isorhamnetin, along with combinations of cisplatin and carboplatin, are used to examine the impact of increasing anticancer activity on these drugs. The results indicated that isorhamnetin, and combinations of cisplatin and carboplatin, had a higher effect in reducing cancer cell propagation, consequently inducing apoptosis than either medication alone [146]. Patients with triple-negative breast cancer (TNBC) continue to face poor survival because of increasing resistance to chemotherapy despite significant improvements in BC therapies [147]. Due to the scarcity of targeted medicine and resistance towards traditional chemotherapeutic drugs, finding new medications for TNBC treatments remains challenging, and a more effective treatment approach is urgently needed. A study found that chloroquine hinders autophagy/mitophagy in estrogen-dependent triple negative breast cancer (TNBC) cells, promoting isorhamnetin-induced mitochondrial fission and apoptosis. Chloroquine (CQ) and isorhamnetin (IH) were combined to treat TNBC cells and xenograft mice. The oxidative stress-induced phosphorylation of Ca^{2+}/calmodulin dependent kinase II (caMKII)(Thr286) and Drp1 (S616), which results from mitochondrial translocation, the impact is intermediated by this mechanism [148].

The second most solid tumor among all malignancies that causes death each year is gastric cancer [149]. Chemotherapy is typically the primary course of treatment for individuals with gastric cancer, after surgery [150]. Although various targeted medicines have been developed, only a small percent of patients respond well to chemotherapy and some show resistance to routinely used medications such as capecitabine [151]. Isorhamnetin (ISO) may increase the gastric cancer treatment effectiveness of capecitabine. In a study, flow cytometric examination of

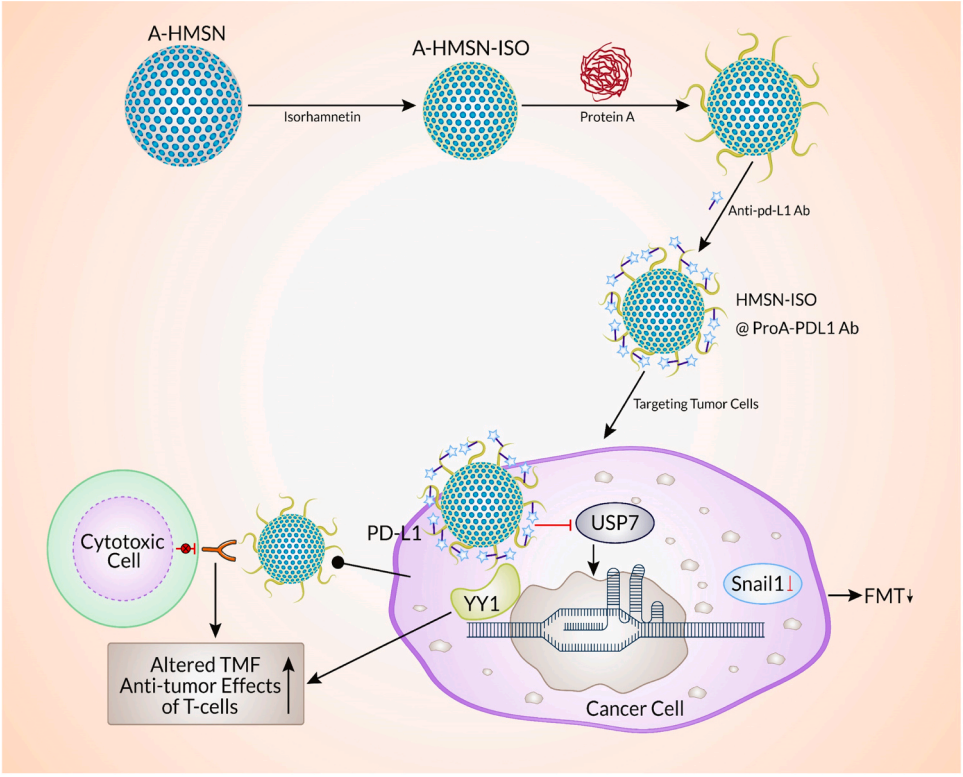

Fig. 8. Isorhamnetin and anti-PD-L1 antibody dual-functional mesoporous silica nanoparticles boost tumor immune microenvironment and suppress YY1-mediated tumor progression. In this pathway, YY1 may bind to deubiquitinase USP7, which may guide the malignant progression of HCC by altering the stability of YY1. So, deubiquitination may be one of the critical techniques to stabilize YY1. In this case, isorhamnetin may target USP9 and inhibit YY1 expression by lowering USP7-mediated YY1 deubiquitination.

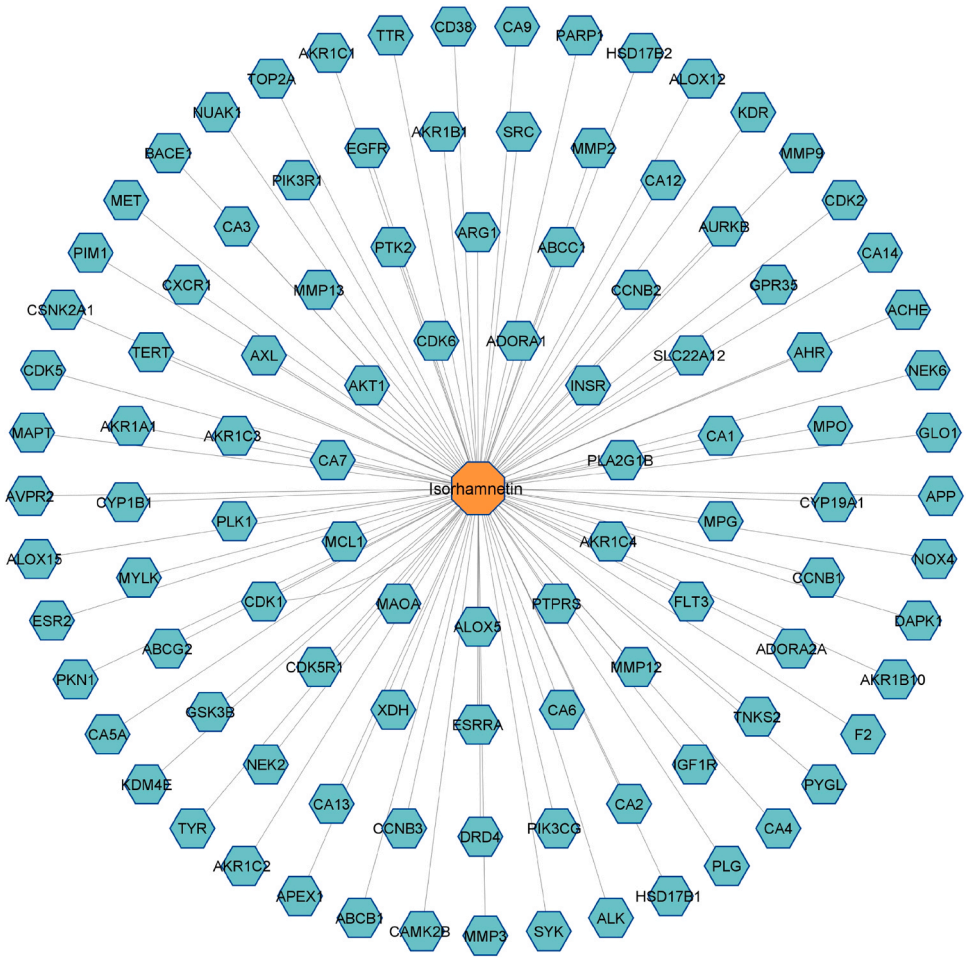

Fig. 9. : The impacts of isorhamnetin in modulating the activity of the most frequent cancer biomarkers. For instance, Isorhamnetin promotes CSK expression and suppresses Src phosphorylation at Y417, Src phosphorylation of β catenin at Y654, and β-catenin nuclear localization in vivo, leading to its separation from its membrane and its nuclear localization.

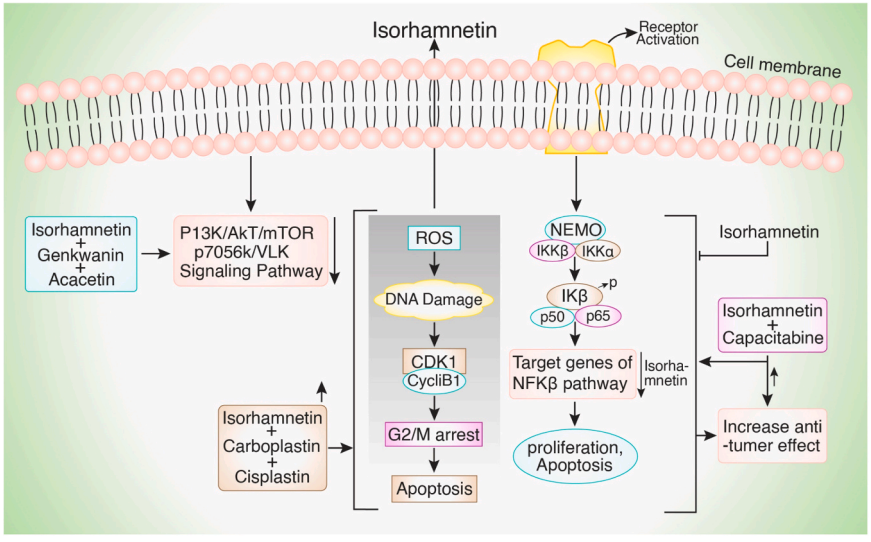

Fig. 10. **:** Schematic representation of synergistic effects of isorhamnetin for cancer treatment. Here the combination of cisplatin isorhamnetin and carboplatin had a more substantial effect on reducing cancer cell proliferation and triggering apoptosis than either medication alone. Isorhamnetin (IH) may increase the gastric cancer treatment effectiveness of capecitabine. Additionally, three flavonoids (GN: genkwanin, IH: isorhamnetin, and Aca: acacetin) inhibited cell proliferation in several human cancer cell lines.

apoptosis, Western blot, DNA binding assays, and MTT assay to determine NF- kB activation were used to understand the possible impact of isorhamnetin on sustainability. The investigation was made into how isorhamnetin affects the progression of subcutaneously implanted tumors in naked mice. Isorhamnetin suppresses NF-kB activation, enhances the programmed cell death effects of capecitabine, decreases the expression of several NF-kB-controlled gene products, and reduces the viability of tumor cells. The tumor growth inhibition in a gastric cancer xenograft model was effectively observed with the administration of IH alone (at a dose of 1 mg/kg body weight, i.p.). Remarkably, IH demonstrated significant efficacy as a standalone treatment and when combined with capecitabine (Fig. 10 and Fig. 11).

Isorhamnetin reduced the NF-kB activity and lessened the expression of many oncogenic and proliferative biomarkers in tumor tissues. Negatively regulating NF-kB-regulated oncogenic genes, isorhamnetin increases capecitabines' anti-tumor activity [152]. In vitro and in vivo quercetin (Que) cytotoxicity has repeatedly been documented, but most of its metabolites are unknown. To investigate the process underlying tumor-inhibitory effects of Que and its water-soluble metabolites, isorhamnetin, and isorhamnetin-3-glucuronide (I3G) on human breast cancer MCF-7 cells, research has studied the cytotoxic effects of Que on these cells. These findings showed that I3G, IS, and Que could inhibit the development of MCF-7 cells in a dose depending on the manner, with Que having the most cytotoxic effect over IS and I3G.

Additionally, IS, I3G, and Que triggered cell cycle arrest in the S phase, followed by a decrease in the number of cells in the G0/G1 and G2/M phase. After being treated with 100 μM doses of IS, I3G, and Que for 48 hours, 70.8 %,68.9 %, and 49.8 % of MCF-7 cells go through first-stage apoptosis, respectively. Additionally, Que, IS, and I3G marginally increased the production of intracellular reactive oxygen species (ROS). These findings demonstrated that the ROS-dependent pathway is a process by which IS, I3G, and Que showed potential cytotoxic effects on MCF-7 cells [153].

Three flavonoids (GN: genkwanin, IH: isorhamnetin, and Aca: acacetin) repressed cell propagation in numerous cancer cell lines. These flavonoids increase apoptosis and autophagy in breast cancer cells and trigger cell cycle arrest at the G2/M phase. According to flavonoids attached, these flavonoids bind significantly, and isorhamnetin

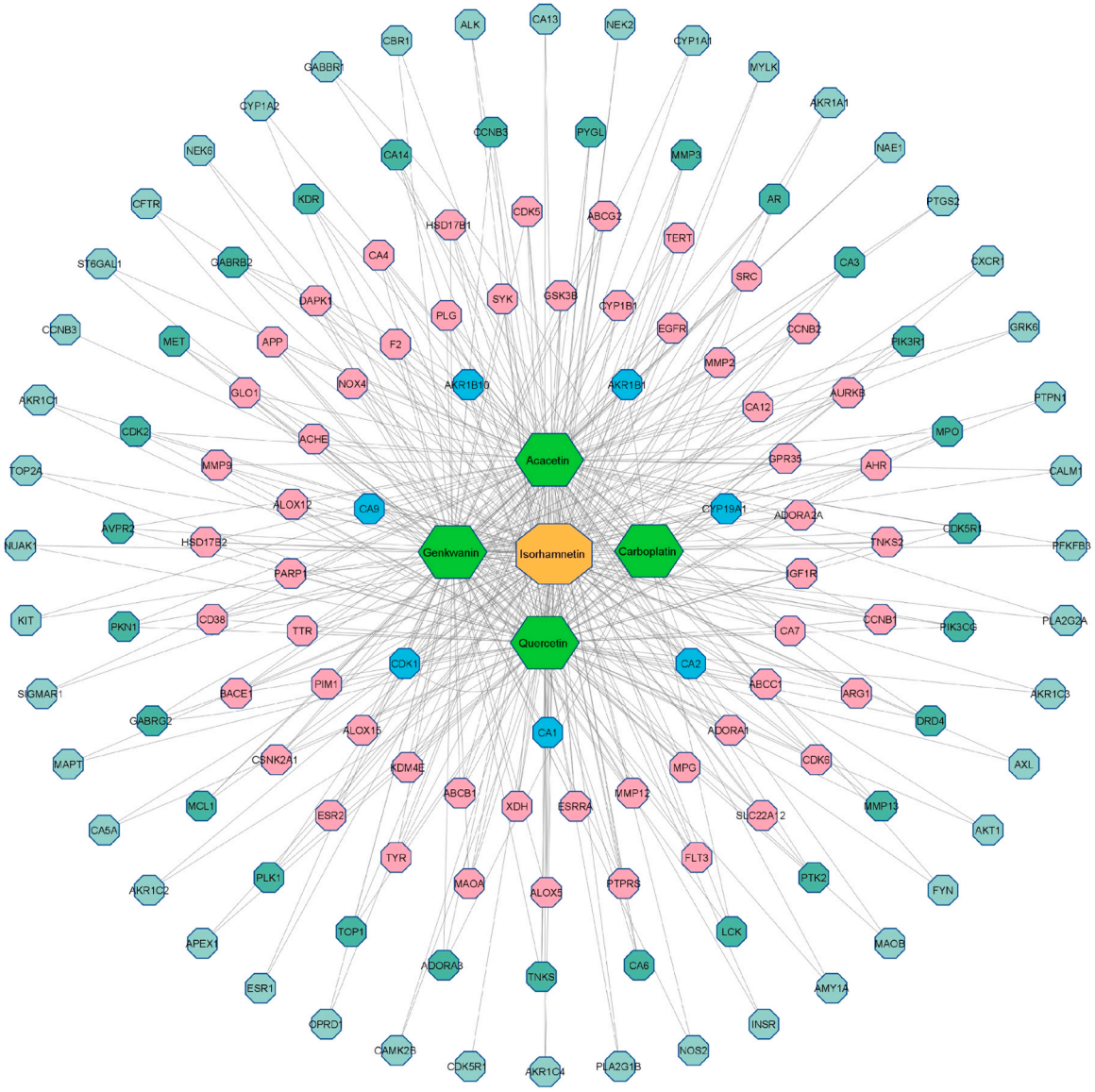

Fig. 11. : Synergistic Effect of isorhamnetin. This figure shows the synergistic effects of isorhamnetin with four different drugs: acacetin, carboplatin, genkwanin, and quercetin. When isorhamnetin interacts with one of these drugs, it offers a broader spectrum of anti-cancer activity against different genes that are responsible for cancer and shows higher potency than alone.

decreases levels. The inactivation of mTOR, ULK, p70S6K, AKT, and apoptosis by flavonoids was improved by the pretreatment of PI3K-specific inhibitor AS605240. These outcomes provide a new method by which flavonoids increase cell cycle arrest at the G2/M phase; apoptosis may be initiated by the downregulation of PI3Ky-p110 and ensuing blockage of ULK/AKT/p70S6K/PI3K/mTOR signaling pathways. Research offers new perspectives on the anticancer properties of particular flavonoids and suggests new applications in cancer treatment [154]. From another study, it is reported that isorhamnetin and caffeic acid obtained from *Potentilla fruticose* leaf extract (C-3) and Ginkgo biloba extracts show strong antioxidant properties. Their combinations exhibit considerable synergy in boosting the production of H_2O_2. The most potent synergy led when isorhamnetin +caffeic acid and C-3 + EGb were combined in 1 one ratio, although no overt improvement of Glutathione peroxidase (GSH-PX) and Peroxidase enzyme activities was seen. The ratio 1:1 showed the highest synergy between the two combinations that raised the expression of Superoxide dismutase (SOD) and Catalase (CAT) [155].

10. Nano formulation strategies of isorhamnetin with aiming better bioavailability in cancer treatment

Flavonoids present in our diet are crucial for preventing cancer. Recent studies, both clinical and epidemiological, have demonstrated that consuming a diet rich in flavonoids is directly connected with a lower incidence of cardiovascular, neurodegenerative, and oncological diseases [156,157]. The limited bioavailability of flavonoids is a significant obstacle affecting their efficacy, among other factors. Therefore, nanoformulation strategies involve using nanotechnology to increase drug solubility, stability, and bioavailability. These strategies include using nanoparticles, liposomes, solid lipid nanoparticles, nanocrystals, and dendrimers. Nano-formulation strategies have shown great potential to improve drugs' pharmacokinetic and pharmacodynamics properties, enhance their therapeutic efficacy, and reduce their side effects [158,159]. Isorhamnetin (Iso), a flavonoid with anti-inflammatory, antioxidant, and anti-cancer properties, has been shown to have potential in cancer treatment. However, its low solubility and bioavailability limit its therapeutic efficacy. Nano-formulation strategies have been used to enhance the bioavailability of Iso in cancer treatment. Here, we discuss Iso's various nano-formulation strategies to improve its bioavailability in cancer treatment (Fig. 12).

One of the strategies used for the nano-formulation of Iso is using nanoparticles. In one study, Iso was loaded into poly (lactic-co-glycolic acid) (PLGA) nanoparticles to improve solubility and bioavailability. The study shows that the PLGA nanoparticles loaded with Iso had better anticancer activity than free Iso due to improved cellular uptake and sustained release of Iso. Another strategy used for the nano-formulation of Iso is liposomes [160]. Iso was encapsulated in liposomes to improve its bioavailability and anticancer activity. The liposomes loaded with Iso had higher cellular uptake and enhanced anticancer activity than free Iso. In addition to nanoparticles and liposomes, other nano-formulation strategies, such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and cyclodextrin-based nano-sponges, have been used to formulate Iso. Iso was encapsulated in SLNs to improve their solubility and bioavailability. The SLNs loaded with Iso had higher cellular uptake and enhanced anticancer activity than free Iso.

Moreover, Iso was loaded into NLCs to improve its solubility and bioavailability. The study demonstrated that the NLCs loaded with Iso had higher cellular uptake and enhanced anticancer activity than free Iso. Again, Iso was encapsulated in cyclodextrin-based nano-sponges to improve its solubility and bioavailability [161]. Even the nano-sponges loaded with Iso had improved cellular uptake and enhanced anticancer activity compared to free Iso. In conclusion, the low solubility and bioavailability of Iso limit its therapeutic efficacy in cancer treatment. Nano-formulation strategies such as using nanoparticles, liposomes, SLNs, NLCs, and cyclodextrin-based nano-sponges have been implemented to increase the bioavailability of Iso in cancer treatment. These strategies have shown excellent results in enhancing the anticancer activity of Iso by improving its solubility and cellular uptake.

The accessibility of isorhamnetin, a naturally derived substance obtained from plants, is limited, leading to increased expenses for customers desiring to get its advantages. Nevertheless, a potential resolution might be found in the augmentation of production capacity by broad treatments spanning metabolic pathways and genetic engineering. The transformational potential of isorhamnetin synthesis may be realized by purposeful modifications of the synthesis processes and by incorporating genes responsible for its production into microbial organisms. The proposed methodology surpasses the constraints associated with plant-based extraction techniques, creating opportunities for significant enhancement in the production of isorhamnetin [157, 162–164]. The desired result is a fundamental change in the prevailing mindset, which addresses the economic challenges caused by limited

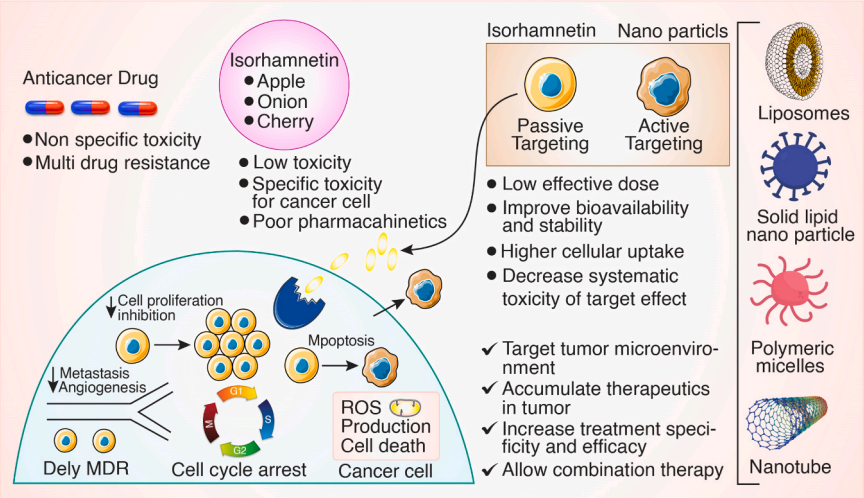

Fig. 12. : Isorhamnetin-loaded nanoparticles in cancer treatment can be beneficial. These nanoparticles can increase the drugs' retention time, improving stability and more prolonged circulation at a lower dose. Active target treatment specifically targets cancer cells while causing the least damage to healthy cells. The anticancer effect of flavonoids-loaded nanoparticles at the location of the tumor includes absorption by cancerous cells, stimulation of the immune system to kill the cancerous cells, attacking cancer energy expenditure, increasing apoptosis, lowering inflammatory process, and postponing the development of multiple treatment resistance.

resources for consumers and significantly improves the availability and ease of access to this vital substance. This comprehensive approach allows the possibility of utilizing the many advantages of isorhamnetin, hence promoting extensive improvements in health and overall well-being (Fig. 13).

11. Conclusion and future perspectives

In conclusion, despite the rise in cancer cases, the limited number of therapeutic alternatives, severe side effects, and their cost, natural remedies like Isorhamnetin have become more and more popular as a safer substitute to available standard treatments. However, before recommending this compound as a viable therapy choice, its efficacy must be thoroughly examined and validated. Due to the multiple anticancer capabilities of Isorhamnetin and the specific molecular pathways that have been established thus far for the claimed benefit of Isorhamnetin as an anticancer medicine, this study evaluated the results of recent studies and highlighted these findings. Several in-vitro and in-vivo research studies have reported that it inhibits the malignant cells by arresting the cell cycle at the G2/M phase and S-phase, down-regulating COX-2 protein expression, PI3K Akt mTOR, MEK1, ERKs, and PI3-K signaling pathways, and up-regulating apoptosis-induced genes (Casp3, Casp9, and Apaf1), Bax, Caspase-3, P53 gene expression and mitochondrial-dependent apoptosis pathway. Multiple in vitro and in vivo preclinical research studies have reported the anti-cancer effects of isorhamnetin, including inhibition of cell cycle progression, suppression of proliferation and metastasis, acceleration of apoptosis, and promotion of autophagy via multiple signaling pathways. Evidence-based findings specified that the combination of Isorhamnetin with other standard drugs substantially reduced cancer cell proliferation, considerably increased anti-tumor effects, and triggered apoptosis than either medication alone. When considered as a whole, isorhamnetin has the potential to be an effective anticancer medicine that is both safe and affordable because it can be easily derived from natural sources.

Isorhamnetin possesses promising anti-cancer capabilities. However, despite this, its clinical usefulness has been constrained by poor pharmacokinetics and low bioavailability. It has been demonstrated that nano-formulation techniques, including the use of nanoparticles, liposomes, SLNs, NLCs, and cyclodextrin-based nano-sponges, significantly increased the bioavailability of Isorhamnetin for the treatment of different cancers. Optimizing the bioavailability and efficacy of Isorhamnetin requires cutting-edge research in the fields of systems biology, proteomics, RNA sequencing, genomics, and bioinformatics. To substantiate Isorhamnetin's efficacy and safety as the best therapeutic option for various malignant conditions, further substantiation-based clinical trials and additional synergistic techniques are also required. All in all, the present study provides a comprehensive understanding of the anti-cancer properties of Isorhamnetin, and its underlying molecular mechanisms, and it might represent an ideal therapeutic candidate for the treatment, management, and prevention of various cancers.

CRediT authorship contribution statement

Md. Ariful Islam Siddiquee: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Partha Biswas:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nasim Ahmed:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Md. Abu Kaium:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Md. Moshiur Rahman:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Delwar Hosen:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Shabana Bibi:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Md. Nazmul Hasan:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation. **Mohamed M. Abdel-Daim:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Formal

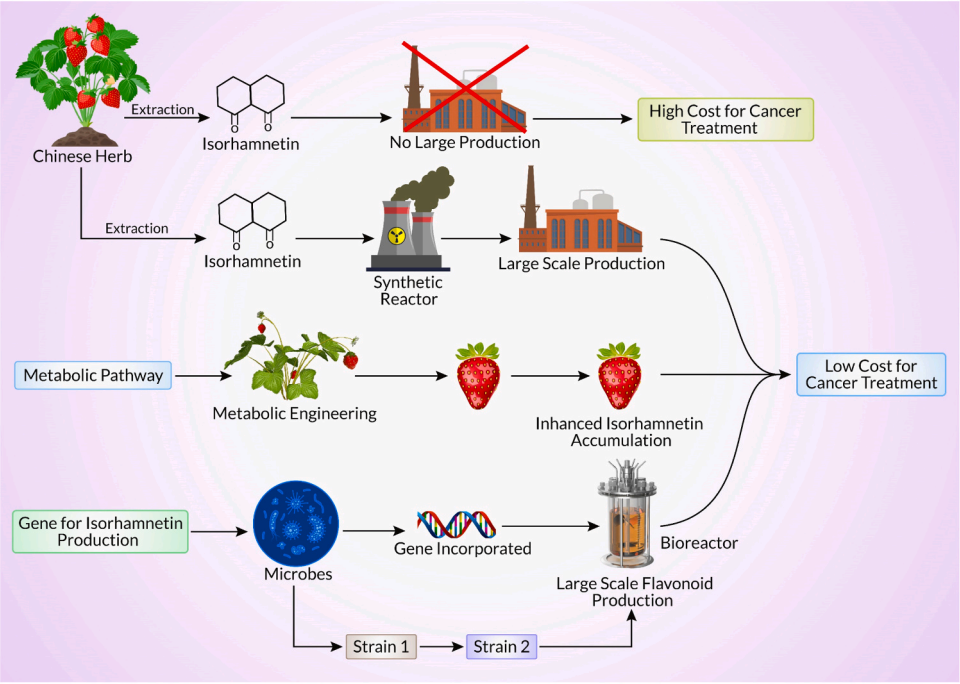

Fig. 13. : The present availability of isorhamnetin, a compound produced from plants, is restricted, leading to increased consumer expenses. To tackle this issue, the enhancement of production may be accomplished by implementing alterations to metabolic pathways and introducing genes responsible for isorhamnetin synthesis into microbial organisms. The use of this strategy approach can greatly enhance the production of isorhamnetin, thereby facilitating its cost-effective accessibility to customers.

analysis, Data curation. **Md Hasibul Hasan:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Mariam K. Alamoudi:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Formal analysis, Data curation. **Anwar Parvez:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Albaraa H. Alhadrami:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Formal analysis, Data curation. **Md Ridoy Hossain:** Writing – original draft, Methodology, Formal analysis, Data curation. **Mohamed Kamel:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Formal analysis, Data curation. **Labib Shahriar Siam:** Writing – original draft, Methodology, Formal analysis, Data curation. **Md Sohel:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Md. Mohaimenul Islam Tareq:** Writing – original draft, Methodology, Formal analysis, Data curation. **Salauddin Al Azad:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Sadia Jannat Tauhida:** Writing – original draft, Methodology, Formal analysis, Data curation.

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. Finally, the authors declare no conflict of interest.

Data Availability

No data was used for the research described in the article.

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