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Review

Licochalcones in Pancreatic Ductal Adenocarcinoma and Type 2 Diabetes Mellitus: Context-Dependent Modulation of Shared Signaling Pathways and an Evidence-Stratified Framework

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Abstract

Background/Objectives: Pancreatic ductal adenocarcinoma (PDAC) and type 2 diabetes mellitus (T2DM) share developmental links that are both driven by metabolic dysfunctions, complicating early diagnosis and treatment. This review systematically explores the shared pathogenic mechanisms and molecular pathways between PDAC and T2DM, including chronic inflammation (NF-κB/JNK/NLRP3), insulin resistance (PI3K/Akt), metabolic reprogramming (AMPK/mTOR), and oxidative stress (ROS/Nrf2). Methods: Licochalcones (LCs) are natural chalcone constituents derived from the roots of licorice (Glycyrrhiza Radix). The pharmacological activities of different subtypes of LCs (LCA-LCE) in the aforementioned common pathways have been comprehensively analyzed. Results: A possible bidirectional regulatory ability of LCs is proposed: it can restore insulin signaling in metabolically impaired tissues and inhibit abnormal oncogenic signaling pathways in PDAC. Although there are experimental bases, clinical studies on the comorbidity of PDAC and T2DM are still insufficient. This review evaluates whether the context-dependent effects of LCs reported in metabolic and tumor models provide a mechanistic basis for investigating PDAC–T2DM comorbidity. Conclusions: Direct PDAC findings are distinguished from metabolic evidence and non-PDAC tumor studies, while simultaneous antitumor and metabolic benefits remain a hypothesis requiring validation.

Keywords: pancreatic ductal adenocarcinoma; type 2 diabetes mellitus; licochalcones; natural products

Academic Editor: Chen Chu

Received: 23 September 2026
Revised: 23 October 2026
Accepted: 27 October 2026
Published: 29 October 2026

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1. The Clinical Dilemma and Molecular Underpinnings of Disease Comorbidity

1.1. The Clinical Predicament of Comorbidity Between PDAC and T2DM

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy and is projected to become the second leading cause of cancer-related deaths by 2030 [1]. The prognosis of PDAC remains dismal, with a five-year survival rate of less than 10% and approximately 60,000 new cases annually. As PDAC is asymptomatic in its early stage,

50% of patients are diagnosed at an advanced stage. Pancreatic cancers are classified into endocrine or exocrine tumors, and PDAC, which is predominantly of exocrine origin, accounts for approximately 90% of all malignant pancreatic tumors. PDAC is preceded by precursor lesions such as pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN), which are considered precancerous. Ductal epithelial cells may undergo malignant transformation via PanIN or IPMN. However, IPMN-derived PDAC accounts for less than 10% of all cases [2], indicating that PanIN hyperplasia is the predominant pathway of malignant transformation.

Type 2 diabetes mellitus (T2DM) is a major global metabolic disease, accounting for approximately 90% of all diabetes cases. Currently, T2DM affects approximately one in every 11 adults worldwide, corresponding to 463 million individuals and the number continues to rise [3]. The pathogenesis of T2DM is generally attributed to insufficient insulin secretion by pancreatic β-cells, tissue insulin resistance (IR) and inadequate compensatory insulin secretion response [4,5]. T2DM can lead to clinical manifestations such as hyperglycemia, polyuria, polydipsia, blurred vision, and altered energy metabolism. Many epidemiological studies have found that approximately 40.2% of pancreatic cancer patients have diabetes within five years prior to cancer diagnosis, and the proportion of new-onset diabetes among pancreatic cancer patients is as high as 52.3% [6].

Drug therapy plays a pivotal role in cancer treatment and encompasses chemotherapy, hormone therapy, targeted therapy, and cancer immunotherapy. Certain chemotherapeutic agents, such as Cisplatin, can reduce insulin receptor sensitivity, aggravate glucose intolerance, and induce transient or persistent hyperglycemia in patients [7]. Gemcitabine is commonly used as the standard first-line treatment for pancreatic cancer; however, long-term use can induce mitophagy and cell death, impair pancreatic β-cell function, reduce insulin secretion, and damage the pancreas [8]. Moreover, the prognostic impact of metformin, a widely used antihyperglycemic agent, on pancreatic cancer remains unclear [9]. Consequently, clinical medication selection is particularly challenging. The interaction between PDAC and T2DM not only complicates early diagnosis but also places clinical management in a difficult position. This complex comorbidity substantially impairs patients' quality of life and has become a critical factor limiting therapeutic efficacy. The lack of an effective clinical therapy capable of simultaneously intervening in both diseases and breaking the vicious cycle of comorbidity represents a key bottleneck for improving patient prognosis.

The relationship between PDAC and diabetes is bidirectional but clinically heterogeneous. Sustaining T2DM may increase PDAC risk through hyperinsulinemia, chronic inflammation, dyslipidemia, and altered tissue metabolism. Conversely, new-onset or rapidly worsening diabetes may represent a paraneoplastic manifestation of occult PDAC, involving tumor–pancreas crosstalk, β-cell dysfunction, peripheral insulin resistance, and systemic metabolic remodeling. These two settings should not be treated as interchangeable, because a compound that improves conventional insulin resistance may not reverse tumor-associated diabetes, and a pathway that is therapeutically inhibited in PDAC may have an opposite function in insulin-responsive tissues. This distinction is central to evaluating whether drugs can provide a genuinely integrated intervention for PDAC–T2DM comorbidity.

1.2. Molecular Underpinnings of Comorbidity and Research Gaps

1.2.1. The Driving Force of Chronic Inflammation

Chronic inflammation arises from the local and systemic regulation of numerous biochemical signals. Through the actions of neutrophils, macrophages, and other immune cells, as well as secreted mediators such as cytokines and chemokines, it eliminates damaged cells and plays a crucial role in tissue repair. In PDAC, oncogenic KRAS mutations

drive tumor cells to secrete inflammatory factors [10], remodel the tumor microenvironment (TME), recruit immune cells and activate pancreatic stellate cells, thereby forming a pro-tumorigenic inflammatory environment [11,12]. In T2DM, systemic chronic inflammation is a major contributor to insulin resistance (IR) [13] and also impairs pancreatic β-cells, leading to β-cell dysfunction [14]. Thus, chronic inflammation is not only a core factor in insulin resistance and T2DM but also remodels the TME, promoting PDAC proliferation, invasion and chemotherapy resistance, thereby serving as a critical link between the two diseases.

1.2.2. Insulin Resistance

Insulin resistance (IR) is the core pathological feature of T2DM, primarily caused by impaired or dysfunctional activity of downstream signaling pathways such as PI3K/Akt [15]. The pancreas produces more insulin to compensate for reduced insulin sensitivity [16], which leads to aberrant activation of this pathway and exacerbates metabolic disorders in peripheral tissues [17]. Moreover, this pathway is a key driver of PDAC cell proliferation [18]. Constitutively activated PI3K/Akt signaling enhances mitochondrial adaptability and antioxidant capacity in cancer cells [19], inactivates pro-apoptotic proteins, and activates the NF-κB pathway to transcribe anti-apoptotic genes, thereby promoting the survival of cancer cells [20].

1.2.3. Metabolic Reprogramming

T2DM-induced hyperglycemia provides a glucose source for tumor proliferation, promoting rapid cell division of tumor cells and enhancing tumor infiltration and invasion [21,22]. The Warburg effect in pancreatic cancer cells increases aerobic glycolysis to support growth under hypoxic conditions [23]. This further aggravates systemic metabolic abnormalities, creating a vicious metabolic cycle that drives the bidirectional deterioration of the comorbidity.

1.2.4. Oxidative Stress

Oxidative stress is strongly associated with PDAC development and T2DM pathogenesis. By activating the inflammatory response [24], oxidative stress not only triggers chronic inflammation-related pathways in both PDAC and T2DM but also accelerates the progression from PanIN to PDAC [25]. Furthermore, oxidative stress also impairs insulin secretion and activates stress-sensitive signaling pathways, exacerbating pancreatic β-cell dysfunction and apoptosis [26].

2. The Molecular Basis of Comorbidity of PDAC and T2DM

2.1. Chronic Inflammation

Systemic low-grade chronic inflammation serves as a crucial pathological link connecting T2DM and PDAC, spanning the initiation and progression of both diseases. For T2DM, chronic inflammation drives metabolic dysfunction, primarily through pro-inflammatory factors (TNF-α, IL-6, etc.) that interfere with insulin signaling to varying degrees [27], thereby inducing peripheral tissue insulin resistance [28]. Additionally, it directly damages pancreatic β-cells, leading to dysfunction of pancreatic β-cells [14] and becoming a core factor in T2DM. The core target pathways of chronic inflammation are the NF-κB signaling pathway, the JNK signaling pathway and the NLRP3 inflammasome. Among these, NF-κB acts as a transcriptional hub regulating the expression of various pro-inflammatory factors and is a major pathway implicated in inducing insulin resistance [29]. C-Jun N-terminal kinase (JNK), activated by inflammatory factors, phosphorylates IRS-1 at Ser307, thereby inhibiting normal insulin signaling and contributing

to pancreatic β-cell dysfunction [30]. Additionally, NOD-like receptor (NLR) family pyrin domain-containing 3 (NLRP3), a downstream component of the inflammatory pathway, is activated and releases pro-inflammatory factors such as IL-1β, resulting in cascade amplification [31]. The combined action of these three factors constitutes the molecular regulatory core of chronic inflammation in T2DM.

For PDAC, systemic chronic inflammation is a fundamental microenvironmental factor driving tumor progression. Chronic inflammation-induced remodeling of the microenvironment provides the basis for tumor growth [32]. It can promote the secretion of various angiogenic factors by tumor cells [33], especially vascular endothelial growth factor (VEGF), thereby accelerating neovascularization. Furthermore, chronic inflammation induces the transformation of fibroblasts into cancer-associated fibroblasts (CAFs), which secrete inflammatory factors that polarize macrophages toward a pro-fibrotic phenotype. CAFs and pro-fibrotic macrophages collectively secrete matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) to enhance extracellular matrix (ECM) deposition and remodeling [34], thereby promoting the TME and accelerating tumor cell proliferation, invasion and metastasis. Chronic inflammation can activate the NF-κB and JNK signaling pathways in the TME, leading to the secretion of inflammatory factors and chemokines that recruit and polarize immunosuppressive cells. These two pathways can inhibit the anti-tumor state and sustain chronic inflammation, which helps tumor cells evade immune surveillance and clearance [35]. The therapeutic challenge of this pathway lies in its induction of chemotherapy resistance. The inflammatory microenvironment synergistically upregulates the transcription of anti-apoptotic genes (Bcl-2, Bcl-xL) by activating the NF-κB and JNK signaling pathways [36,37]. Moreover, activation of the NF-κB signaling pathway upregulates the expression of the drug efflux pump P-gp [38], thereby reducing the intracellular concentration of chemotherapeutic drugs, which represents a primary mechanism of PDAC resistance to agents such as gemcitabine. Hence, targeting chronic inflammation is necessary to achieve a combined inhibitory effect on T2DM and PDAC. Inhibiting core pathways such as NF-κB, NLRP3, and JNK not only improves the metabolic disorder of T2DM but also disrupts the microenvironmental support of PDAC and reverses drug resistance. This provides highly promising molecular targets for the collaborative treatment of T2DM and PDAC and represents an important direction for future clinical translation.

2.2. Insulin Resistance and the PI3K/Akt Signaling Axis

The core pathological mechanism of T2DM is insulin resistance, the essence of which is impaired insulin signal sensitivity. The sensitivity of target organs such as liver, muscle, and adipose tissue to insulin is significantly reduced, resulting in impaired insulin-mediated glucose uptake and metabolism, which is a fundamental initiating factor in T2DM pathogenesis [39]. Insulin recruits PI3K by phosphorylating the tyrosine and serine/threonine residues on insulin receptor substrates (IRSs) [40], activating downstream targets Akt and its substrate AS160 via phosphorylation. Subsequently, glucose transporter 4 (GLUT4) translocates from the cytoplasm to the cell membrane, allowing glucose entry [41] and participation in various metabolic pathways, including glycogen synthesis, glucose production, glycolysis, and lipid synthesis [42]. The inhibition of IRS phosphorylation interrupts signal transmission, leading to impaired GLUT4 membrane translocation, directly blocking cellular glucose uptake and exacerbating hyperglycemia and metabolic disorders [41].

The KRAS mutation-induced PI3K/Akt signaling axis drives the oncogenic signaling in PDAC [43]. Frequent mutations in genes such as PIK3CA in PDAC cause the PI3K/Akt pathway to escape upstream regulation and remain constitutively activated, serving as a

key driver of the malignant phenotype. Activation of the PI3K/Akt pathway not only promotes tumor cell proliferation and anti-apoptotic capacity but also enhances cancer cell invasiveness by inducing epithelial–mesenchymal transition (EMT) [44], accelerating local infiltration and distant metastasis. This signaling axis plays a role in the coordinated regulation of metabolism and tumorigenesis. It can correct metabolic disorders by improving peripheral insulin resistance. Moreover, in metabolic tissues, restoration of impaired IRS/PI3K/Akt signaling may improve glucose disposal, whereas inhibition of constitutively activated PI3K/Akt signaling in tumor cells may restrain tumor growth. These effects should not be interpreted as a single systemic mechanism, because pharmacological PI3K inhibition may induce hyperglycemia, compensatory hyperinsulinemia, and feedback reactivation of tumor signaling.

2.3. Energy Metabolism Reprogramming

The core mechanism of energy metabolism reprogramming converges on the AMPK/mTOR signaling pathway. As the principal regulator of cellular energy sensing and growth control, this pathway serves as a hub linking metabolic homeostasis and tumor development. Under energy-deprived conditions such as glutamine deprivation, metabolic stress, and nutrient limitation, cancer cells phosphorylate multiple downstream targets via the AMPK signaling pathway, thereby activating the TCA cycle [45], glutaminolysis [46], and glycolysis [47] and inducing autophagy [48] to promote metabolic reprogramming and survival adaptation. Notably, AMPK can also suppress the anti-tumor activity of NK cells by promoting M2-type macrophage polarization and the production of immunosuppressive factors [49,50]. When amino acids and glucose are abundant, mTOR is activated. Activated mTOR can exert its effects through multiple pathways: it phosphorylates and inactivates 4E-BP1, releasing eIF4E to initiate 5′ cap-dependent mRNA translation and promote cell cycle protein synthesis [51], and it also phosphorylates and activates S6K1 to enhance ribosomal translation elongation efficiency [52]. In addition to promoting protein synthesis, activated mTOR can also activate HIF-1α, shifting metabolism from oxidative phosphorylation to aerobic glycolysis (i.e., the Warburg effect) [53]. Furthermore, mTOR inhibits autophagy to prevent premature degradation of newly synthesized cellular components and to suppress AMPK pathway activation [54]. The imbalance between AMPK and mTOR constitutes a common molecular basis for metabolic diseases and tumor development.

T2DM provides a favorable metabolic environment for tumor growth. Hyperglycemia and IR supply abundant glucose and energy substrates to tumors, leading to reduced AMPK activity. Excessive activation of the mTOR pathway further drives aberrant cell proliferation and metabolic reprogramming, creating a vicious cycle of metabolic disorder promoting carcinogenesis. In PDAC, Warburg effect-driven metabolic adaptation occurs, in which glycolysis is prioritized even under aerobic conditions. High expression of key enzymes such as HK2 and LDHA not only meets the energy demands of rapid tumor proliferation but also provides nucleotides and lipids for biosynthesis, enhancing tumor invasiveness and drug resistance [55,56].

Activation of AMPK or inhibition of mTOR may theoretically improve metabolic homeostasis and restrict tumor biosynthetic activity. However, this represents a testable mechanistic hypothesis rather than an established duo mechanism. No study has yet demonstrated that an LC suppresses PDAC growth through AMPK activation or mTOR inhibition while simultaneously improving glucose metabolism in a matched PDAC–T2DM model.

2.4. Oxidative Stress Regulation

The dynamic imbalance between oxidative stress and apoptosis is the core molecular link connecting T2DM and PDAC. These two conditions are intertwined through multiple signaling pathways and play a crucial driving role in the development of comorbidity. In T2DM, oxidative damage drives metabolic disorders. Excessive reactive oxygen species (ROS) can lead to the oxidative dysfunction of pancreatic β-cells. When blood glucose levels rise, circulating glucose increases, pancreatic β-cells can transport glucose into the cells via GLUT2, thereby activating the glucose metabolism pathway, increasing the intracellular ATP/ADP ratio, closing potassium channels on the cell membrane, inducing membrane depolarization, opening voltage-dependent Ca^{2+} channels, and allowing Ca^{2+} influx. The resulting increase in intracellular Ca^{2+} concentration triggers insulin granule secretion and fusion with the cell membrane, leading to insulin exocytosis [57,58]. Excessive ROS production impairs Ca^{2+} signaling and promotes pancreatic β-cell apoptosis [59]. Activation of the JNK pathway is involved in pancreatic β-cell dysfunction in T2DM. ROS activates the JNK pathway to induce the nuclear translocation of PDX-1, thereby reducing its DNA binding activity and inhibiting insulin biosynthesis [60]. Oxidative damage also exacerbates insulin resistance. ROS can induce the phosphorylation of IRS-1 at Ser307 via p38 MAPK activation, blocking insulin signal transduction and further impairing insulin sensitivity in peripheral tissues [61]. Moreover, in T2DM, Nrf2 and HO-1 mRNA expression in peripheral blood is significantly reduced [62]. This reduction in Nrf2/HO-1 antioxidant pathway activity impairs the elimination of excessive free radicals, creating a vicious cycle of oxidative damage [63].

For PDAC, oxidative stress is associated with resistance to apoptosis and malignant tumor proliferation. Oxidative stress induces genomic instability. When ROS levels exceed the capacity of antioxidant defense mechanisms, the resulting imbalance leads to oxidative stress, which directly or indirectly damages nucleic acids, proteins, and lipids [64]. Persistent DNA damage and gene mutations activate proto-oncogenes such as KRAS, promoting the malignant transformation of pancreatic cells [65]. Oncogenic KRAS regulates mitochondrial metabolism and ROS generation by modulating hypoxia-inducible factors (HIFs), HIF-1α and HIF-2α [66]. In addition, oncogenic KRAS activates the NF-κB pathway [67], mediating cell proliferation and downregulating tumor suppressor genes such as TP53 and SMAD4 [68,69]. Oxidative stress also promotes the evasion of apoptosis and tumor-promoting remodeling of the microenvironment. In PDAC cells, oxidative stress regulates the expression balance of Bcl-2 family proteins (i.e., upregulating Bcl-2 and downregulating Bax) by influencing signaling pathways such as Akt and p38 MAPK, thereby inhibiting the caspase cascade and enabling cells to acquire resistance to apoptosis and unrestricted proliferation [70]. Single-cell analysis revealed that Nrf2 and oxidative stress responses were significantly activated in immunoregulatory CAFs and specific subgroups of PDAC-associated pericytes, demonstrating that oxidative stress promotes the activation of tumor-associated fibroblasts [71]. ROS can also enhance the angiogenic properties of tumor endothelial cells by regulating Nrf2, driving vascular tumor formation [72] and by activating the ERK signaling pathway, driving the polarization of tumor-associated macrophages (TAMs) to an immunosuppressive M2 phenotype [73], thus creating a favorable microenvironment for tumor invasion. Therefore, potential targets and strategies for comorbidity intervention include, on the one hand, activating pathways such as Nrf2 to enhance the body's antioxidant defenses and improve metabolic disorders in T2DM. On the other hand, drugs such as BH3 mimetics can target and break the apoptosis resistance of tumor cells [74], achieving dual synergistic therapeutic effects (Figure 1).

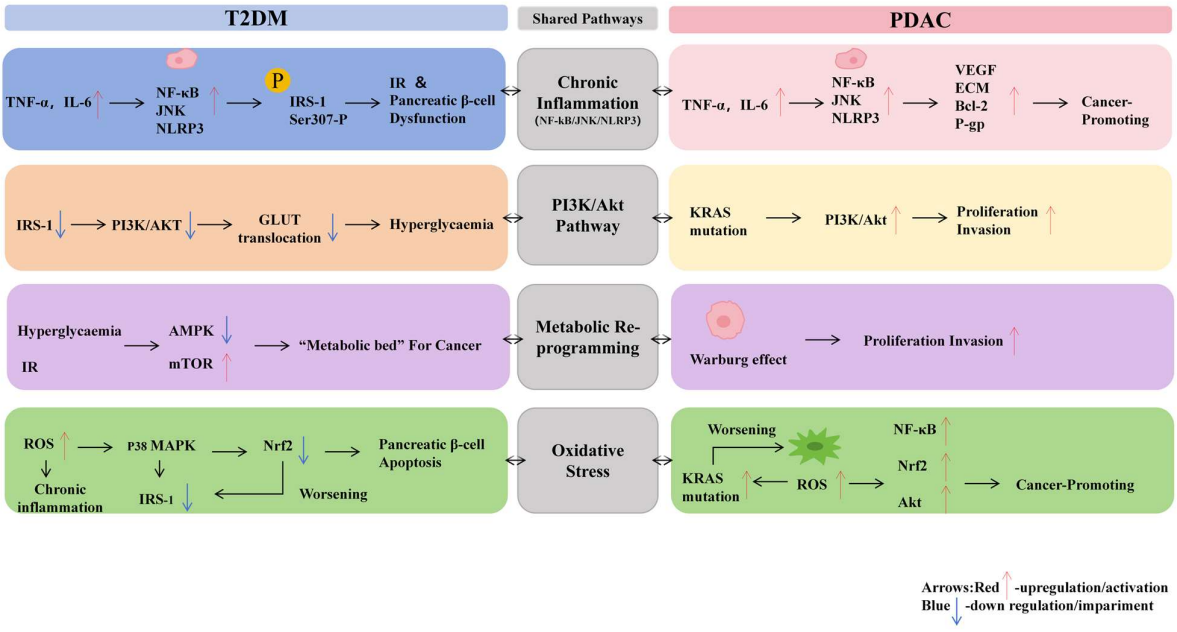


Figure 1. Shared molecular hubs linking T2DM and PDAC. Four mechanistic axes: inflammation (NF-κB/NLRP3/JNK), insulin signaling (PI3K/Akt), energy metabolism, and oxidative stress.

3. Licochalcone

3.1. Licorice

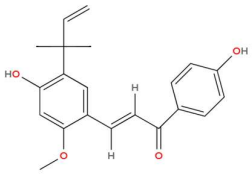
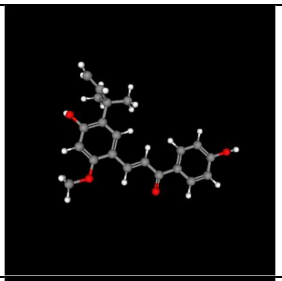
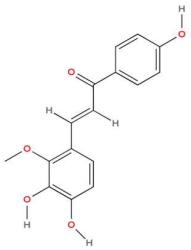
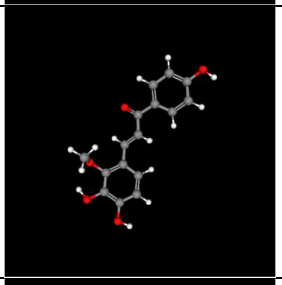
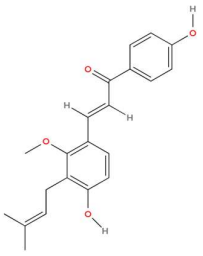
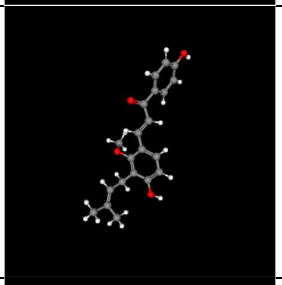
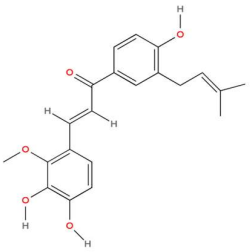
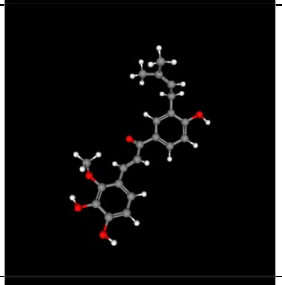
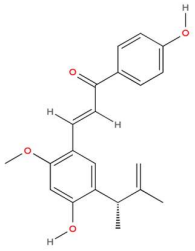
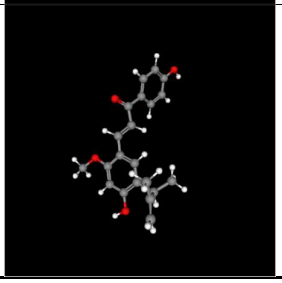
Licorice, a member of the genus Glycyrrhiza in the legume family, is a well-known traditional Chinese herbal medicine [75]. Its dried roots are among the most commonly used Chinese herbal medicines. The Chinese Pharmacopoeia defines licorice as three species of the genus Glycyrrhiza: Glycyrrhiza uralensis Fisch., Glycyrrhiza inflata Bat. and Glycyrrhiza glabra L. Because of its diverse pharmacological activities, including anticancer, anti-inflammatory, antiviral, antioxidant, and antitumor effects [76,77], licorice has attracted considerable research interest in the field of natural medicine. With advances in modern chemical technology, hundreds of compounds have been extracted from licorice, mainly including triterpenoid saponins, flavonoids, polysaccharides and coumarins, etc. These compounds have been proven to have a wide range of pharmacological effects, including anti-inflammatory, antioxidant, anti-viral and anti-tumor effects [78]. Most of these bioactivities are attributed to triterpenoid saponins and flavonoids [79].

3.2. Licochalcones

Licochalcones (LCs) are a collective term for valuable flavonoid chalcone compounds isolated from the rhizome of the medicinal plant Glycyrrhiza uralensis Fisch. ex DC. [80]. They belong to the chalcone subclass of flavonoids and serve as the major bioactive constituents of licorice. To date, more than 300 flavonoids have been isolated from licorice, and licochalcones are one class of them. LCs include several subtypes, such as licochalcone A (LCA), licochalcone B (LCB), licochalcone C (LCC), licochalcone D (LCD), and licochalcone E (LCE) (Table 1), among which LCA and LCB possess the most significant biological activities. Licochalcones exhibit broad-spectrum pharmacological activities, including anti-inflammatory, antioxidant, glucose and lipid metabolism-regulating [81], and tumor cell proliferation- and metastasis-inhibiting effects. The substitution pattern of phenolic hydroxyl and methoxy groups is a key structural determinant of their biological activities, such as anti-inflammatory and antitumor effects. A greater number of phenolic hydroxyl groups correlates with stronger antioxidant capacity [82]. The influence of methoxy

groups is position-dependent. Substitution at certain positions (e.g., the 3-, 4-, and 5-positions) can enhance anti-inflammatory activity by inducing heme oxygenase-1 (HO-1) [83].

Table 1. The 2D and 3D structures of major licochalcones from licorice (derived from the MolView software version 5.8.0).

Name	2D Structure	3D Structure
Licochalcone A		
Licochalcone B		
Licochalcone C		
Licochalcone D		
Licochalcone E		

4. LCs and Core Targets of PDAC and T2DM

4.1. Targeted Regulation of Chronic Inflammation Pathways

LCs can modulate chronic inflammatory responses through multiple signaling nodes. Existing in vitro and animal studies suggest that LCs may attenuate T2DM-associated chronic low-grade inflammation and regulate tumor-associated inflammatory signaling. However, these findings are scattered across different LC subtypes, cell types, and disease models, and most studies have not employed PDAC or T2DM–PDAC comorbidity models. Therefore, the effects of LCs on the inflammatory mechanisms of both diseases currently only suggest potential biological links and can merely provide new directions for combined interventions targeting metabolic diseases and cancer.

4.1.1. Targeted Regulation of the NF-κB Core Pathway

As the most extensively studied subtype in the licochalcone (LC) family, LCA at 10 μM inhibits the phosphorylation and degradation of IκBα, blocks the nuclear translocation of the NF-κB p65 subunit, and suppresses the initiation of inflammation at the transcriptional level, significantly downregulating the expression of key pro-inflammatory factors such as TNF-α, IL-6, and COX-2, and thereby reducing the systemic and local inflammatory burden in RAW264.7 cells [84]. This result supports the notion that LCA can attenuate inflammatory responses in the corresponding experimental models by intervening the NF-κB signaling axis. In addition to LCA, LCB, LCC, LCD, and LCE have also been shown to inhibit NF-κB signaling in different experimental models. However, the cell types, stimuli, and dosages used in these studies are inconsistent: 1–20 μmol/L LCB dose-dependently inhibits NF-κB nuclear translocation in LPS-stimulated RAW 264.7 cells [85], and 1–25 mg/kg LCB also dose-dependently and synergistically downregulates p38 MAPK to enhance anti-inflammatory effects in a CCl_4-induced liver injury mouse model [86]; 25 μM LCC suppresses NF-κB-mediated inflammatory expression in LPS-stimulated H9c2 cardiomyocytes [87]; 2–8 μg/ml LCD dose-dependently inhibits RANKL-induced phosphorylation of NF-κB p65 and IκBα in mouse bone marrow-derived macrophages (BMMs) [88]. Furthermore, in LPS-stimulated RAW 264.7 macrophages, 2.5–7.5 μmol/L LCE similarly dose-dependently inhibits AKT and MAPK activation, blocks IκBα phosphorylation and degradation as well as p65 nuclear translocation, and thereby suppressing NF-κB transcriptional activity [89].

Overall, the available evidence consistently supports the ability of LC subtypes to inhibit stimulus-induced NF-κB activation and indicates that some subtypes can synergistically inhibit MAPK. The aforementioned studies examined IκBα phosphorylation and degradation, p65 nuclear translocation, NF-κB transcriptional activity, and inflammatory mediator expression by employing heterogeneous models, including RAW264.7, H9c2 cardiomyocytes, BMMs, and animal models of liver injury. Consequently, the current findings do not permit the conclusion that individual LC subtypes act on specific nodes (such as proximal membrane receptor signaling → IKK → IκBα → p65) within the same cell type, nor do they allow for comparison of the inhibitory potency of different subtypes on the NF-κB pathway. Most of the available evidence is derived from non-PDAC and non-T2DM models. Although LCs possess the potential to inhibit the NF-κB pathway, thereby exerting anti-inflammatory effects and restoring insulin sensitivity, systematic comparisons of NF-κB signaling modulation by different LC subtypes in PDAC cells, T2DM cells, or T2DM–PDAC comorbidity cell models are still lacking. Therefore, the existing findings primarily provide mechanistic clues for LC-based intervention in comorbidity-associated inflammation, and whether LCs can reshape the inflammatory microenvironment of PDAC and ameliorate T2DM-related chronic inflammation warrants direct validation.

4.1.2. Targeted Regulation of the JNK Signaling Pathway

Among the LCs subtypes, LCA at 5–20 μM has the prominent concentration-dependent targeted regulatory effect on the JNK signaling pathway. It can inhibit the transcriptional activity of downstream c-Jun and NF-κB by targeting and inhibiting the JNK signaling pathway, thereby suppressing the migration of Human Hepatocellular Carcinoma Cells [90]. In the pancreatic cancer cell PANC-1, LCA inhibited proliferation and anchorage-independent colony formation, with JNK1-knockdown experiments supporting the involvement of JNK1. The G1 cell-cycle arrest, apoptosis, and xenograft findings reported in the same study were obtained in HCT116 colorectal cancer models [91]. Additionally, in RAW264.7 macrophages stimulated by LPS, LCE can significantly reduce the expression of c-Jun [89].

In contrast to these subtypes, LCB, LCC and LCD are more likely to activate JNK to inhibit cancer cell growth. LCB at the concentrations of 10–30 μM induces apoptosis in colorectal cancer cells in a dose-dependent manner by increasing ROS production to mediate the phosphorylated JNK/p38 MAPK signaling pathway [92]. Similarly, 10–30 μM LCC induces mitochondrial dysfunction and apoptosis in human esophageal squamous cell carcinoma cells through ROS-mediated activation of the JNK/p38 MAPK pathway [93], whereas LCD exerts anticancer effects in colorectal cancer cells at concentrations of 2–6 μM by triggering excessive ROS generation to induce JNK and p38 MAPK phosphorylation [94].

It should be noted that the evidence for NF-κB inhibition and JNK activation by LCB, LCC, and LCD is derived primarily from different cell types and stimulation conditions. They indicate that the same LC subtype may exert context-dependent effects on NF-κB and JNK, and that the two branches have not been examined under identical experimental conditions. Their NF-κB inhibitory effects have been observed in LPS-stimulated macrophages, H9c2 cardiomyocytes and in RANKL-stimulated BMMs, respectively [85,87,88]. On the other hand, the JNK activation effects have been primarily observed in tumor cells treated with higher concentrations of LCs. Therefore, these findings should not be interpreted as evidence that a single LC subtype simultaneously inhibits NF-κB and activates JNK under identical conditions. Rather, they reflect the current lack of such direct comparative evidence. In tumor models, JNK activation induced by LCB, LCC, and LCD has been attributed to elevated ROS levels, suggesting that ROS-mediated stress signaling may constitute the principal upstream mechanism of JNK activation [92–94]. By contrast, in inflammatory models, LCs primarily suppress LPS or RANKL-induced IκBα phosphorylation, p65 nuclear translocation, and pro-inflammatory gene expression. The current findings therefore serve to reflect cell type and stimulus-dependent regulation of two signaling branches by LCs: NF-κB and ROS-JNK/p38 MAPK.

There is indeed signaling crosstalk between NF-κB and JNK. Classic studies have demonstrated that activated NF-κB can transcriptionally upregulate negative regulatory proteins such as A20 and XIAP, thereby inhibiting the sustained activation of JNK induced by TNF-α [95,96]. Therefore, NF-κB inhibition may theoretically attenuate the negative feedback regulation of JNK. However, this mechanism is context-dependent and has not been directly validated in tumor cells treated with LCB, LCC, or LCD. Likewise, there is currently no evidence demonstrating that LCA and LCE act as JNK inhibitors owing to their weaker ROS-inducing capacity. Thus, NF-κB–JNK crosstalk and the differential ROS-inducing abilities of distinct subtypes can presently serve only as candidate explanations and still require validation through NF-κB restoration, ROS scavenging, and JNK blockade experiments.

The cellular consequences of JNK activation are also influenced by cell type, activation intensity, and duration. In certain tumor cells, transient JNK activation may partici-

pate in stress adaptation, whereas sustained activation can promote pro-apoptotic signaling. Previous studies have shown that sustained, rather than transient, JNK/p38 MAPK activation is associated with apoptosis in tumor cells [97]. By contrast, in metabolic tissues, aberrant JNK activation is closely associated with impaired insulin signaling and insulin resistance [98]. However, these two lines of evidence are derived from different cell models and therefore cannot be used to conclude that LC necessarily exerts opposite directional regulation of JNK in tumor versus metabolic tissues.

In the context of T2DM, aberrant activation of JNK and NF-κB has been linked to insulin resistance and pancreatic β-cell dysfunction [99,100]. However, there is currently no direct evidence demonstrating that a specific LC subtype ameliorates T2DM-related insulin resistance or pancreatic β-cell dysfunction specifically through direct inhibition of the NF-κB/JNK axis, although LCs have been shown to modulate these pathways in various models. Nevertheless, LCA has been shown to attenuate hepatic inflammation and improve glucose and lipid metabolism as well as insulin resistance in db/db diabetic mice [101]. However, this study primarily attributed the relevant effects to gut microbiota-derived metabolites and PPAR signaling regulation, without verifying whether these outcomes were mediated by NF-κB/JNK inhibition.

The evidence that LCD activates JNK is derived from specific cancer cell models, whereas LCD improves insulin resistance comes from a high-glucose-induced AML12 hepatocyte model, in which JNK activity was not examined. Therefore, the available studies neither demonstrate that LCD can still improve insulin signaling after activating JNK in hepatocytes nor exclude the possibility that LCD activates JNK and exerts adverse effects in metabolic tissues. A more accurate interpretation is that the currently observed JNK activation and insulin sensitization are derived from different experimental models, and it has not yet been demonstrated that both occur simultaneously under identical cell type, dose, and time conditions.

In summary, LCA and LCE act as JNK inhibitors in certain inflammatory or tumor models, whereas LCB, LCC, and LCD can promote apoptosis in some tumor cells through the ROS–JNK/p38 MAPK axis. This discrepancy suggests that the regulation of JNK by LCs may be cell type- and pathological context-dependent; however, it is not yet possible to conclude that LCB, LCC, or LCD necessarily upregulate JNK in metabolic tissues. Future studies should compare the effects of LCs on ROS generation, JNK phosphorylation, and insulin signaling in both tumor cells and metabolic tissues under identical dose and time conditions, and further validate their metabolic safety in T2DM–PDAC comorbidity animal models.

4.1.3. Precise Inhibition of NLRP3 Inflammasome

In addition to the NF-κB pathway, the inhibitory effect of LCs on the NLRP3 inflammasome has also attracted considerable attention. At 1–20 μM, LCA dose-dependently inhibits NLRP3 inflammasome assembly and activation in primary mouse macrophages and human SZ95 sebocytes, thereby blocking downstream caspase-1 cleavage and activation, reducing the maturation and secretion of IL-1β and IL-18, attenuating tissue damage and fibrosis, and suppressing mitochondrial ROS production [102]. This result suggests that LCA may attenuate inflammatory responses by simultaneously intervening in mitochondrial oxidative stress and inflammasome activation. In contrast, in mouse bone marrow-derived macrophages (BMDMs), LCB (5–40 μM) dose-dependently binds directly to NEK7 (never in mitosis A (NIMA)-related kinase 7), thereby blocking the association of NEK7 with the NLRP3 inflammasome [103]. This result suggests that LCB may act directly on the inflammasome assembly stage, rather than solely through inhibiting NF-κB-mediated inflammasome priming signals. However, whether LCB simultaneously affects NF-

κB-dependent NLRP3 transcription in PDAC cells still needs to be determined experimentally. In palmitic acid-induced insulin-resistant HepG2 cells, LCE at 10–40 μM dose-dependently downregulates the expression of NLRP3 and caspase-1 [104]. However, a decrease in expression levels alone does not demonstrate that LCE acts directly on NLRP3. Therefore, its direct targets and site of action remain unclear. Currently, there is also a lack of evidence that LCC and LCD directly bind to or inhibit the NLRP3 inflammasome. Due to the fact that NF-κB is involved in the transcriptional priming of NLRP3 [105], the NF-κB inhibitory effects of LCC and LCD in other models suggest that they may indirectly affect NLRP3 signaling. However, this inference still requires direct validation (Figure 2).

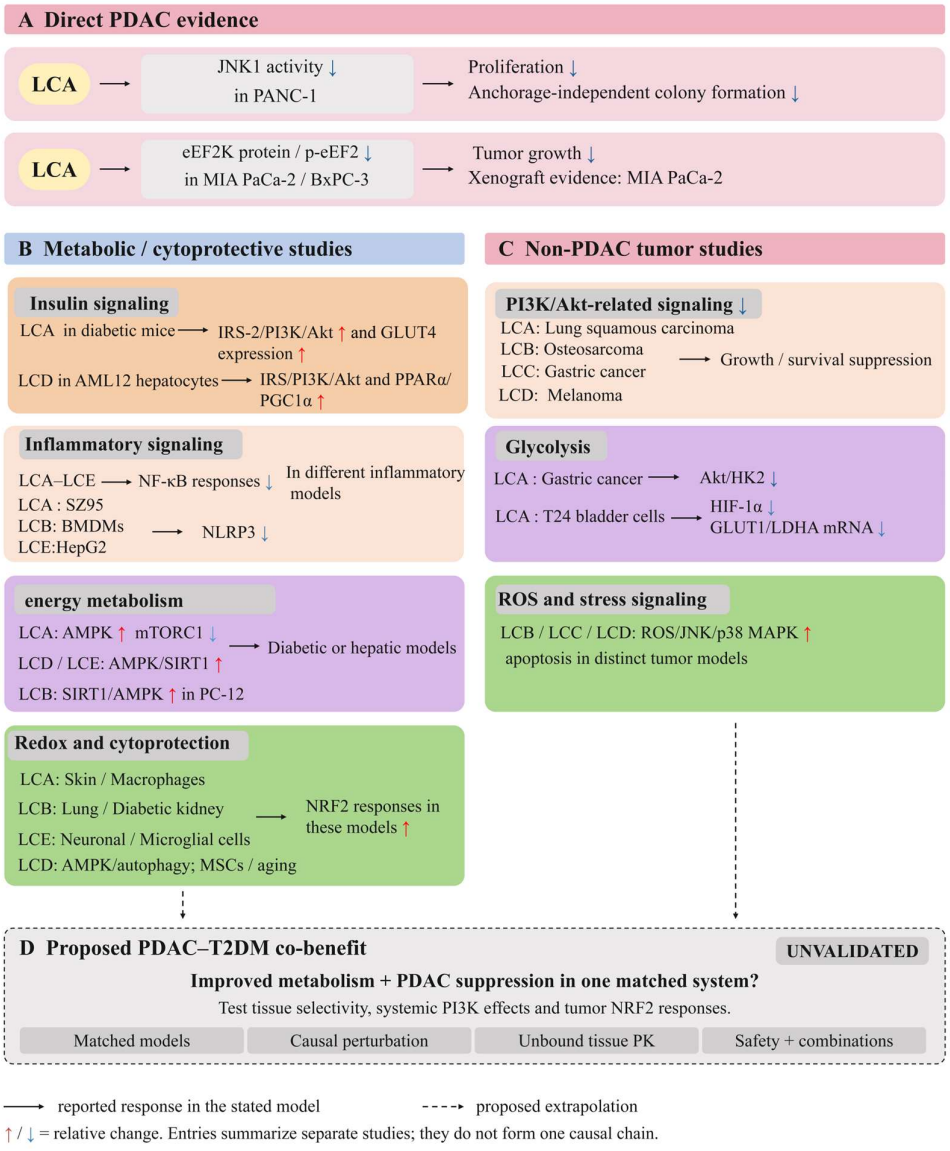


Figure 2. Evidence-stratified map of LC subtype effects on shared PDAC–T2DM pathways. The figure separates (**A**) direct PDAC evidence, (**B**) metabolic/cytoprotective evidence from non-tumor models, (**C**) non-PDAC tumor evidence, and (**D**) a proposed but unvalidated PDAC–T2DM co-benefit.

In summary, the LCs can modulate NF-κB, JNK, and the NLRP3 inflammasome in different experimental models, but the targets and regulatory directions of different subtypes are not entirely consistent (Table 2). In T2DM, these inflammatory pathways are

associated with impaired insulin signaling. In PDAC, they may participate in inflammatory microenvironment remodeling, tumor cell survival, and therapeutic tolerance. Therefore, the regulation of these pathways by LCs provides mechanistic clues for understanding their potential value in comorbidity intervention. However, the available evidence remains theoretical and is insufficient to directly demonstrate that LCs can simultaneously ameliorate T2DM and inhibit PDAC through the same inflammatory mechanism. The ROS causes JNK activation induced by LCB, LCC, and LCD in tumor cells cannot be directly extrapolated to normal metabolic tissues. The inhibition of the NLRP3 inflammasome by LCA and LCB has also not been validated in T2DM-PDAC comorbidity models. In addition, the relevant NF-κB and NLRP3 studies have mainly employed human SZ95 sebocytes, BMDMs, HepG2 cells, or other non-PDAC models. Whether these effects can further improve the immunosuppressive microenvironment and therapeutic tolerance of PDAC still requires validation in models in which tumor cells, immune cells, and metabolic tissues coexist.

4.2. Targeted Regulation of the PI3K/Akt Pathway

Available evidence suggests that LCs may exert opposite directional regulation of the PI3K/Akt pathway in tumor cells and normal metabolic tissues. In certain tumor cells, LCs exert anti-tumor effects by inhibiting aberrantly activated PI3K/Akt pro-survival signaling. In insulin resistance models, some LCs can restore impaired IRS/PI3K/Akt signaling. However, these two lines of evidence are derived from different LC subtypes, disease models, and dosing conditions, so it has not yet been demonstrated that the same LC can simultaneously achieve tumor suppression and metabolic improvement in the T2DM-PDAC comorbidity state. Therefore, this bidirectional regulation should currently be regarded as a tissue or context-dependent effect awaiting validation, rather than an established synergistic therapeutic mechanism.

4.2.1. Regulation of the PI3K/Akt Pathway in PDAC

In tumor models, 10–40 μmol/L of LCA concentration-dependently inhibited PI3K and Akt phosphorylation in human lung squamous carcinoma cells and 15 mg/kg of LCA suppressed H226 tumor growth in mice [106]. At 2.5–20 μM, LCB concentration-dependently inhibited PI3K, Akt, and mTOR phosphorylation in osteosarcoma tumor cells, thereby inducing autophagy and tumor cell death [107]. LCC and LCD mainly act by modulating upstream regulators of the PI3K/Akt pathway. LCC can directly bind to RAC3 and inhibit its GTPase activity, thereby blocking RAC3-mediated PI3K/Akt/mTOR signaling. This effect has been validated in AGS and MKN45 human gastric cancer cells and in patient-derived gastric cancer organoids, with IC_{50} values of 36.7 μM and 23.6 μM for AGS and MKN45 cells, respectively [108]. Similarly, 2.5–10 μM of LCD downregulated the Akt upstream regulator BI-1 (TMBIM6) and reduced Akt and mTOR phosphorylation levels in human melanoma cell lines SK-MEL-5 and SK-MEL-28 [109]. These results suggest that LCC and LCD may inhibit tumor cell growth by modulating upstream targets of the PI3K/Akt pathway, rather than by directly inhibiting PI3K or Akt itself. Currently, there is no direct evidence that LCE can inhibit aberrantly activated PI3K/Akt/mTOR signaling in tumor cells. Previous studies have shown that LCE can inhibit LPS-induced Akt phosphorylation. However, this effect has mainly been interpreted as part of its inhibition of NF-κB and AP-1 transcriptional activity and its attenuation of inflammatory responses, and cannot directly demonstrate that LCE exerts an inhibitory effect on tumor PI3K/Akt signaling [89]. In PDAC models, LCA has been shown to inhibit the growth of MIA PaCa-2 and BxPC-3 cells and xenograft tumors in nude mice. However, this effect is mainly attributed to the direct binding and inhibition of eEF2K by LCA, which induces pyroptosis in tumor cells, rather than to PI3K/Akt pathway inhibition [110]. Therefore, although the

available results support the notion that LCA possesses anti-cancer activity in PDAC, they may not prove that this effect is mediated by PI3K/Akt inhibition. For LCB, LCC, LCD, and LCE, direct evidence that they control PDAC growth through PI3K/Akt pathway inhibition is also currently lacking.

Overall, the evidence that LCs inhibit PI3K/Akt signaling is mainly derived from non-PDAC models, including lung cancer, osteosarcoma, gastric cancer, and melanoma. Extrapolating these findings to PDAC is mechanistically plausible but remains a hypothesis that requires validation. Future studies should simultaneously assess tumor growth and PI3K/Akt pathway activity in PDAC cells, organoids, and in vivo models, and confirm the causal relationship between the two through pathway restoration or target knockdown experiments.

4.2.2. Improving Insulin Resistance

Regarding insulin resistance, 15–50 mg/kg of LCA has been demonstrated to concentration-dependently upregulate the IRS-2/PI3K/AKT pathway and GLUT4 expression in T2DM mouse models, promote glucose uptake in skeletal muscle and adipose cells, also significantly attenuate pancreatic β-cell atrophy, thereby protecting β-cells and improving insulin resistance [111]. LCB has not yet been directly demonstrated to improve T2DM through the PI3K/Akt pathway. However, 20 and 40 mg/kg of LCB can alleviate diabetic nephropathy in HFD/STZ mice, accompanied by upregulation of the Nrf2/HO-1 antioxidant pathway [112]. Because this study did not examine PI3K/Akt signaling, the nephroprotective effect of LCB cannot be attributed to this pathway.

Currently, there is no direct evidence that LCC ameliorates insulin resistance in T2DM. In contrast, LCD shows considerable potential for the treatment of insulin resistance. Lee et al. demonstrated that 1–2 μM of LCD concentration-dependently promoted glucose consumption and uptake, inhibited the expression of gluconeogenic genes, and promoted glycogen synthesis in a high-glucose-induced insulin-resistant AML12 hepatocyte model. These changes were accompanied by activation of the IRS/PI3K/Akt and PPARα/PGC1α pathways and improvement in mitochondrial function [113]. However, this study did not examine JNK phosphorylation. Therefore, it cannot be determined whether LCD alters JNK activity while improving insulin signaling. The improvement in insulin resistance by LCE is mainly associated with the attenuation of inflammatory responses and the downregulation of NLRP3/caspase-1 signaling [104]. Whether it directly restores IRS/PI3K/Akt signaling still requires validation.

There is complex crosstalk between inflammatory signaling and insulin signaling pathways. JNK activated by TNF-α can interact with IRS-1 and promote phosphorylation of IRS-1 at Ser307, thereby affecting insulin signaling [30]. Moreover, IRS-1, as the direct substrate of IKK, participates in the activation of the NF-κB pathway [114]. These mechanisms provide a theoretical basis for the indirect improvement in insulin signaling by LCs through their anti-inflammatory effects. However, there is currently insufficient evidence to demonstrate that LCB, LCC, or LCD act primarily through the sequential mechanism of "NF-κB inhibition → IRS-1 restoration → PI3K/Akt reactivation." These mechanisms are not mutually exclusive. However, the available evidence does not establish whether LCD improves insulin signaling primarily through JNK/IKK suppression, IRS/PI3K/Akt restoration, PPARα/PGC1α activation, or a combination of these effects. Therefore, it cannot be inferred solely from the ability of LCs to inhibit NF-κB in other cell types that they will necessarily restore IRS-1 function in metabolic tissues. It should also be noted that the role of IRS-1 Ser307 is context-dependent in vivo. Subsequent mouse studies have shown that Ser307 does not exert an inhibitory effect under all conditions, while its phosphorylation in some settings helps to maintain proximal insulin signaling [115]. Therefore, a single IRS-1 phosphorylation site should not be regarded as the sole mechanism by which

JNK induces insulin resistance, nor should it be inferred solely from this site that JNK activation by LCs necessarily leads to insulin resistance.

In T2DM-related metabolic tissues including the muscles, IRS/PI3K/Akt signaling is typically impaired by inflammation or other factor. The pathway activation exhibited by some LCs is more consistent with restoration of insulin signaling. In contrast, in tumor cells, the PI3K/Akt pathway may be constitutively activated by oncogenes, receptor signaling, or other upstream abnormalities. The inhibition of this pathway by LCs in certain models primarily serves to attenuate pro-survival signaling in tumor cells. These two lines of evidence are derived from different tissues and experimental conditions. Therefore, it is speculated that LCs may exert tissue-selective signal correction of the PI3K/Akt pathway (Table 2.).

More importantly, inhibition of tumor PI3K/Akt signaling cannot be interpreted as "glycemic control", which will impair insulin action in the liver, skeletal muscle, and adipose tissue, leading to hyperglycemia and compensatory hyperinsulinemia. The elevated insulin may in turn reactivate PI3K-related signaling in tumors, thereby attenuating the anti-tumor efficacy [116]. Therefore, if LC causes extensive inhibition of PI3K/Akt in the body. The risks of hyperglycemia, compensatory hyperinsulinemia, and reactivation of tumor signals still need to be considered. Thus, the proposed "glycemic control" by LCs should only be positioned to restore the impaired IRS/PI3K/Akt signaling in metabolic tissues, rather than systemic inhibition of PI3K/Akt. In contrast, tumor PI3K/Akt inhibition is intended to block oncogenically activated pro-survival signaling and is not by itself a glucose-lowering mechanism (Figure 2).

4.3. Intervention in Energy Metabolism Reprogramming

LCs have been reported to regulate pathways involved in cellular energy-sensing and substrate metabolism. These observations raise the possibility that LC-mediated AMPK/mTOR modulation could improve metabolic homeostasis in T2DM while affecting tumor bioenergetics. However, this potential dual action remains a mechanistic hypothesis, of which no study has directly demonstrated that an LC suppresses PDAC growth through AMPK activation or mTOR inhibition.

AMPK and mTOR serve as two master nutrient and energy sensing kinases that form a mutually antagonistic axis to maintain cellular metabolic homeostasis [117]. AMPK is typically activated under energy stress, initiating catabolism and inhibiting anabolism. While mTOR senses nutrient sufficiency to promote protein and lipid synthesis, thereby driving cell growth and proliferation. As a positive driver of the Warburg effect, mTOR upregulates hypoxia-inducible factor 1α (HIF-1α) expression [118], whereas AMPK activation directly antagonizes mTOR signaling and suppresses aerobic glycolysis [119]. These observations at pathway level provide biological plausibility, but they are neither LC-specific nor PDAC-specific. Therefore, AMPK activation or mTOR inhibition cannot be assumed to suppress PDAC without direct pathway-specific evidence.

Evidence that LCs regulate this axis is currently derived mainly from metabolic and non-PDAC models. LCA concentration-dependently orchestrates glucose and lipid metabolism in T2DM mouse models by simultaneously activating AMPK and suppressing mTORC1 signaling, at 5–50 μM in HepG2 and INS-1 cells and 5–10 mg/kg body weight in HFD-induced diabetic mice [120]. Evidence for AMPK pathway regulation is most robust for LCD, which activates the hepatic AMPK/SIRT1 axis and reduces lipid accumulation in MASLD mouse models at 1 mg/kg/day, with 10 μM identified as the effective concentration in FFA-induced HepG2 cells [121]. In contrast, in PC-12 cells, LCB concentration-dependently activated the SIRT1/AMPK pathway at 10–40 μM. Current research on this subtype primarily focuses on neuroprotection rather than metabolic disorders [122]. LCE concentration-dependently inhibits hepatic lipid production by activating the AMPK/Sirt1

pathway at 5–10 μM [123], although this study did not evaluate T2DM or PDAC models. Meanwhile, LCA has been demonstrated to inhibit tumor growth by suppressing Akt signaling and downregulating key glycolytic enzymes, such as HK2, in a concentration-dependent manner at 30–60 μM in gastric cancer cells and at 10 mg/kg body weight in MKN45 xenograft mice and to inhibit glycolysis and proliferation in human bladder cancer T24 cells at 20–100 μM, with reduced HIF-1α expression and decreased GLUT1 and LDHA mRNA levels [124,125]. Importantly, the reduction in GLUT1 in T24 cells is not inherently inconsistent with improved insulin signaling or GLUT4-dependent glucose disposal in metabolic tissues. GLUT1 and GLUT4 are distinct transporters in different regulatory programs. In T24 tumor cells, LCA reduced HIF-1α expression, GLUT1 and LDHA mRNA levels, glucose uptake, and lactate production, consistent with the suppression of tumor-associated glycolysis [125]. In contrast, PI3K/Akt-mediated GLUT4 translocation primarily supports glucose disposal in insulin-responsive tissues. These findings therefore indicate context-dependent regulation of glucose handling rather than a uniform stimulatory or inhibitory effect. However, because the observations derive from separate experimental models, they do not establish that LCA selectively suppresses tumor GLUT1 while enhancing GLUT4 in metabolic tissues. These findings support potential metabolic effects of LCs, but they do not establish an AMPK/mTOR-dependent antitumor mechanism in PDAC. Although LCA has demonstrated anti-PDAC activity, the reported mechanism involves eEF2K inhibition and pyroptosis rather than AMPK/mTOR modulation [110] (Table 2.).

Taken together, current evidence supports two separate observations: selected LCs regulate AMPK/mTOR-related signaling and improve metabolic parameters in metabolic disease models, whereas LCA can restrict glycolysis or tumor growth in several non-PDAC cancer models. It does not yet demonstrate that these effects occur simultaneously or that LC-mediated AMPK activation or mTOR inhibition suppresses PDAC growth. Accordingly, the AMPK/mTOR axis should be regarded as a candidate mechanistic link rather than an established dual-action pathway in PDAC-T2DM comorbidity. Direct validation will require PDAC-specific cell, organoid, and in vivo models that combine LC treatment with pathway perturbation and measurements of AMPK/mTOR activity, glycolytic flux, tumor growth, and systemic metabolic outcomes (Figure 2).

4.4. Regulation of Oxidative Stress

Oxidative stress is intimately linked with inflammatory pathways, serving as a key driver that triggers and amplifies inflammatory cascades [126]. Therefore, ROS and redox signaling are involved in both metabolic dysfunction and tumor progression. However, the biological consequences of redox modulation depend on the cell type, disease state, basal antioxidant capacity, stimulus, exposure level, and treatment duration. Therefore, findings obtained from metabolic, inflammatory, and tumor models should not be combined as evidence for a single universal LC-mediated redox mechanism.

In non-tumor models, selected licochalcone subtypes have been associated with activation of antioxidant or cytoprotective pathways. LCA has been shown to reduce intracellular ROS in primary human dermal fibroblasts exposed to solar-simulated radiation and in fMLP-stimulated human neutrophils, in a concentration-dependent manner (0.6–9 μM and 1–10 μM, respectively), accompanied by Nrf2 nuclear translocation (9 μM) and increased HO-1 and GCLM expression. In pancreatic cancer Mia PaCa-2 cells, LCA instead triggers ROS bursts and induced pyroptosis through the inhibition of eEF2K. These findings indicate that the redox effects of LCA are model- and context-dependent. Antioxidant effects have been reported in non-tumor systems, whereas ROS-associated pyroptosis in PDAC cells has been attributed to eEF2K inhibition [127,128]. Research on the antioxidant properties of LCB is more thoroughly characterized. In LPS-challenged human

pulmonary microvascular endothelial cells (HPMECs) and in LPS-induced acute lung injury mice, LCB activated the Keap1/Nrf2 pathway in a concentration-dependent manner (400 nM in vitro and 10–40 mg/kg in vivo), increasing Nrf2, HO-1 and NQO1 while reducing Keap1, and it attenuated apoptosis and the expression of key pro-inflammatory cytokines, including TNF-α, IL-1β and IL-6 [129]. In high-fat diet/streptozotocin (HFD/STZ)-induced mouse models of diabetic nephropathy, LCB significantly reduced blood glucose levels and attenuated renal injury [112]. LCE concentration-dependently reduced 6-OHDA-induced LDH release in SH-SY5Y cells at 0.1–2 μM, and LPS-induced NO production and IL-1β/TNF-α expression in BV2 cells at 1–5 μM, with Nrf2/ARE activation (as evidenced by Nrf2 nuclear translocation, HO-1, NQO1) confirmed at 2–5 μM [130]. LCD exerted antioxidant effects through AMPK/autophagy at a single concentration of 1 μg/mL in hBM-MSCs and 0.5 mg/kg/day in D-galactose-treated mice [131], rather than directly relying on Nrf2 transcriptional activation. This autophagy-dependent antioxidant paradigm offers new insights into the LC family's role in the crosstalk between metabolic reprogramming and oxidative stress (Table 2.). These studies indicate that selected LCs can modulate redox homeostasis in specific non-tumor systems. They do not establish that the same effects occur in pancreatic β-cells or in the PDAC microenvironment.

The interpretation of NRF2 activation is particularly important in PDAC. In pancreatic cancer, NRF2 can support tumor maintenance by preserving redox balance, protein translation, and survival signaling [132]. NRF2-related signaling has also been implicated in acquired gemcitabine resistance in PDAC cells [133]. Thus, NRF2 activation observed in metabolic or inflammatory models cannot automatically be considered beneficial in PDAC. Conversely, the direct anti-PDAC activity of LCA reported in MIA PaCa-2 and BxPC-3 models was attributed mainly to eEF2K inhibition and pyroptosis, rather than to NRF2 activation [110]. These findings should therefore be discussed as separate mechanisms rather than as evidence of a confirmed ROS-dependent switch between normal and tumor tissues.

At present, no study has demonstrated that one LC subtype simultaneously activates antioxidant defenses in pancreatic β-cells or insulin-responsive tissues while inducing selective oxidative death in PDAC cells within the same experimental system. The apparent contrast between antioxidant and pro-death effects may reflect differences in basal redox state, KEAP1/NRF2 activity, ROS-buffering capacity, cellular uptake, metabolism, and exposure. However, this tissue-selective redox mechanism remains a hypothesis. Direct validation will require matched metabolic–tumor models, measurement of free LC concentrations and ROS flux, NRF2 perturbation experiments, and simultaneous assessment of β-cell function, insulin sensitivity, tumor growth, and treatment response (Figure 2).

Table 2. Evidence-stratified summary of LCs subtype, experimental models, doses, molecular targets and outcomes.

LCs Subtypes	Experimental Model	Dose/Concentration	Main Target/Pathway	Observed Outcome	Evidence Category	Ref.
LCA	PANC-1 cells	10 μM in vitro	JNK1	Reduced proliferation and colony formation	Direct PDAC	[91]
	MIA PaCa-2 and BxPC-3 models	7.5–12.5 μM in vitro	eEF2K/pyroptosis	Antitumor activity and pyroptotic cell death	Direct PDAC	[110]
	T2DM mouse models	15–50 mg/kg in vivo	IRS-2/PI3K/Akt/GLUT4	Improved glucose uptake and insulin resistance	Metabolic model	[111]
	HepG2/INS-1 cells and diabetic mice	5–50 μM in vitro; 5–10 mg/kg in vivo	AMPK/mTORC1	Improved glucose and lipid metabolism	Metabolic model	[120]
	Gastric cancer cells and xenografts	30–60 μM in vitro; 10 mg/kg in vivo	Akt/HK2	Reduced glycolysis and tumor growth	Non-PDAC tumor	[124]
	T24 bladder cancer cells	20–100 μM in vitro	HIF-1α/GLUT1/LDHA	Reduced glucose uptake and lactate production	Non-PDAC tumor	[125]
LCB	BMDMs	5–40 μM in vitro	NEK7/NLRP3	Reduced inflammasome activation	Inflammatory model	[103]
	HPMECs and acute lung injury mice	400 nM in vitro; 10–40 mg/kg in vivo	Keap1/NRF2/HO-1	Reduced oxidative and inflammatory injury	Non-tumor model	[129]
	HFD/STZ diabetic nephropathy mice	20–40 mg/kg in vivo	NRF2/HO-1	Reduced renal injury	Metabolic model	[112]
	Oxaliplatin-resistant colorectal cancer cells	10–30 μM in vitro	ROS/JNK/p38	Induced apoptosis	Non-PDAC tumor	[92]
LCC	H9c2 cardiomyocytes	25 μM in vitro	PI3K/Akt/eNOS and NF-κB/iNOS	Reduced inflammatory signaling	Non-tumor model	[87]
	Gastric cancer cells AGS and MKN45 cells	IC_{50} = 36.7 and 23.6 μM in vitro	RAC3/PI3K/Akt/mTOR	Reduced growth and enhanced 5-FU sensitivity	Non-PDAC tumor	[108]
LCD	AML12 insulin-resistant hepatocytes	1–2 μM in vitro	IRS/PI3K/Akt; PPARα/PGC1α	Improved glucose uptake and mitochondrial function	Metabolic model	[113]
	MASLD models	1 mg/kg/day in vivo; 10 μM in vitro	AMPK/SIRT1	Reduced lipid accumulation	Metabolic model	[121]
	Colorectal cancer cells	2–6 μM in vitro	ROS/JNK/p38	Induced apoptosis	Non-PDAC tumor	[94]

https://doi.org/10.3390/biomedicines14112489

LCE	Palmitate-treated HepG2 cells	10–40 μM	NLRP3/caspase-1	Improved insulin sensitivity	Metabolic model	[104]
	Neuronal and microglial cells	0.1–2 μM in SH-SY5Y neuronal cells and 1–5 μM in BV2 microglial cells	NRF2/ARE	Reduced oxidative and inflammatory injury	Non-tumor model	[130]

4.5. Potential Modulation of Drug-Resistance Mechanisms by LCs: Evidence from Non-PDAC Models

Current evidence that LCs modulate anticancer drug resistance is derived predominantly from non-PDAC models. In MDR1-transfected KB cells, LCA increased the intracellular accumulation of P-gp substrates, stimulated P-gp ATPase activity, and sensitized the cells to vinblastine [134]. LCA also resensitized ABCG2-overexpressing multidrug-resistant cancer cells to ABCG2-substrate chemotherapeutics by impairing transporter-mediated drug efflux [135]. At the level of resistance-associated signaling, LCB induced ROS-dependent JNK/p38-mediated apoptosis in oxaliplatin-resistant colorectal cancer cells [92]. LCD has also been examined in NSCLC models. In HCC827 cells and the gefitinib-resistant subline HCC827GR (5–20 μM, 48 h; IC_{50} = 17.9 ± 0.97 and 19.1 ± 0.5 μM, respectively), LCD inhibited EGFR/MET signaling and reduced viability while inducing apoptosis in both gefitinib-sensitive and gefitinib-resistant cells [136]. LCC reverses drug resistance by suppressing P-gp expression through targeting the RAC3/PI3K/Akt/mTOR signaling axis [108]. Collectively, these studies identify two candidate resistance-modulating activities of LCs regarding interference with ABC-transporter function and disruption of survival pathways that maintain acquired resistance. Nevertheless, the relevance of these observations to PDAC remains unproven.

ABCG2 is a biologically plausible target in PDAC because Wnt5a/FZD7-dependent ABCG2 upregulation increased gemcitabine resistance in Capan-2 cells, while gemcitabine-resistant AsPC-1, Capan-2, and PANC-1 derivatives exhibited increased ABCG2 expression [137]. However, no study has tested whether an LC inhibits ABCG2 or restores chemotherapy sensitivity in these PDAC models. Although LCA has demonstrated anti-PDAC activity through eEF2K inhibition and pyroptosis [110], this study merely compared LCA with gemcitabine rather than testing an LCA–gemcitabine combination and did not evaluate resistant PDAC cells or drug-efflux reversal. Evidence from other tumor types therefore cannot be interpreted as demonstrating that LCs reverse chemoresistance in PDAC. Direct validation should employ paired parental and chemotherapy-resistant PDAC cells, patient-derived organoids, and stromal co-culture models. LC–chemotherapy combinations should be evaluated using dose–response matrices and formal synergy analyses, together with intracellular drug accumulation and efflux assays, ABCB1/ABCG2 expression and ATPase measurements, and transporter- or pathway-specific knockdown and rescue experiments. In vivo studies should further determine tumor response, systemic exposure, toxicity, and metabolic outcomes in PDAC–T2DM models. Until such evidence is available, LCs should be regarded as candidates for investigating PDAC chemoresistance (Table 3).

Table 3. Evidence for LC-mediated modulation of drug resistance.

Core Resistance/Reversal Strategy	LCs Subtypes	Experimental Model	Dose/Concentration	Specific Molecular Effect	Observed Outcome	Ref.
Direct inhibition of drug efflux	LCA	KB/MDR1 cells	- 5 μM for vinblastine sensitization - 50 μM for daunorubicin/rhodam-ine 123 accumulation—100 μM for P-gp ATPase assay	Increased P-gp ATPase activity and intracellular accumulation of P-gp substrates	Enhanced vinblastine sensitivity	[134]
		ABCG2-overexpressing multidrug-resistant cancer cells	- 0.5–3 μM for 72 h - 10 μM with 5 μM topotecan - 20 μM for transport assay ABCG2 transport inhibition - EC_{50} approximately 14 μM in ATPase assay	ABCG2 overexpressing multidrug-resistant cancer cells	Resensitization to ABCG2-substrate chemotherapeutics	[135]
Suppression of resistance-associated signaling	LCB	Oxaliplatin-resistant colorectal cancer cells	- 10–30 μM	ROS induces JNK/p38 activation	Increased apoptosis	[92]
	LCC	Human gastric cancer cells AGS and MKN45 cells	- IC_{50} = 36.7 μM in AGS - IC_{50} = 23.6 μM in MKN45	RAC3/PI3K/Akt/mTOR inhibition and P-gp downregulation	Enhanced 5-FU sensitivity	[108]
	LCD	HCC827 and Gefitinib-resistant NSCLC cells HCC827GR	- 5–20 μM for 48 h - IC_{50} = 17.9 ± 0.97 and 19.1 ± 0.5 μM	EGFR/MET inhibition	Reduced viability and induced apoptosis in both gefitinib-sensitive and gefitinib-resistant NSCLC cells	[136]

5. Translational Boundaries and Future Research Prospects

5.1. Evidence Boundaries and Pharmacokinetic Constraints

The current evidence supports a mechanistic framework, but not a validated dual-action therapy for PDAC–T2DM comorbidity. Direct evidence on PDAC remains focused in LCA, particularly on the JNK1-related effects reported in pancreatic cancer cells including PANC-1 [91], and the eEF2K-mediated pyroptosis reported in MIA PaCa-2 and BxPC-3 models [110]. In contrast, most evidence concerning NF-κB, PI3K/Akt, AMPK/mTOR, NRF2, glycolysis, and drug-resistance modulation comes from metabolic models or non-PDAC tumor systems. Recent subtype-focused reviews also indicate that the pharmacological evidence for LCB, LCC, LCD, and LCE remains limited to directly connect to PDAC than those for LCA [138,139].

Pharmacokinetic translation represents a second major constraint. In rats, LCA showed an absolute oral bioavailability of approximately 3.3% [140]. Studies using human liver microsomes and hepatocytes indicate that LCA undergoes extensive phase-II metabolism, particularly glucuronidation [141]. Recent reviews further identify poor aqueous solubility, intestinal first-pass metabolism, and limited systemic exposure as barriers to the development of LCA-based therapies [138,142]. Consequently, micromolar concentrations used in cell experiments cannot be directly compared with oral doses reported in mice without measuring free drug concentrations and active metabolites.

LCA produced concentration-dependent cytotoxicity in cultured mammalian cells at higher micromolar concentrations, whereas the absence of obvious toxicity in selected in vivo studies cannot establish broad safety [143]. In vitro studies further showed that LCA inhibits several human CYP enzymes, including CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A4, with inhibition constants in the sub-micromolar-to-low-micromolar range [144]. These findings raise the possibility of interactions with concomitant medications, although direct interaction studies with gemcitabine-based regimens or antidiabetic drugs remain limited. Formulation strategies such as self-microemulsifying drug-delivery systems can increase LCA exposure, but higher systemic exposure may also alter tissue distribution and toxicity [145]. Therefore, efficacy and safety should be evaluated together in integrated pharmacokinetic–pharmacodynamic studies.

5.2. Future Perspectives

The most informative next step is the development of matched PDAC–T2DM models that combine tumor cells or patient-derived organoids with insulin-resistant hepatocytes, adipocytes, β-cells, immune cells. These models should compare the same LC subtype across metabolic cells and tumor cells using matched dose, exposure duration, and drug concentration.

Mechanistic studies should distinguish pathway association from pathway dependence. For example, AMPK/mTOR, PI3K/Akt, NRF2, JNK, and drug-efflux effects should be tested using selective inhibitors, genetic knockdown, rescue experiments, target-engagement assays, and metabolic-flux measurements. In PDAC, LC–gemcitabine combinations should be evaluated in parental and resistant cells, organoids, and xenografts using formal synergy analysis, intracellular drug-accumulation assays, and ABCB1/ABCG2 functional measurements.

Pharmacokinetic and pharmacodynamic studies should quantify compounds and major metabolites in plasma, tumor, liver, skeletal muscle, adipose tissue, and pancreas. Efficacy should be related to unbound tissue exposure rather than nominal concentration alone. Finally, subtype-comparative studies are needed to determine whether the apparent tissue selectivity of LCs is a context-dependent bidirectional regulation activity or simply a consequence of differences in model, dose, and exposure.

https://doi.org/10.3390/biomedicines14112489

6. Conclusions

PDAC and T2DM intersect through chronic inflammation, the PI3K/AKT pathway, metabolic reprogramming and redox imbalance, but these pathways do not necessarily operate in the same direction or carry the same therapeutic meaning in metabolic tissues and tumor cells. LCs are therefore best viewed as context-dependent pathway modulators rather than uniformly bidirectional agents. The current literature supports two partially independent observations. First, selected LCs improve inflammatory or metabolic phenotypes in diabetes-related and other non-tumor models. Second, LCA has direct anti-cancer activity in PDAC through mechanisms including JNK1 inhibition in PANC-1 cells and eEF2K-associated pyroptosis in other PDAC models. These findings help to establish biological plausibility for further investigation, but they do not demonstrate that an LC can simultaneously improve systemic metabolic homeostasis and suppress PDAC growth in a PDAC–T2DM comorbidity model.

The main contribution of this review is the construction of an evidence-stratified framework that separates direct PDAC findings from metabolic evidence, non-PDAC tumor evidence and mechanistic extrapolation. We further propose a central hypothesis: the key question is not whether LCs generally activate or inhibit a given pathway, but whether a defined LC subtype can achieve therapeutic tissue selectivity at pharmacologically achievable concentrations. Addressing this question will require matched metabolic–tumor models, causal pathway perturbation, tissue pharmacokinetics, toxicity profiling, and combination studies with standard PDAC and antidiabetic treatments.

Author Contributions: All authors contributed to the original draft preparation, review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This work is supported by the National Natural Science Foundation of China (No. 82505177), the Guangdong Science and Technology Department (No. 2025A1515011390), Innovation and Technology Fund in Hong Kong (No. ITS/032/25FX), and General Research Fund, Research Grants Council in Hong Kong (HKBU-12103925, HKBU-12103926).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

PDAC	Pancreatic ductal adenocarcinoma
T2DM	Type 2 diabetes mellitus
PanIN	Pancreatic intraepithelial neoplasm
IPMN	Intraductal papillary mucinous neoplasm
IR	Insulin resistance
KRAS	Kirsten rat sarcoma
TME	Tumor environment
PI3K	Phosphatidylinositol-3 kinase
AKT	Protein kinase B
NF-κB	The transcription factor nuclear factor-κB
TNF-α	Tumor necrosis factor-α
IL-6	Interleukin-6

JNK	The c-Jun NH2-terminal kinase
NLRP3	NOD-like receptor (NLR) family pyrin domain-containing 3
IL-1β	Interleukin-1β
Ser 307	Serine 307
IRS-1	Insulin-receptor substrate-1
VEGF	Vascular endothelial growth factor
CAFs	Cancer-associated fibroblasts
MMPs	Matrix metalloproteinases
TIMPs	Tissue metalloproteinase inhibitors
ECM	Extracellular matrix
Bcl-2	B cell CLL/lymphoma-2
Bcl-xl	B cell CLL/lymphoma-Extra large
P-gp	P-glycoprotein
GLUT4	Glucose transporter 4
EMT	Epithelial–mesenchymal transition
AMPK	The AMP-activated protein kinase
mTOR	The mammalian target of rapamycin
TCA	The tricarboxylic acid
4E-BP1	The eIF4E-binding protein 1
eIF4E	The eukaryotic translation initiation factor 4E
S6K1	70 kDa ribosomal protein S6 kinase 1
HIF-1α	Hypoxia-inducible factor-1α
HK2	Hexokinase 2
LDHA	Lactate dehydrogenase A
ROS	Reactive oxygen species
GLUT2	Glucose transporter 2
PDX-1	Pancreatic duodenal homeobox-I
MAPK	Mitogen-activated protein kinase
Nrf2	Nuclear factor E2-related factor 2
HO-1	Heme oxygenase-1
HIF-2α	Hypoxia-inducible factor-2α
Tp53	Tumor protein p53
SMAD4	Mothers Against Decapentaplegic Homolog 4
Bax	Bcl-2-associated X protein
ERK	Extracellular signal-regulated kinase
TAM	Tumor-Associated Macrophage
LC	Licochalcone
LCA	Licochalcone A
LCB	Licochalcone B
LCC	Licochalcone C
LCD	Licochalcone D
LCE	Licochalcone E
COX-2	Cyclo-oxygenase-2
LPS	Lipopolysaccharide
IKK	IκB kinase
NEK7	Never in mitosis A (NIMA)-related kinase-7
RAC3	Ras-related C3 botulinum toxin substrate
BI-1	Bax inhibitor-1
AP-1	Activator Protein-1
eEF2K	Eukaryotic elongation factor 2 kinase
PPARα	Peroxisome proliferator-activated receptor α
PGC1α	Peroxisome proliferator-activated receptor γ coactivator-1α
mTORC1	The mechanistic target of rapamycin complex I
MASLD	Metabolic dysfunction-associated steatotic liver disease
SIRT1	The silent information regulator sirtuin 1

ALX	Alloxan
ABCG2	ATP-binding cassette (ABC) transporter
EGFR	Epidermal growth factor receptor
MET	Tyrosine kinase receptor MET
TKIs	Tyrosine kinase inhibitors

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