Mechanism of PI3K/Akt-mediated mitochondrial pathway in obesity-induced apoptosis (Review)

JIARUI LI[1,2], MINGXIU SUN[1], MING TANG[1], XIN SONG[1], KAIZE ZHENG[3], TIANWEI MENG[1,2], CHENGJIA LI[1,2] and LIKUN DU[2]

[1]Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang 150040, P.R. China; [2]First Affiliated Hospital, Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang 150040, P.R. China; [3]Liaoning University of Traditional Chinese Medicine Xinglin College, Shenyang, Liaoning 110167, P.R. China

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Abstract. Obesity is a pervasive global health challenge that substantially reduces the quality of life of millions of individuals and impedes social and economic advancement. Obesity is an independent risk factor that contributes to a range of chronic non-communicable metabolic diseases, significantly affecting energy metabolism, mental health, cancer susceptibility, sleep quality, and other physiological processes. The PI3K/AKT signaling pathway, a significant glucose, lipid, and protein metabolism regulator, is integral to cellular growth, survival, and apoptosis. Apoptosis is a highly regulated form of programmed cell death that is critical for immune cell maturation and tissue repair. The present review examines the association between obesity, the PI3K/AKT pathway, and mitochondrial apoptosis to elucidate the potential mechanisms by which obesity may activate apoptotic pathways. These findings provide a theoretical foundation for mitigating obesity-related complications by targeting these critical pathways.

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Correspondence to: Dr Likun Du, First Affiliated Hospital, Heilongjiang University of Chinese Medicine, 26 Heping Road, Xiangfang, Harbin, Heilongjiang 150040, P.R. China
E-mail: dulikun@hljucm.edu.cn

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1. Introduction

Obesity, which often results from an imbalance between energy intake and expenditure, is characterized by excessive or abnormal fat accumulation and serves as an independent risk factor for various chronic non-communicable metabolic diseases, including diabetes, hypertension, osteoarthritis, and coronary heart disease. This condition exerts substantial adverse effects on the quality of life of patients and the broader social economy (1,2). Adipose tissue functions as an energy storage depot and endocrine organ, secreting bioactive molecules known as adipokines that broadly affect the metabolic processes of the body. Adipokines are pivotal in regulating insulin sensitivity, lipid and glucose metabolism, and energy balance. The PI3K/AKT signaling pathway, a central mediator of glucose, lipid, and protein metabolism, is vital for the regulation of cell growth, survival, and apoptosis. Apoptosis, a controlled form of programmed cell death, is a 'double-edged sword' that occurs under various physiological and pathological conditions. Central to apoptosis is the mitochondrial pathway, also known as the 'executor' of apoptosis, which plays an essential role in maintaining tissue homeostasis. Obesity impairs mitochondrial function and subsequently affects the process of cell apoptosis. Thus, investigating how the PI3K/AKT signaling pathway modulates mitochondrial function to mediate obesity-induced apoptosis is of substantial theoretical and clinical relevance. This research not only deepens our understanding of the pathological mechanisms of obesity but may also identify novel targets and strategies for treating obesity and its related diseases. By advancing mechanistic insights, the present review seeks to foster more effective interventions to improve the metabolic health and quality of life of individuals with obesity.

2. Epidemiology

From 1975 to 2014, the global average body mass index (BMI) for men increased from 21.7 to 24.2 kg/m^2 (3), and for women it increased from 22.1 to 24.4 kg/m^2. A 2023 study by the Chinese People's Liberation Army General Hospital (Beijing, China), which included 1,577,094 adults across China, found that 34.8% of the participants were overweight and 14.1% were

classified as obese, with BMI showing a positive correlation with obesity-related complications (4).

3. Overview

PI3K/AKT signaling pathway. The PI3K/AKT signaling pathway is integral to numerous physiological and pathological processes, including cell growth and proliferation, survival and apoptosis, metabolic regulation, angiogenesis, immune response, and cell migration and invasion (5). This pathway plays an essential role in adipogenesis, adipocyte differentiation, and energy storage within adipose tissue (6). In the pancreas, it supports the function and growth of islet β cells. In the muscle tissue, it regulates glucose uptake, protein synthesis, and vasodilation (7).

Activation of this pathway consists of multiple stages. Initially, extracellular signals such as growth factors and hormones bind to receptors on the cell membrane, initiating signal transduction. Receptor activation subsequently activates PI3K, which triggers downstream signaling cascades. PI3K is a heterodimer composed of catalytic subunits (p110α, p110β, p110δ, p110γ) and regulatory subunits (p85α, p55α, p50α, p85β, p55γ, p101, p84, p87). P110α is the main insulin-responsive kinase in adipocytes and muscle ducts, and the localization of p110δ and p110γ isoenzymes is mainly limited to immune cells (8,9). Activated PI3K phosphorylates the precursor protein phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol (3,4,5)-triphosphate (PIP_3), which acts as a second messenger, and the conversion of PIP_2 to PIP_3 promotes the recruitment of 3-phosphoinositide dependent protein kinase 1 (PDK1) (10). Finally, PDK1 and mammalian rapamycin target protein complex 2 (mTORC2) activate AKT on the membrane. PDK1 completely activates AKT by phosphorylation of the AKT threonine residue at Thr308 and mTORC2 by phosphorylation of AKT's serine residue of AKT at Ser473 (11). AKT1 is generally expressed, AKT2 isoenzymes are characteristic in insulin-sensitive tissues (such as muscle, fat and liver tissues), and AKT3 is mostly expressed in the nervous system, pancreas, heart, and kidney (12).

Inhibition of this pathway is orchestrated through multiple mechanisms, including the dephosphorylation of PIP_3 to PIP_2 by phosphatases and inhibitors such as phosphatase and tensin homolog (PTEN), leading to a reduction in PIP_3 levels, a pivotal modulator of AKT activation at the membrane (13). Additionally, negative regulators, such as pro-inflammatory cytokines (including TNF-α and IL-6), transcription factors, and microRNAs, play integral roles in the negative regulation of the pathway (14).

Apoptosis. Under physiological conditions, apoptosis is a genetically regulated programmed cell death process that facilitates the timely removal of damaged or dysfunctional cells. It plays a pivotal role in critical biological processes, including development, immune surveillance, and tissue homeostasis, and is indispensable for maintaining cellular equilibrium. Apoptosis serves as a key defense mechanism in the immune system, enabling the elimination of infected cells and irreparable DNA damage (15). The three major apoptotic pathways are the extrinsic death receptor pathway, the intrinsic mitochondrial pathway, and the endoplasmic reticulum pathway, which intersect and interact with one another (16). The hallmarks of apoptosis include cell shrinkage, membrane blebbing, chromatin condensation, formation of apoptotic bodies, and subsequent clearance by phagocytic cells or the immune system (17).

The excessive inhibition or aberrant activation of apoptosis can have deleterious effects. For instance, cancer cells evade normal cell death mechanisms by inhibiting apoptosis, thereby facilitating unchecked cell proliferation (18). In patients with systemic lupus erythematosus, dysregulation of apoptosis prevents the effective clearance of autoantigenic cells, triggering an autoimmune response that attacks self-tissues (19). Research has shown that the adipose tissue in obese mice and humans, induced by high-fat diets, exhibits a pro-apoptotic phenotype. Caspase activation and adipocyte apoptosis are significantly increased, which is considered a key initiating event leading to macrophage infiltration and insulin resistance in obese adipose tissue (20). Furthermore, increased hepatocyte apoptosis has been observed in high-fat diet-induced obese mice, and is recognized as a critical factor in the progression of obesity (21).

Mitochondrial pathway. Mitochondria, as cellular powerhouses, are central to ATP production and utilize most of the oxygen during oxidative phosphorylation. A small amount of residual oxygen forms superoxide anions, initiating the generation of reactive oxygen species (ROS). Excessive ROS accumulation can trigger mitochondrial swelling, alter membrane permeability, and activate apoptotic pathways by releasing cytochrome *c* (Cyt c) and other apoptotic factors (22).

Changes in the mitochondrial membrane potential (MMP) is a critical event that initiates apoptosis. Typically, the MMP is maintained at a stable level to support efficient ATP production. However, when cells are subjected to various stressors, the MMP becomes depolarized, which increases membrane permeability. The loss of MMP triggers the release of key pro-apoptotic factors, such as Cyt c, through a process known as mitochondrial outer membrane permeabilization, a key 'point of no return' in apoptosis. The B-cell lymphoma 2 (Bcl-2) protein family is integral to MMP regulation. For example, the anti-apoptotic protein, Bcl-2, blocks MMP depolarization, thereby shielding cells from apoptosis (23).

The specific mechanism of mitochondrial pathway activation under obesity is as follows. First, this classical intrinsic apoptotic pathway is triggered by endogenous signals in response to cellular stress or damage (24). Pro-apoptotic members of the Bcl-2 family translocate to the inner mitochondrial membrane, inducing alterations in membrane permeability. These changes facilitate the release of endogenous apoptotic factors such as Cyt c into the cytoplasm. Cyt c binds to the apoptotic protease-activating factor 1 (Apaf-1) to form an apoptosome complex. Formation of the apoptosome activates caspase-9, which in turn activates the downstream effector caspase-3 (25). Caspase-3 cleaves multiple cellular substrates and is a key enzyme in apoptosis (Fig. 1). Subsequently, effector caspases degrade critical cellular proteins, leading to membrane blebbing, cell fragmentation into apoptotic bodies, and eventual phagocyte clearance without inducing inflammation. The release of Cyt c and activation of caspases generate a feedback loop in which caspase-3 cleaves anti-apoptotic Bcl-2

Table I. Summary of mechanisms through which obesity induces cell apoptosis.

Mechanism	In obesity	Inducing apoptosis mechanism	(Refs.)
Insulin resistance	Insufficient activation of the PI3K/AKT signaling pathway prevents glucose from entering cells effectively, leading to impaired glucose metabolism and excessive ROS production.	Elevated ROS levels cause cellular damage and activate pro-apoptotic pathways: ① Dephosphorylation of Bad enhances its binding with Bcl-2 family members; ② FOXO activation promotes the expression of pro-apoptotic genes such as Bim and FasL; ③ dephosphorylation of GSK-3β inhibits the anti-apoptotic function of Bcl-2.	(24)
Oxidative stress	Excessive fat accumulation, increased fatty acid oxidation, and enhanced adipocyte metabolism contribute to a greater production of ROS.	Excessive ROS results in: ① DNA damage (including DNA strand breaks and base oxidation), triggering DNA repair mechanisms or apoptosis; ② protein damage (loss of protein function or conformational changes), leading to cellular dysfunction; ③ lipid peroxidation (generation of lipid peroxides), disrupting membrane integrity and intracellular signaling.	(49-51)
Inflammatory response	① Macrophage infiltration into adipose tissue is a hallmark of chronic low-grade inflammation; ② increased secretion of pro-inflammatory cytokines, chemokines, and adipokines.	① Pro-inflammatory cytokines activate the NF-κB signaling pathway (upregulating pro-apoptotic genes such as FasL and Bax); ② activation of the JNK pathway promotes the expression of Bim and Bid; ③ activation of the p38 MAPK pathway upregulates the expression of p53 and Bax, enhancing apoptosis.	(52,53)
Endoplasmic reticulum stress	Adipocyte expansion induces ER stress: ① Increased protein folding and processing load; ② activation of the UPR.	① The UPR transcription factor CHOP is upregulated, promoting apoptosis; ② JNK activation enhances Bax and Bim expression, leading to apoptosis.	(54-56)
Lipotoxicity	Accumulation of free fatty acids and triglycerides exacerbates lipotoxicity, damaging cell membranes and organelles.	① Increased cell membrane permeability causes cell rupture; ② Excessive lipid droplet accumulation disrupts cellular signaling, amplifying oxidative stress and inflammation; ③ Cross-talk with mitochondrial dysfunction mechanisms contributes to apoptosis.	(57,58)
Death receptor pathway	Binding of death receptors with ligands plays a critical role in chronic inflammation and directly initiates apoptosis.	① Recruitment of TRADD, FADD, and caspase-8; ② activation of caspase-8 initiates the apoptotic process; ③ formation of the DISC, leading to cytochrome *c* release from mitochondria through tBid (truncated form of Bid protein).	(59)

ROS, reactive oxygen species; FOXO, forkhead box O; Bim, Bcl-2-interacting mediator of cell death; FasL, Fas ligand; Bid, BH3-interacting domain death agonist; ER, endoplasmic reticulum; UPR, unfolded protein response; CHOP, C/EBP homologous protein (also known as DDIT3); TRADD, TNF receptor-associated death domain; FADD, Fas-associated death domain; DISC, death-inducing signaling complex.

proteins, further amplifying Cyt c release and reinforcing the apoptotic cascade (25).

4. Summary of mechanistic analysis

Mechanism of apoptosis induced by obesity. Obesity is strongly associated with the development of various diseases, particularly through its effect on apoptosis, which has been extensively studied. In individuals with obesity, the prevalence of apoptotic cells in the cardiac tissue is higher than that in those with normal weight, which correlates with obesity-induced cardiac remodeling and dysfunction (26). Obesity also contributes to pancreatic β-cell failure, primarily due to increased apoptosis. In addition, the obesity-induced apoptosis of ovarian granulosa cells may affect fertility. Thus, obesity-induced apoptosis is a result of metabolic dysregulation and is a key mechanism in disease pathogenesis (27). The multifactorial mechanisms driving obesity-related apoptosis involve oxidative stress, inflammation, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, lipotoxicity, cytokine signaling, and death receptor activation (Table I).

Impact of obesity on the PI3K/AKT pathway. Obesity disrupts PI3K/AKT signaling through insulin resistance, chronic inflammation, and lipotoxicity. It increases the serine phosphorylation of insulin receptor substrates (IRS), inhibits tyrosine phosphorylation, blocks PI3K p85 binding, and impairs PI3K activation. Serine 307 phosphorylation of

Table II. Structures of active components of Traditional Chinese medicine and their effects on the PI3K/AKT pathway and apoptosis.

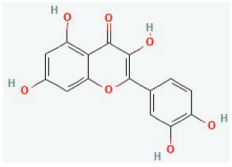
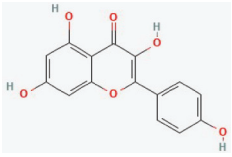
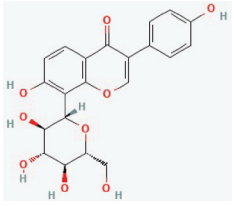
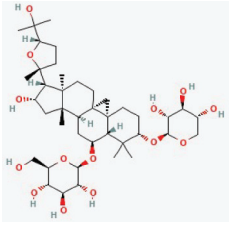
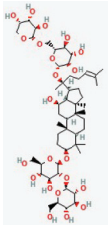
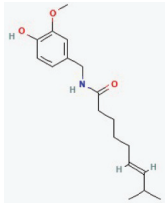
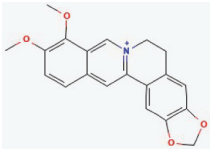
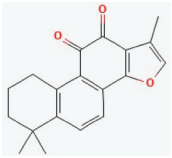
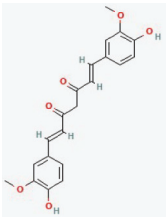
Compound	Molecular formula	2D Structure	Mechanism of action
Quercetin	$C_{15}H_{10}O_7$		Inhibits AKT phosphorylation via the PI3K/AKT axis, downregulates Bcl-2, and upregulates Bax and caspase-3,facilitating apoptosis in cancer cells (60). Regulates the PI3K/AKT pathway to boost insulin sensitivity (61) and mediates anti-inflammatory effects through PI3K/AKT/NF-κB and STAT3 signaling (62).
Kaempferol	$C_{15}H_{10}O_6$		Modulates insulin signaling via the PI3K/AKT pathway, promoting cancer cell apoptosis by inhibiting AKT activation and enhancing caspase family activity (63). Commonly used in the treatment of cardiovascular diseases and cancers (64).
Puerarin	$C_{21}H_{20}O_9$		Enhances insulin sensitivity via the PI3K/AKT pathway and induces apoptosis by increasing caspase activity and downregulating Bcl-2 expression (65). Commonly used in the treatment of metabolic disorders.
Astragaloside IV	$C_{41}H_{68}O_{14}$		Regulates lipid metabolism and improves insulin resistance via the PI3K/AKT pathway. Induces apoptosis by downregulating Bcl-2 expression (66). Commonly used in the treatment of obesity.
Ginsenoside Rb2	$C_{53}H_{90}O_{22}$		Modulates caspase activity via the PI3K/AKT pathway, influencing apoptosis (37). Commonly studied for antidiabetic and anti-aging effects.
Capsaicin	$C_{18}H_{27}NO_3$		Modulates caspase family activity via the TRPV1/PI3K/AKT pathway, inducing apoptosis. Commonly used for anti-inflammatory and anticancer therapies (67).
Berberine	$C_{20}H_{18}NO_4^+$		Enhances insulin sensitivity via the PI3K/AKT signaling pathway, alleviating metabolic disorders (68) and reducing adipose tissue inflammation (69).

Table II. Continued.

Compound	Molecular formula	2D Structure	Mechanism of action
Tanshinone IIA	$C_{19}H_{18}O_3$		Promotes apoptosis by inhibiting the PI3K/AKT signaling pathway and activating caspase-3 and caspase-9 (70).
Curcumin	$C_{21}H_{20}O_6$		Modulates anti-inflammatory effects and protects pancreatic function via the PI3K/AKT pathway (71). Promotes apoptosis by increasing Bax and caspase activity and inhibiting Bcl-2 expression (72).

PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; Bad, Bcl-2-associated death promoter; caspase-9, cysteinyl aspartate specific protease 9; caspase-3, cysteinyl aspartate specific protease 3.

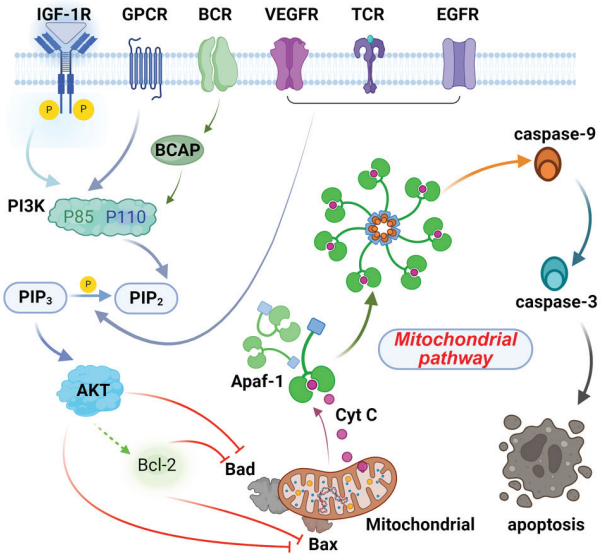


Figure 1. Mechanism of apoptosis regulation in the mitochondrial pathway by PI3K/AKT. IGF-1R, insulin-like growth factor 1 receptor; GPCR, G-protein coupled receptor; BCR, B-cell receptor; VEGFR, vascular endothelial growth factor receptor; TCR, T-cell receptor; EGFR, epidermal growth factor receptor; IRS-1, insulin receptor substrate 1; PI3K, phosphoinositide 3-kinase; PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol (3,4,5)-triphosphate; AKT, protein kinase B; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; Bad, Bcl-2-associated death promoter; Cyt c, cytochrome *c*, Apaf-1, apoptotic protease activating factor 1; caspase-9, cysteinyl aspartate specific protease 9; caspase-3, cysteinyl aspartate specific protease 3. (Created in BioRender. Li, J. (2024) https://BioRender.com/y00e363).

IRS-1 is a known marker (28) of insulin resistance. Obesity is often accompanied by chronic low-grade inflammation, characterized by elevated pro-inflammatory cytokines, such as TNF-α and IL-6, intensifying local inflammation and impairing systemic metabolic homeostasis. These cytokines activate signaling pathways, including the mitogen-activated protein kinase (MAPK) and Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathways, which can indirectly modulate the PI3K/AKT cascade. Furthermore, they upregulate suppressors of cytokine signaling (SOCS), which bind to IRS, promote IRS degradation, weaken insulin signaling, and ultimately drive metabolic dysfunction. Additionally, high free fatty acids (FFAs) and ceramides induce lipotoxicity: FFAs activate Toll-like receptors (TLRs), aggravating inflammation and insulin resistance, while ceramides inhibit AKT. Moreover, in obesity, adipose tissue secretes various adipokines, such as adiponectin and leptin, which modulate PI3K/AKT pathway activity and influence cellular insulin sensitivity (29). Finally, obesity upregulates microRNAs, such as miR-221, which suppress PI3K and increase insulin resistance (30).

These aforementioned pathways modulate the PI3K/AKT signaling cascade through interactions with cell surface receptors, principally engaging receptor tyrosine kinases (RTKs), TLRs, and B-cell antigen receptors (BCRs). RTKs (31), including epidermal growth factor receptors (EGFRs), vascular endothelial growth factor receptors (VEGFRs), and fibroblast growth factor receptors (FGFRs), are activated by ligands such as growth factors, cytokines, and hormones. The BCR is essential for B cell development, activation, and differentiation, and activates downstream pathways through B-cell receptor-associated protein (BCAP). Additionally, G-protein-coupled receptors (GPCRs), the largest family of cell surface receptors, activate specific signaling cascades by recognizing and responding to a wide variety of ligands (32).

Flavonoids, including quercetin (33), kaempferol (34), and puerarin (35); terpenoids, such as astragaloside IV (36) and ginsenoside Rb2 (37); and alkaloids, such as capsaicin (38) and berberine (39), regulate glucose and lipid metabolism, facilitate weight loss, and exert anti-inflammatory effects by modulating the PI3K/AKT signaling pathway (Table II). Glinides, a class of drugs that are frequently used in endocrinology, enhance insulin secretion and ameliorate insulin resistance by activating the PI3K/AKT pathway (40). Buparlisib, which is used

to treat cancer, functions as a pan-PI3K inhibitor and improves obesity-related metabolic disorders (41).

PI3K/AKT pathway mediates the mitochondrial pathway. The PI3K/AKT pathway is a critical signaling cascade that regulates mitochondrial apoptosis by modulating the expression of various proteins, including members of the Bcl-2, Bax, Bad, and caspase families (Fig. 1).

AKT regulates mitochondrial membrane permeability by influencing the Bcl-2 family proteins and Bad. It enhances the anti-apoptotic functions of the Bcl-2 family members, such as Bcl-2 and Bcl-xL, through phosphorylation (42). At the same time, AKT inhibits the pro-apoptotic activity of proteins such as Bax and Bak, preventing their ability to form membrane pores. This reduces the release of mitochondrial apoptotic signals such as Cyt c and diminishes apoptotic body formation. Additionally, AKT phosphorylates Bad, facilitating its binding to 14-3-3 proteins, which reduces competition with Bcl-2/Bcl-xL, further stabilizing the mitochondrial membrane and reinforcing its anti-apoptotic function. Furthermore, AKT activates mTORC1, thereby improving the cellular energy supply. Mitochondrial function is preserved by upregulating antioxidant enzymes such as SOD2, thereby reducing oxidative stress-induced mitochondrial damage (43).

Research has demonstrated that the activation of the PI3K/AKT pathway effectively inhibits apoptosis and promotes cell growth and proliferation. In numerous types of cancer, the aberrant activation of this pathway enables tumor cells to bypass normal apoptotic mechanisms, facilitating sustained tumor growth and metastasis. Research has confirmed that astragaloside IV (44), tanshinone IIA (15), and curcumin (45) modulate mitochondrial apoptosis by regulating the PI3K/AKT pathway. Benazepril, a commonly prescribed antihypertensive agent used for cardiovascular diseases, indirectly alleviates PI3K/AKT pathway dysregulation and mitochondrial dysfunction by lowering blood pressure and improving cardiac function (46). Gefitinib, an EGFR inhibitor, promotes apoptosis in cancer cells by downregulating the PI3K/AKT signaling cascade (47). Additionally, MK-2206, a selective AKT inhibitor, directly induces apoptosis in cells (48).

5. Conclusion and outlook

The present review summarized various mechanisms underlying obesity-induced apoptosis, focusing on the role of the PI3K/Akt-mediated mitochondrial pathway. Analysis of drugs and natural compounds that may act on this pathway revealed its bidirectional regulatory function in maintaining cellular survival and metabolic homeostasis; it promotes cell growth and survival under normal conditions but becomes dysregulated under oxidative stress and inflammatory conditions, leading to the initiation of apoptosis. This highlights key directions for future research: First, to investigate the interactions between the PI3K/Akt pathway and other cell death pathways, and second, to develop small-molecule drugs or biologics targeting this pathway to improve clinical efficacy. Additionally, the influence of genetic, environmental, and lifestyle factors on the PI3K/Akt signaling pathway could provide deeper insights into the prevention and reversal of obesity and its metabolic complications.

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Availability of data and materials

Not applicable.

Authors' contributions

The study was conceived and designed by JL. The original draft of the manuscript was written by JL, MS, MT and XS. The literature review was conducted by KZ and CL. The design of the tables was performed by TM. The manuscript was reviewed and edited by JL and LD. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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