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Review

Targeting PI3K/AKT signaling pathway in obesity

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ABSTRACT

Obesity is a disorder with an increasing prevalence, which impairs the life quality of patients and intensifies societal health care costs. The development of safe and innovative prevention strategies and therapeutic approaches is thus of great importance. The complex pathophysiology of obesity involves multiple signaling pathways that influence energy metabolism in different tissues. The phosphatidylinositol 3-kinases (PI3K)/protein kinase B (AKT) pathway is critical for the metabolic homeostasis and its function in insulin-sensitive tissues is described in the context of health, obesity and obesity-related complications. The PI3K family participates in the regulation of diverse physiological processes including but not limited to cell growth, survival, differentiation, autophagy, chemotaxis, and metabolism depending on the cellular context. AKT is downstream of PI3K in the insulin signaling pathway, and promotes multiple cellular processes by targeting a plethora of regulatory proteins that control glucose and lipid metabolism. Natural products are essential for prevention and treatment of many human diseases, including obesity. Anti-obesity natural compounds effect multiple pathophysiological mechanisms involved in obesity development. Numerous recent preclinical studies reveal the advances in using plant secondary metabolites to target the PI3K/AKT signaling pathway for obesity management. In this paper the druggability of PI3K as a target for compounds with anti-obesity potential is evaluated. Perspectives on the strategies and limitations for clinical implementation of obesity management using natural compounds modulating the PI3K/AKT pathway are suggested.

1. Introduction

Natural products are a vital component of the prevention and treatment of human diseases. Medicinal plants have been used for centuries as a source of potent bioactive compounds that target specific pathologies. Many studies have highlighted the ability of both plant extracts [1–3], or specific secondary metabolites [4–7] to manipulate the pathophysiological mechanisms involved in obesity development. The potential of natural compounds in obesity management by modulation of different molecular pathways has been previously reviewed in detail [8].

Obesity is a worsening health problem that co-locates with non-communicable diseases such as type 2 diabetes (T2D), metabolic syndrome, cardiovascular disease, non-alcoholic fatty liver disease

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(NAFLD), among others. The excessive increase of fat tissue is a result from both abnormal fat cell lipid accumulation (adipocyte hypertrophy) and development of new adipocytes by commitment of their precursors, known as hyperplasia [9,10]. Comorbidities that accompany obesity worsen the quality of life of patients [11], corresponding with an increase in the health care costs proportionally with body-mass index [12,13]. It was recently reported that if the present tendency in obesity and overweight prevalence does not change, the approximate economic costs will grow to 3.29% of global gross domestic product [14]. Collectively, these considerable socio-economic burdens to the world's population related to therapy of the late and irreversible consequences of obesity has drawn the attention to exploration of innovative and safe prevention and early interventions in the management of obesity [15].

The phosphatidylinositol 3-kinases (PI3K) family comprises three classes (I, II and III) of lipid kinases that control the synthesis of phosphatidylinositol (PI) second messengers PI(3)P, PI(3,4)P_2 and PI(3,4,5)P_3. The PI lipids participate in the regulation of diverse physiological processes including but not limited to cell growth, survival, differentiation, autophagy, chemotaxis, and metabolism depending on the cellular context [16–18]. Among the PI3K classes, the kinases of class I are of utmost importance for the cellular homeostasis and regulation. Moreover, class I PI3K function is associated with multiple human pathologies including certain types of cancer (such as breast cancer, lymphoma, glioblastoma, *i.a.*), *PI3KCA*-related overgrowth syndromes (PROS) and metabolic dysregulations [16,19,20]. As an obligated heterodimer, PI3K is composed of both catalytic and regulatory subunit which control the binding, activation and localization of the latter [21]. For the class I PI3K the following catalytic (p110α, p110β, p110δ, and p110γ) and regulatory (p85α, p55α, p50α, p85β, p55γ, p101, p84, p87) subunits have been described [22]. The members of class I PI3K are activated by tyrosine kinases (such as the insulin receptor) or G protein-coupled receptors to generate PIP_3 which further activate downstream effector such as protein kinase B (AKT), the Tec family and the Rho family GTPases. Localization of the p110γ and p110δ isoforms is primarily restricted to immune cells [23], whereas p110α and p110β are ubiquitous – though they also exhibit isoform-specific cell-type- and context-dependent requirements [22,24]. Among class I PI3K isoforms p110α is the primary insulin responsive kinase in adipocytes and myotubes [17,25]. Simultaneously, the class I PI3Ks are the most exhaustedly investigated PI3Ks as drug targets in respect to metabolic regulation [17,24,26,27] and so the current review PI3K will refer to class I, unless stated otherwise.

Following the PI3K in the insulin signaling pathway is the AKT family which is composed of three isoforms differing in their intracellular and tissue-specific abundance. The AKT2 isoform is characteristic for insulin-sensitive tissues, such as muscle, adipose and hepatic tissues. The third isoform AKT3 is expressed in the nervous system [28] also in the adult pancreas, heart, and kidney [29], while AKT1 appeared ubiquitously expressed [28].

The present review attempts to critically discuss the literature on the modulation of the PI3K/AKT signaling pathway to target obesity and its related complications published over the period of past 10 years. The following keyword combinations were used to retrieve the relevant articles from scientific databases: "PI3K", "AKT", "obesity", "diabetes", and "natural compound". The searched databases were Scopus, PubMed and ClinicalTrials.gov. Additional articles were found by tracking citations from the selected publications or by directly exploring the journals' website. The following inclusion criteria were used in the selection of articles: (i) articles that investigated the modulation of PI3K/AKT signaling by natural compounds using *in vitro* and *in vivo* obesity or obesity-related disease models or obese human subjects; (ii) articles written in English; (iii) published after 2012.

Advances in modulation of the PI3K/AKT signaling pathway that target obesity management is the main objective of this review. The PI3K/AKT pathway function in insulin-sensitive tissues is described in health and in the context of obesity and obesity-related complications. Evaluation of translational studies that involve natural compounds influencing the PI3K/AKT signaling is provided. Moreover, druggability of PI3K as a target against obesity is discussed. Further, perspectives on the strategies for clinical implementation of natural compounds that modulate the PI3K/AKT pathway to manage obesity are suggested.

2. Distinct function of the PI3K/AKT signaling pathway in different organs and systems with focus on insulin-sensitive metabolic tissues

Insulin is a peptide hormone, responsible for energy deposition, metabolism and growth. Increased glucose levels in the circulation stimulate insulin release from the β-cells of the pancreas. Binding of insulin to its receptor is followed by phosphorylation of the insulin receptor substrate (IRS). This triggers a cascade of reactions leading to the activation of the PI3K/AKT and Ras/mitogen activated protein kinase (MAPK) signaling pathways [30]. Downstream signals of PI3K are mediated by multiple serine/threonine (Ser/Thr) kinases, including phosphoinositide-dependent protein kinase 1 (PDK1), AKT, mammalian target of rapamycin complex (mTORC), protein kinase C (PKC), ribosomal protein S6 kinase (S6K), AKT substrate of 160 kDa (AS160) and glycogen synthase kinase 3 (GSK3), which regulate the activity of various transcriptional factors, such as Forkhead box protein O1 (FOXO1), peroxisome proliferator-activated receptors (PPARs), PPARγ coactivator-1 alpha (PGC1α), and sterol regulatory element-binding proteins (SREBPs). These promote the metabolic actions of insulin on glucose, lipid, and mitochondrial metabolism, as well as effects on cell proliferation, differentiation, growth and apoptosis [30–37].

Summary of the insulin action mediated downstream through the PI3K/AKT signaling pathway activation in different tissues and organs is depicted in Fig. 1. The main insulin-responsive organs include the liver, muscle, and adipose tissue, but considering that insulin receptors are ubiquitously expressed, we cannot omit the importance of its effect in other organs and systems. Therefore, the role of insulin signaling in the brain, pancreas and vasculature is briefly commented as well.

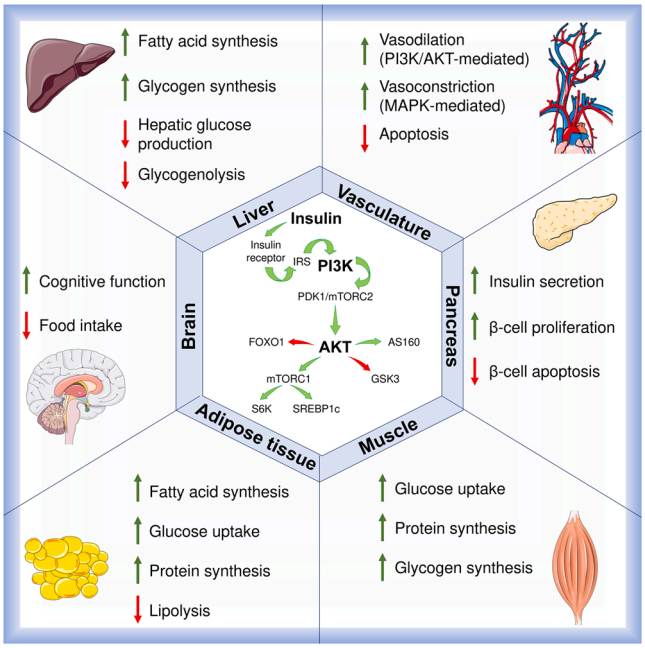

Fig. 1. Summary of the insulin-dependent activation of the PI3K/AKT signaling pathway and the induced effects in the main insulin-responsive tissues and organs. Color coding: green arrow - activation; red arrow - inhibition.

2.1. Role of PI3K/AKT in adipose tissue

Adipose tissue is a structurally heterogeneous endocrine organ that consists of fat cells (adipocytes) and their precursors (preadipocytes) [38], as well as fibroblasts, endothelial cells, vascular cells [10], resident immune cells (predominantly macrophages) [39], and neuronal cells [40]. These different cell types are essential for the physiological role of the adipose tissue, but they often interact in the pathophysiological complications of obesity. Functionally, the adipose tissue could be classified to white adipose tissue (WAT) being mainly responsible for storing energy as triglycerides, while beige and brown adipose tissues (BAT) burn energy through their high rates of mitochondrial respiration due to the abundant expression of uncoupling protein 1 (UCP1). Indeed, insulin is an important regulator of brown and white adipogenesis and adipocyte survival. Moreover, it promotes energy storage by inhibiting lipolysis and elevating glucose uptake and its conversion into lipids. Inversely, when caloric supply is limited (*e.g.*, during fasting), lower circulating insulin level leads to disinhibition of lipolysis and mobilization of lipids to meet energy demand. Thus, insulin sensitivity of the adipose tissue plays a critical role in normal metabolic homeostasis [30].

Upon binding to its receptor on the adipocyte surface, insulin stimulates glucose uptake, protein synthesis and lipogenesis. The adipogenic effect of insulin is mediated by PI3K/AKT signaling which, through mTORC1, upregulates PPARγ and CCAAT/enhancer-binding protein alpha (C/EBPα), the major pair of adipogenic transcription factors which orchestrate the terminal differentiation of fat cells [3,6,31]. Upon activation (in mature adipocytes), PI3K/AKT signaling enhances the glucose uptake by the glucose transporter 4 (GLUT4) membrane translocation [41,42], lipid biogenesis [43] and a decrease in lipid degradation [44]. The anti-lipolytic effect of PI3K/AKT activation in fat tissue is mediated by phosphodiesterase 3B through by a decrease in cAMP levels and thus reduced phosphorylation and inactivation of the hormone-sensitive lipase [44]. Key for the lipid metabolism downstream effectors of AKT are SREBP-1c and FOXO1 [43]. In relation to their energy-storing function, adipocytes are capable reconstructing and accumulating the fats absorbed from the food, as well as of synthetizing triglycerides from non-lipid metabolite sources, also known as *de novo* lipogenesis (DNL). Essential for DNL are fatty acid synthase (FAS) and acetyl CoA carboxylase (ACC), which are abundantly expressed in adipose tissue under the control of SREBP-1c [45].

The adipose tissue macrophages (ATMs) are essential for maintenance of adipose tissue energy homeostasis and inflammatory response [30]. In an obese state, resident ATMs shift their phenotype from anti-inflammatory (M2) to proinflammatory (M1) which aggravates the vicious cycle of the chronic low-grade inflammation during excess adiposity [8]. Reported macrophage-intrinsic PI3K signaling in a subset of ATMs protects from lipotoxicity by activating catabolic processes [46], which additionally reveals the importance of PI3K in macrophages for the maintenance of metabolic health in the adipose tissue.

Adipose tissue is not a static energy-storing organ but fulfils endocrine functions as well by releasing many biologically active factors including hormones, cytokines, extracellular matrix proteins, and growth and vasoactive factors, which are commonly termed adipokines. They affect different tissues and organs and regulate feeding behavior, inflammatory and immune response, metabolism of glucose and lipids, and blood pressure control. Therefore, there is elevated scientific interest toward adipokines for clarifying their function in normal and pathological conditions. As ubiquitously presented, the PI3K/AKT pathway acts as a messenger for the effect of some adipokines, among which are - leptin, adiponectin, vaspin, apelin, *etc.*, reviewed by Recinella et al. [47]. Thus, when secreted from the adipocytes into circulation, adipocytokines transmit information from the fat tissue to other metabolic tissues/organs. For instance, adiponectin, which maintains insulin sensitivity, binds to two types of adiponectin receptors (AdipoR1 and AdipoR2) expressed mainly in liver and skeletal muscle. Adiponectin mediates fatty acid oxidation and glucose metabolism, mainly *via* AMP-activated protein kinase (AMPK) and PPARα signaling. Furthermore, AdipoR1 signaling could also trigger the PI3K/AKT pathway in hepatocytes that affects insulin sensitivity, cell proliferation and apoptosis [48]. Another adipocytokine, visfatin, predominantly produced in visceral fat, may exerts some insulin-mimetic effects, such as enhancing glucose uptake and inhibiting hepatocyte glucose release. Visfatin was also found to have important proinflammatory and immunoregulating properties. In obese patients with or without T2D the plasma levels of visfatin appeared significantly elevated [49]. Moreover, elevated visfatin levels are associated with various obesity-related metabolic dysregulations, including cardiovascular complications through activation of p38 MAPK/PI3K/AKT signaling in human microvascular endothelial cells [50]. The C1q/tumor necrosis factor-related protein 1 (CTRP1) is an adipokine secreted by adipose tissue, which activate PI3K/AKT signaling. Increased plasma CTRP1 levels ameliorated obesity, hyperglycemia, insulin resistance, and fatty liver in HFD-fed mice and STZ-induced diabetic mice. Moreover, decrease in food intake and increase in energy expenditure were correlated with increased CTRP1 levels [51]. Irisin is an adipo-myokine secreted mainly by skeletal muscle and targeting, among others, adipose tissue. Irisin affects mitochondrial respiration and lipolysis in a time-dependent manner through the regulation of PI3K-AKT pathway. Moreover, in BAT it upregulates UCP1 and thus induces thermogenesis [52].

Taken all together, the PI3K/AKT pathway plays an important role in transmitting insulin action in adipose tissue in adipogenesis of both WAT and BAT. Activation of PI3K/AKT signaling is crucial for initiation of adipogenic transformation and adipocyte hyperplasia. Also, in fed state, insulin stimulates glucose uptake and protein synthesis, and inhibits lipolysis in the fat cells and further orchestrates DNL. These processes protect the organism from toxicity of increased concentration of glucose and free fatty acids (FFA) upon feeding. Moreover, the PI3K/AKT signaling pathway mediates the effects of some of adipokines which is essential for adequate communication between all metabolic-related organs. Thus, preservation of insulin sensitivity in the adipose tissue appears essential for systemic energy balance.

2.2. Role of PI3K/AKT in hepatic tissue

In the liver, insulin-mediated activation of the PI3K/AKT pathway restrains gluconeogenesis, glycogenolysis and stimulates lipogenesis and glycogen synthesis [53,54], as well as normal function of the hepatocyte insulin receptor is required to maintain the liver clock and associated circadian gene expression patterns [55]. The hepatic lipid storage capacity is determined through the harmonization of several processes including DNL, fatty acid uptake, triglyceride synthesis, fatty acid oxidation, and triglyceride export. As a downstream effector of insulin signaling, AKT regulates the DNL in the liver by activating SREBP-1c, through mTORC1-dependent and independent pathways, and by inhibiting AMPK. The mTORC1 functions as a key for the adaptive switch between catabolic and anabolic processes, and its tight and reciprocal regulation by AMPK and AKT counteracts NAFLD that accompanies obesity [34]. The mTORC1-dependent activation of SREBP-1c is achieved through downregulation of its inhibitor insulin induced gene 2 A (*INSIG2A*) [53,56]. Alternatively, AMPK-mediated DNL inhibition is achieved by inhibitory phosphorylation of both SREBP-1c and ACC1, which catalyzes the rate-limiting step in fatty acid synthesis by converting acetyl-CoA to malonyl-CoA [53]. Further, SREBP-1c regulates gene-encoding proteins that are attached to both cholesterol genesis and lipogenesis, such as FAS and stearoyl-coenzyme A desaturase 1 [57]. Another key PI3K/AKT-dependent pathway for lipid metabolism in the liver is PGC1α/PPARα signaling triggered by fluctuations in the feed-fast cycle. During fasting the PGC1α/PPARα complex synchronizes a set of genes involved in fatty acid transport and β-oxidation [53,56] such as the carnitine palmitoyltransferase I alpha [57].

As a key organ for the energy metabolism, the liver responds to PI3K/

AKT-mediated insulin signaling with a decrease in glycogenolysis and gluconeogenesis and elevation in the synthesis of glycogen and fatty acids.

2.3. Role of PI3K/AKT in muscle tissue

Skeletal muscle is the primary and largest site for modulating normal glucose concentrations in the postprandial state in humans. More than 80% of glucose uptake activity is mainly regulated in skeletal muscle under euglycemic hyperinsulinemic conditions [58,59]. In skeletal muscle, insulin binds to the insulin receptor, which leads to activation of PI3K and an increase in the level of intracellular PIP_3. The PIP_3 activates AKT2 at the plasma membrane, which is necessary for subsequent glucose uptake into the skeletal muscle through GLUT4 membrane translocation [59,60]. Incorporated glucose is converted to glycogen for storage or enters the glycolytic pathway where it is oxidized for energy production [61]. Increased protein synthesis upon insulin signaling in muscles is mediated *via* FOXO, mTORC1, and Rho GTPases [62].

Another crucial function of the PI3K/AKT signaling pathway in muscle tissue is insulin-mediated vasodilation which additionally assists the access of insulin to its receptors on the muscle cells surface [63]. In muscle, perivascular adipose tissue (PVAT) and vascular insulin signaling regulate muscle perfusion. After a meal, the physiological rise in plasma insulin levels induces pleiotropic effects on the muscle vasculature to facilitate its access to myocytes. Insulin delivery in skeletal muscle interstitium is the rate limiting step for insulin's metabolic actions that promote glucose disposal. In muscle microvessels, insulin induces vasoconstriction through extracellular signal-regulated kinase (ERK)-dependent endothelin-1 (ET-1) production and vasodilatation through IRS1/2- and AKT-dependent nitric oxide (NO) production. While insulin's vasodilator action predominates in normal conditions, insulin's vasoconstrictor effect is dominant in obesity and T2D, as a result of the increased ET-1 production and decreased NO production [64].

The important role of muscle tissue in maintenance of normal glucose levels is also mediated by the PI3K/AKT signaling pathway and is in close communication with the respective cellular signaling molecules within PVAT and the vasculature.

2.4. Role of PI3K/AKT in the cardiovascular system

Taking into consideration that the vascular system is a mediator of the nutrient transport across all organs and systems, the endothelial cells and vascular smooth muscle cells insulin sensitivity is hence essential. These aspects are reviewed previously in details elsewhere [65]. Since cardiovascular diseases are among the most frequently diagnosed obesity comorbidities, a summary is provided of PI3K/AKT signaling function on vascular endothelium, vascular smooth muscle cells, cardiac tissue, and also the regulatory function of the PVAT surrounding the vasculature.

The effect of insulin on blood vessels could be anti-atherogenic, mediated by the IRS1/PI3K/AKT pathway or pro-atherogenic *via* the MAPK-dependent pathways [65]. The PI3K/AKT signaling regulates the endothelial nitric oxide synthase (eNOS)/NO signaling pathway in the vascular endothelium and the cardiac tissue, which controls myocardial cell growth, cardiac hypertrophy, and heart failure [66]. Activated AKT phosphorylates eNOS to produce NO, which maintains and improves local coronary blood flow, and exerts myocardial protection. The increase in the expression of p-eNOS protein can provoke NO cardiovascular protection and reduce myocardial oxidative stress damage [67,68].

Apart from the well-described adipose depots, the PVAT surrounds all blood vessels, excluding the cerebral vasculature [64]. Although it is well known that PVAT plays a structurally supportive and connective function for the blood vessels, it also plays a critical role in vascular function and remodeling. For example, the PVAT regulates vascular inflammation *via* the secretion of pro- or anti-inflammatory adipokines. Moreover, PVAT maintains the vascular tone through releasing vessel relaxing factors, as well as vasoconstrictors. Under physiological conditions, the principal function of PVAT is to prevent vasoconstriction and may be dependent on PVAT mass. In the setting of obesity with or without established hypertension, the secretory profile of PVAT shifts from anti-contractility to contractility which aggravates the obesity-related cardiovascular complications [69].

Understanding the signaling interplay between the PVAT and vasculature would potentially reveal new therapeutic targets to alleviate the cardiovascular complications related to obesity.

2.5. Role of PI3K/AKT in the pancreas

The endocrine pancreas consists of five types of endocrine cells, among which α-, and β-cells secrete glucagon and insulin, respectively, in accordance with blood glucose levels. The other islet cell types, γ-, δ- and ε-cells, release pancreatic polypeptide, somatostatin and ghrelin, respectively, which contribute to the regulation of α- and β-cell secretory activity [70,71]. The PI3K/AKT pathway not only mediates the pleiotropic effects of insulin in the regulation of metabolic processes, but it also maintains β-cell function and growth [70]. Distinctly complex interactions between the aforementioned islet endocrine cell-types are crucial for blood glucose homeostasis maintenance, *e.g.*, glucagon or glucagon-like peptide 1 directly stimulate insulin secretion, while somatostatin directly inhibits insulin and glucagon secretion. Also, insulin indirectly inhibits glucagon release by promoting somatostatin secretion. Consequently, disruption of these pathways controlling endocrine cell-type identity and hormone production apparently impacts their function and undoubtedly is implicated in development of metabolic diseases [70].

Insulin signaling requires IRS1-mediated activation of the PI3K/AKT pathway in the pancreatic β-cells [72]. Correspondingly, mice lacking IRS show pancreatic insulin resistance (IR) and β-cell failure, resulting in peripheral IR and T2D [64]. In addition, FOXO1 is recognized as a small inhibitor of pancreatic and duodenal homeobox factor 1 (Pdx1) and critical for the early development of the pancreas and the differentiation of late-stage β-cells [72]. Indeed, Pdx1, a downstream effector of PI3K/AKT signaling, participates in the maintenance of the secretory function of β-cells by regulating the expression of insulin-related genes, such as GLUT2 which is critical for glucose sensing in β-cells [73]. Apart from insulin secretion, insulin-mediated PI3K/AKT signaling in the pancreas is crucial for its integrity and normal functioning.

2.6. Role of PI3K/AKT in the metabolic regulation in the brain

The maintenance of euglycemia is critical for brain function as glucose is its main energy source. Despite the ability of the brain to uptake glucose independently of insulin, it is reported that insulin receptors are highly expressed in brain regions related to the regulation of cognition and feeding behavior [74]. The control of hypoglycemia is coordinated by a distributed glucose sensing system which comprises hypoglycemia-activated neurons, secreting the counterregulatory hormones glucagon, epinephrine, norepinephrine, corticosterone and growth hormones. Moreover, hypoglycemia also triggers the appetite for sugar-containing food in order to restore the body glucose stores. The secretion of counterregulatory hormones is mainly triggered by a fall in blood glucose concentration but is also under the regulatory influence of other metabolic signals. For instance, activation by hypoglycemia of the parabrachial neurons, which stimulate glucagon secretion is markedly decreased by leptin. Thus, there is evidence that the overall counterregulatory response, although directed by the glucose levels, is also under the control of signals of the whole-body energy status [75].

The adipose hormone leptin critically regulates body weight and metabolism through decrease in food intake and acceleration in energy expenditure, thus disruption of leptin/leptin receptor (LepR) signaling

results in morbid obesity and severe metabolic syndromes. The LepRs are widely expressed in the hypothalamus, including the preoptic area, lateral hypothalamus, dorsomedial hypothalamus, ventromedial hypothalamus, and arcuate nucleus (ARC). In the hypothalamic ARC, the leptin-sensitive anorexigenic proopiomelanocortin (POMC) and orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons coordinately regulate food intake and energy expenditure, as well as peripheral tissue glucose homeostasis and energy partitioning through insulin, leptin and nutrients [26]. Leptin exerts its anti-obesity action by activating LepR signaling in the hypothalamic energy balance circuits, however it remains elusive whether leptin regulates energy expenditure *vs.* energy intake by similar or discrete pathways. Leptin signaling is mediated by the tyrosine kinase Janus kinase 2 (JAK2) that interacts with the long-form LepRb1 [76]. This form of LepR was found to activate the JAK2/ signal transducer and activator of transcription 3 (STAT3) pathway, which in turn decreases the appetite and activates IRS1/PI3-K/AKT signaling to enhance insulin sensitivity [1]. Of note, a number of negative regulators of JAK2, *e.g.,* suppressor of cytokine signaling 3 and tyrosine-protein phosphatase non-receptor type 1 (PTP1B) have been reported to promote obesity, supporting the notion that JAK2 inhibitory molecules increase the risk from leptin resistance, obesity, and metabolic syndrome [76].

As summarized above, insulin affects not only the major insulin-sensitive tissues, but almost every cell type in the organism, mediated through the PI3K/AKT signaling cascade. Collectively, the PI3K/AKT pathway integrity is essential for the maintenance of energy balance. Thus, deep understanding of its pathophysiological role in obesity development is of critical importance and is commented in the next section.

3. The role of PI3K/AKT signaling pathway in obesity and obesity-related pathologies

Obesity is characterized by excessive accumulation of WAT that impairs major signaling pathways critical for the metabolic homeostasis including the insulin/PI3K/AKT pathway [26,36]. As discussed below, PI3K play a crucial role in the development of obesity and obesity-related metabolic disorders, either on the level of tissue inflammation or in the regulation of energy homeostasis. The clinical use of many known PI3K inhibitors (listed in Table 1) confirms the importance of PI3K/AKT signaling in the metabolic regulation as these drugs induce hyperglycemia and IR as side-effects of their anti-cancer activity (comprehensively reviewed in detail by [16,19,20].

Table 1
Selected examples of PI3K inhibitors and their clinical application.

PI3K inhibitor	Isoform selectivity	Company (clinical trial number)	Clinical application
LY294002	Non-selective	-	-
Wortmanin	Non-selective	-	-
Copanlisib	Non-selective	Bayer (NCT02728258)	Endometrial cancer, lymphoma
Alpelisib	PI3Kα	Novartis (N212526)	ER+ /HER2- advanced metastatic breast cancer
GSK2636771	PI3Kβ	GlaxoSmithKline (NCT01458067)	Solid tumors
IPI-549	PI3Kγ	Infinity (NCT03980041)	Immuno-oncology
Idelalisib	PI3Kδ	Gilead Science (N205858)	Chronic lymphocytic leukemia
Duvelisib	PI3Kδ/γ	Verastem (N211155)	Small lymphocytic lymphoma
Pictilisib	PI3Kα/β	Piramed (NCT01740336)	Breast cancer
Paxalisib	Dual pan-PI3K/mTOR	Kazia Therapeutics (NCT03522298)	Glioblastoma multiforme

Abbreviations: ER, estrogen receptor; HER, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase.

The expansion of fat stores in obesity is often associated with a low-grade inflammation, caused by the infiltration of pro-inflammatory immune cells [77–79], and elevated non-esterified fatty acids serum levels, which both contribute to the development of IR. The FFA-mediated IR involves the activation of the Toll-like receptor 4/nuclear factor kappa B (NFκB) pathway [80], while inhibition of the signaling downstream of the insulin receptor is the primary mechanism of inflammatory IR development [35,79]. The elevated oxidative stress present in obesity is disrupting the insulin receptor clustering that is another mechanism decreasing the insulin sensitivity in adipose and hepatic tissues [35]. Notably, activation of multiple Ser/Thr kinases by inflammatory or stress stimuli is likely involved in the blockade of PI3K signaling downstream the insulin receptor [81]. For example, treatment of murine adipocytes with tumor necrosis factor alpha (TNF-α) inhibits insulin signaling at the level of IRS1 [82] thereby inhibiting PI3K activity further downstream [83]. In turn, blocking of inflammatory mediators protects against IR in mouse models [37,84,85]. However, PI3K are not only crucial in mediating insulin response in adipose tissue, but are involved in recruitment of inflammatory cells as well, as PI3K are activated by cytokine and chemokine receptors in immune cells [23,86]. Early studies using pan-PI3K inhibitors reveal the role of PI3K in innate immune response by demonstrating that wortmannin or LY294002 impaired neutrophil function [87,88] and macrophage recruitment and activation [89,90]. Of note, regulation of immune cell recruitment seems to be specific to PI3Kγ, as shown in *in vitro* experiments using p100γ-deficient neutrophils and macrophages [91,92]. On a systemic level, mice lacking PI3Kγ were protected against obesity-induced inflammation and IR [93]. Further, treatment with the PI3Kγ-selective inhibitor AS-605240 improved blood glucose levels and insulin sensitivity, and reduced macrophage infiltration into the adipose tissue in leptin-deficient *ob/ob* mice [93]. Taken together, these data clearly indicate that PI3Kγ is eventually a central mediator of inflammation and IR in obesity, and thus might be a potential target for obesity therapy.

Besides in the regulation of the inflammatory response, PI3K plays an important role in the systemic energy balance. Mice with reduced PI3K signaling due to overexpression of phosphatase and tensin homolog (PTEN), show elevated energy expenditure and improved insulin sensitivity [94], and are protected from obesity and metabolic syndrome [95]. This is in line with the association of hyperactive PI3K with obesity in patients with PTEN haploinsufficiency [96]. Interestingly, the inhibition of single PI3K isoforms leads to similar metabolic effects as demonstrated in the murine models discussed below. In contrast however, myeloid-specific PTEN overexpression in mice results in impaired metabolic health, *e.g.*, development of IR and liver steatosis while PTEN depletion in the myeloid compartment improves metabolism upon high fat diet (HFD) feeding [46]. This indicates that, although PI3Ks inhibition might be a therapeutic strategy for obesity-related metabolic disease, this could also be paralleled by unpredictable effects on myeloid cells.

In line with the role of PI3Ks in insulin signaling, mice with heterozygous overexpression of an inactive PI3Kα variant were hyperinsulinemic, glucose intolerant, hyperphagic and developed obesity at a young age. However, these mice are not diabetic, as defined by hyperglycemia [24]. Surprisingly, the same group later found that long-term PI3Kα inhibition protects from age-related reduction in insulin sensitivity, glucose tolerance and fat accumulation [27]. Adipose tissue-specific PI3Kα inhibition prevents fat accumulation and preserves glucose tolerance despite the IR in mice [17]. Mechanistically, inhibition of PI3Kα seems to foster β3-adrenergic signaling, leading to increased energy expenditure *via* recruitment of thermogenic adipocytes in WAT [17].

Mice deficient for the PI3Kγ isoform are protected from obesity and had markedly improved insulin sensitivity compared to wild-type

animals upon HFD feeding [93,97]. Using transplantation models, the role of non-hematopoietic and hematopoietic cells was investigated leading to controversial results [93,97], thus adipocyte-specific mouse models are needed to further elucidate the role of immune cells and adipocytes in the context of PI3Kγ in obesity.

In line with the previous data, combined inhibition of PI3Kβ and γ isoforms leads to reduced fat mass and increased energy expenditure in mice [98]. As in PI3Kα-deficient mice [17], this was accompanied by increased adrenergic tone leading to recruitment of thermogenic adipocytes in white fat, a process referred to as "browning". Interestingly, this was dependent on the melanocortic 4 receptor signaling in the brain, which could be modulated by central delivery of PI3Kβ/γ-selective inhibitors [98].

Besides regulating energy metabolism in adipose tissue, the PI3K signaling is involved in central regulation of satiety by leptin action in the brain [99]. In this aspect, it has been shown that central administration of the PI3K inhibitor LY294003 prevents the reduction in food intake by leptin [100]. In the ARC, leptin activates PI3K in the POMC neurons, while indirectly inhibiting PI3K in the NPY/AgRP neurons [101], leading to suppression of food intake. *In vivo* studies with neuron-specific PI3K ablation have pointed to a role of PI3K in leptin-mediated feeding behavior and body weight regulation. Mice with POMC-specific depletion of PI3K regulatory subunits p85α and p85β have normal food intake and body weight but fail to suppress food intake upon acute leptin administration [99]. In line with previous reports on PTEN overexpression regulating energy expenditure, mice with selective overexpression of PTEN in leptin-expressing neurons are leaner compared to controls and are protected from getting obese on an obesogenic genetic background [102]. Interestingly, this was driven by increased energy expenditure based on WAT browning in these animals.

Taken together, inhibition of PI3K leads to a systemic increase in energy expenditure mediated by a recruitment of thermogenic adipocytes in the white fat. This renders PI3K as a promising target to pharmacologically treat obesity and obesity-related metabolic disorders. Indeed, treatment with pan-PI3K inhibitors could both prevent and treat obesity in mice and were also effective in weight loss in a primate model [103].

4. Preclinical obesity research targeting PI3K/AKT signaling pathway through natural compounds

Class I PI3K are actively involved in the metabolic regulation in both physiological and pathological processes [17,26,36]. Modulation of the PI3K/AKT signaling pathway in insulin-sensitive tissues with regards to the energy metabolism leads to diverse context-specific outcomes [18,104]. Non-selective long-term inhibition of all class I PI3K isoforms could lead to reduction of the insulin sensitivity in adipose tissue as well as in the adipose tissue, the liver and the skeletal muscles in obesity [24,27,105]. However, acute selective inhibition of PI3Kα during the early stages of adipogenic differentiation could suppress lipid accumulation and adipocyte hyperplasia at the onset of obesity [5,6,106]. Selective knock-out of the PI3Kγ isoform in mice have been reported to prevent HFD-induced obesity and to elevate insulin sensitivity compared to wild-type animals [93,97]. Additionally, long-term tissue-specific inactivation of PI3Kα in the adipose tissue depot results in predominantly beneficial metabolic effects as it correlates with enhanced β-adrenergic signaling (browning of WAT) in obesity [17,25,107]. Even though fact that the mechanistic studies on PI3K inhibition to target obesity are controversial, they provide solid indicators that fine-tuning in PI3K/AKT signaling that is tissue- and context-specific worth exploration as therapeutic approach.

The development of PI3K modulators, mainly PI3K inhibitors, has been intensified through the last decades due to the increased interest in such compounds in oncology [16,19,108]. The metabolic side-effects that have been reported upon PI3K inhibitors clinical use justify their off-label application as a precision therapy against PROS [17,19]. Accordingly, drug repurposing through rationalization in the dose regimen and personalized therapy approach of PI3K inhibitors could be exploited to manage obesity and its related complications.

Medicinal plants and bioactive phytochemicals are frequently included in obesity management as an adjunct to the conventional therapy as they promote their biological effect through multiple mechanisms [4,8]. However, the pleiotropy ascribed to many natural compounds requires mechanistic research justification prior to potential clinical implementation. Therefore, identifying the molecular targets and the involvement of major signaling pathways such as PI3K/AKT pathway in the anti-obesity effect of bioactive phytochemicals is of great importance for their translation from bench to bedside.

Ethnopharmacological data suggest that in every part of the world there are valuable medicinal plants used to alleviate and prevent metabolic dysregulations such as obesity and T2D that could be exploited as a source for potent bioactive leads [8,109,110]. The first-line antidiabetic drug metformin is a classic example as it is a derivative of the natural compound galegine isolated from *Galega officinalis* L. (Leguminosae), a plant traditionally used for the treatment of diabetes [111]. The increased research interest in natural compounds that fights against obesity has provided solid evidence that PI3K/AKT pathway modulation is involved in the anti-obesity effect of numerous plant extracts and secondary metabolites [4,7,110]. For instance, extract from *Garcinia cambogia* Roxb. and raspberry ketone that are widely consumed as food supplements against obesity induce AKT phosphorylation and subsequent inhibition of GSK3 that leaded to improvement in IR and body weight reduction in HFD-induced obesity murine model [1]. Another interesting study revealed that pomegranate flower extract inhibits adipocyte differentiation and apoptosis in 3T3-L1 cells through PI3K/AKT-dependent mechanism [2]. Treatment with *Alchemilla monticola* Opiz extract inhibits the PI3K/AKT signaling pathway during early phase adipogenic differentiation in human adipocytes [112]. Activation of the AMPK/PI3K/AKT/GSK3 signaling was found to be involved for the anti-diabetic and lipid reducing effect of *Hypericum attenuatum* Choisy extract in KK-Ay mice [113]. Similarly, fraction enriched in triterpenic acids of *Cyclocarya paliurus* (Batal.) Iljinsk. extract improved insulin sensitivity and hepatic steatosis in HFD-fed C57BL/6 J mice and HepG2 cells through activation of the PI3K/AKT signaling [114]. These studies pointed towards modulation of the PI3K/AKT pathway as one of the mechanisms for the biological activity of these natural products. However, as plant extracts consint of complex mixtures of compounds, the clarification of the exact molecular mechanisms of action or isolation of a single compound responsible for the extract`s bioactivity is often described as "looking for a needle in a haystack". Despite that impediment, contemporary "-omics" approaches (genomics, transcriptomics, proteomics and metabolomics) in combination with advanced biotechnological isolation and biosynthesis techniques are likely to accelerate the process of natural products drug discovery [115].

Here, we discuss in detail a diverse group of natural compounds from different chemical classes that have been examined as potential PI3K/AKT modulators in obesity and obesity-related disease models. Selected data from the evaluated original research papers are summarized in Table 2. Classification in regards to their chemical nature displays that flavonoids are among the most frequently identified natural compounds to modulate the PI3K/AKT signaling pathway [5,31,49,106] followed by the group of the terpenoids [58,116–118] and the alkaloids [53,60,119], *i.a.*. The chemical structures of the selected natural compounds and the mode of influence on PI3K/AKT signaling (activation/inhibition) are presented schematically in Fig. 2.

4.1. Flavonoids and flavonoid glycosides

The chemical class of flavonoids are phenolic compounds found abundantly in herbs, medicinal plants, fruits and vegetables [4]. Various dietary and health promoting effects such as anti-bacterial, anti-inflammatory, anti-adipogenic and anti-diabetic effect have been ascribed

Table 2
Summary of preclinical studies targeting PI3K/AKT signaling pathways in obesity and T2D models through natural bioactive compounds.

Compound	Model system (intervention)	Treatment (concentrations and period)	PI3K/AKT pathway modulation	Molecular target (s)	Biological effect	References
Flavonoids and flavonoid glycosides						
Amentoflavone (biflavonoid)	HepG2 hepatocytes	9.3, 13.94 and 18.59 nM for 36 h	Activation	GSK3	Improved insulin resistance, elevated glycogen synthesis and inhibited gluconeogenesis	[49]
Isoliquiritigenin (flavonoid)	3T3-L1 murine adipocytes	100 μM for 30 min	Inhibition	PTP1B	Inhibition in early phase adipogenic differentiation	[5]
Kaempferol (flavonoid)	3T3-L1 murine adipocytes	100 μM for 24 h	Activation	PI3K	Improved insulin signaling and counteracted the obesity-related inflammation induced with macrophages conditioned media	[106]
Maackiain (pterocarpan)	SGBS human adipocytes	5, 10 and 25 μM for 8 days	Inhibition	PI3K AKT	Inhibition in early phase adipogenic differentiation	[3]
Ononin (isoflavone glycoside)	SGBS human adipocytes	5, 10 and 25 μM for 8 days	Inhibition	PI3K AKT	Inhibition in early phase adipogenic differentiation	[3]
Orientin (flavonoid)	3T3-L1 murine adipocytes	10, 25 and 50 μM for 6 days	Inhibition	FOXO1	Inhibition in early phase adipogenic differentiation	[31]
Puerarin (isoflavone)	Wistar rats HepG2 hepatocytes	300 mg/kg bw for 4 weeks 10, 100 and 1000 μM for 24 h	Activation	FOXO1	Decrease in body weight, improved glucose uptake in hepatocytes and in rats with HFD/STZ-induced T2D model	[120]
	Spargue-Darwey rats HepG2 hepatocytes	0.2% of HFFD for 16 weeks 75 and 150 μM for 24 h	Activation	AMPK	Prevented HFFD-induced weight gain, improved glucose uptake in hepatocytes	[121]
Quercetin (flavonoids)	C57BL/6 J mice HepG2 hepatocytes	0.05% w/w of the HFFD for 10 weeks 10 μM alone or 5 μM in combination with EGCG for 24 h	Activation	FOXO1	Increase in GLUT4 expression and insulin sensitivity in HFFD-fed mice and PA-stimulated hepatocytes	[134]
Terpenoids and terpenoid glycosides						
Astragaloside IV (saponin)	Kunming mice HepG2 hepatocytes	25, 50 and 100 mg/kg bw for 10 weeks 12.5, 25 and 50 μM for 48 h	Activation	AMPK SIRT1 PI3K AKT	Hypoglycemic and hepatoprotective action in hepatocytes and in mice with HFSD/STZ-induced T2D model	[123]
Betulinic acid (pentacyclic triterpenoid)	SGBS human adipocytes	0.25, 0.5 and 1 μM for 8 days	Inhibition	PI3K AKT	Inhibition in early phase adipogenic differentiation	[6]
Carbenoxolone (Semi-synthetic derivative of glycyrrhizic acid)	C57BL/6 J mice	15 mg/kg bw for 12 weeks	Activation	PI3K AKT	Improved insulin resistance and decreased lipid accumulation in liver and muscle tissues of HFD-fed obese mice	[124]
Catalpol (iridoid glucoside)	C57BL/6 J mice HepG2 hepatocytes	100 and 200 mg/kg bw for 4 weeks 20, 40 and 80 μM for 24 h	Activation	AMPK GSK3 FOXO1	Improved insulin resistance and decreased lipid accumulation in glucosamine-induced hepatocytes and in mice with HFD/STZ-induced T2D model	[117]
Celastrol (pentacyclic triterpenoid)	C2C12 myotubes	10, 20, 30, 40, 50 and 60 nM for 16 h	Activation	p85 PI3K p-Ser473-AKT	Improved insulin sensitivity, mitochondrial activity and glucose uptake in palmitate-stimulated myotubes	[58]
	Spargue-Darwey rats	1 and 3 mg/kg bw for 8 weeks	Activation	AMPK SIRT1	Improved inflammatory markers, mitochondrial activity and glucose uptake in HFD-fed obese rats	[126]
Ginsenoside Rb2 (tetracyclic triterpenoid)	C57BL/6 J mice 3T3-L1 murine adipocytes	40 mg/kg bw for 10 days 25 μM for 24 h	Activation	p85 PI3K p-Ser473-AKT	Improved glucose utilization and insulin sensitivity in TNF-α-treated adipocytes and decreased body weight, lipid accumulation and size of WAT in mice with DIO	[116]
Glycyrrhetinic acid (pentacyclic triterpenoid)	Kunming mice HepG2 hepatocytes	25, 50 and 100 mg/kg bw for 2 weeks 0.1, 1, 5, 10–20 μM for 6 h	Activation	p-Ser307-IRS1 p-Ser473-AKT GSK3	Improved insulin sensitivity, reduced hyperglycemia	[118]
Alkaloids						
Capsaicin (alkaloid)	HepG2 hepatocytes	200 μM for 24 h	Inhibition	AMPK p-Ser473-AKT	Decreased lipid content and *de novo* lipogenesis while stimulated β-oxidation through activation of AMPK and inhibition on AKT/mTORC1/S6K pathway	[53]
Nigelladine A,B and C (alkaloids)	L6 myoblasts	12.5 μM for 1 h	Activation	AKT GSK3 PTP1B	Improved glucose utilization	[60]
Oxyberberine (alakloid)	Sprague-Dawley rats	25, 50 and 100 mg/kg bw for 4 weeks	Activation	AMPK GSK3 NRF2	Improved insulin sensitivity, reduction in body and induced hypoglycemic effect in rats with STZ-induced T2D model	[119]
	Sprague-Dawley rats	25, 50 and 100 mg/kg bw for 8 weeks	Activation	AMPK	Improved lipid and glucose serum profile, restored the insulin sensitivity in liver and WAT and reduced WAT expansion in rats with HFD-induced NAFLD model	[131]
Other chemical classes						

(*continued on next page*)

Table 2 (*continued*)

Compound	Model system (intervention)	Treatment (concentrations and period)	PI3K/AKT pathway modulation	Molecular target (s)	Biological effect	References
Epigallocatechin gallate (polyphenol)	IRC mice L6 myoblasts	0.75, 7.5 and 75 mg/kg bw for 1 h 10, 100 and 1000 nM for 15 min	Activation	PI3K AMPK	Activate GLUT4 translocation and increase glucose utilization in L6 myotubes	[62]
	C57BL/6 J mice HepG2 hepatocytes	0.05% w/w of the HFFD for 10 weeks 10 μM alone or 5 μM in combination with quercetin for 24 h	Activation	FOXO1	Increase in GLUT4 expression and insulin sensitivity in HFFD-fed mice and PA-stimulated hepatocytes	[134]
	3T3-L1 murine adipocytes	10, 50 and 100 μM for 8 days	Inhibition	IRS1 PI3K	Inhibition of adipogenesis during adipocyte differentiation	[135]
Pterostilbene (stilbenoid, phenylpropanoid)	Spargue-Darwey rats	20, 40 and 80 mg/kg bw for 10 weeks	Activation	PI3K p-Ser473-AKT	Hypoglycemic effect in rats with STZ-induced T2D model	[136]
Resveratrol (stilbenoid, phenylpropanoid)	*ob/ob* mice HK-2 kidney cells	10 mg/kg bw for 10 weeks 10 μM for 12 h	Activation	FOXO1	Restrained dapagliflozin-induced renal gluconeogenesis in HK-2 cells and in HFD-fed *ob/ob* mice	[137]

Abbreviations: AKT, protein kinase B; AMPK, AMP-activated protein kinase; bw, body weight; DIO, diet-induced obesity; FOXO1, Forkhead box protein O1; GLUT4, glucose transporter 4; GSK3, glycogen synthase kinase 3; HFD, high fat diet; HFFD, high fat fructose diet; HFSD, high fat sucrose diet; IRS1, Insulin receptor substrate 1; mTORC1, mammalian target of rapamycin complex 1; NAFLD, non-alcoholic fatty liver disease; NRF2, nuclear factor erythroid 2-related factor 2; p85 PI3K, PI3K regulatory subunit p85; p-Ser307-IRS1, IRS1 phosphorylated at serine 307; p-Ser473-AKT, AKT phosphorylated at serine 472; PA, palmitic acid; PI3K, phosphatidylinositol 3-kinases; PTP1B, tyrosine-protein phosphatase non-receptor type 1; S6K, ribosomal protein S6 kinase; SIRT1; sirtuin 1; STZ, streptozotocin; T2D, type 2 diabetes; TNF-α, tumor necrosis factor alpha; WAT, white adipose tissue.

to flavonoids like apigenin, kaempferol, and quercetin, among others [3,6,106]. Modulation of energy metabolism in insulin-sensitive tissues by flavonoid compounds is mediated at least partly through the PI3K/AKT signaling pathway [4].

The early stages of obesity involve adipocyte hyperplasia, thus modulation in adipogenic transformation is a key approach in obesity management at this point [3,25]. The licorice (*Glycyrrhiza glabra* L.) root is widely exploited in the food industry as a natural flavor and sweetener. Its constituent isoliquiritigenin is an abundant dietary flavonoid that inhibits lipid accumulation and adipogenic differentiation in murine adipocytes. The molecular mechanism behind the anti-adipogenic effect of isoliquiritigenin is a suppression of PTP1B oxidation, hence, increase in PTP1B activity and subsequent inhibition of IRS1/PI3K/AKT signaling [5]. During the early phase of adipogenic differentiation activation of the PI3K/AKT signaling pathway induce suppression of FOXO1 binding to PPARγ and thus stimulate the preadipocyte maturation. Treatment with orientin appeared to obstruct this process by inhibiting the PI3K/AKT pathway through enhancing FOXO1 activity during the differentiation of 3T3-L1 cells [31]. The extract from *Ononis spinosa* L. roots is used ethnopharmacologically to aid weight reduction [3]. Phytochemical characterization of *O. spinosa* extract through nuclear magnetic resonance-based metabolomics resulted in selection of two flavonoid derivatives: maackiain, a pterocarpan and ononin - an isoflavone glycoside; as potentially active anti-obesity compounds. Treatment with maackiain and ononin inhibited the adipogenic differentiation of human SGBS cells by suppressing the PI3K/AKT signaling pathway. The *in silico* analysis suggested the PI3K p85 subunit as the most probable direct target for their molecular action that was further confirmed at a protein expression level [3].

Hepatic IR that accompanies obesity is characterized with dysregulated PI3K/AKT signaling. The treatment of HepG2 cells with amentoflavone improves IR through suppression of the GSK3 and re-activation of the PI3K/AKT pathway [49]. Similarly, the natural isoflavone puerarin alleviates hepatic IR in HepG2 cells [120] and in high fat and fructose diet (HFFD)-fed rats [121] by re-activating the PI3K/AKT pathway through FOXO1 phosphorylation and AMPK induction.

Chronic low-grade inflammation is a common pathological feature of obesity. In an experimental model of obesity-related inflammation and IR coffee silverskin and coffee husk aqueous extracts were found to stimulate the GLUT4 translocation *via* modulation of the insulin/PI3K/AKT signaling pathway. Among the evaluated bioactive secondary metabolites from the two coffee-based extracts, kaempferol was determined as the most potent in regards to the PI3K/AKT pathway activation in murine 3T3-L1 adipocytes [106].

Collectively, the flavonoid compounds modulate the PI3K/AKT pathway in both positive and negative manner that is time-, tissue- and context-dependent. The aforementioned studies support the statement that during the early stage of obesity inhibition PI3K/AKT pathway activity is beneficial as it leads to adipocyte hyperplasia suppression. Conversely, in the presence of obesity-related complications such as IR or chronic inflammation activation of the PI3K/AKT signaling pathway is required to alleviate obesity-induced consequences.

4.2. Terpenoids and terpenoid glycosides

The terpenoids are one of the largest class of plant-derived secondary metabolites that are biosynthesized mainly through the mevalonic acid pathway by condensation of isoprene units in a complex reaction sequence, catalyzed by geranyl diphosphate synthase, farnesyl diphosphate synthase and geranylgeranyl diphosphate synthase [111,122]. This class of natural compounds is characterized with great phytochemical diversity and substantial pharmacological activity, including anti-inflammatory, cardioprotective and anti-diabetic as recently reviewed by Mohammed et al. [111].

For instance, astragaloside IV, a bioactive triterpene saponin found in the dried root of *Astragalus mongholicus* Bunge, is reported to induce hypoglycemic effect in T2D. Gong et al. [123] reported that the anti-diabetic effect of astragaloside IV is mediated *via* re-activation of the suppressed AMPK/sirtuin 1 (SIRT1) and PI3K/AKT signaling pathway in hepatocytes both *in vivo* and *in vitro*. Upregulation in the protein abundance of SIRT1 that induces the phosphorylation of AKT has been identified as the main mechanism of astragaloside IV bioactivity [123]. Catalpol is a terpenoid isolated from the root of *Rehmannia glutinosa* (Gaertn.) DC. that was found to activate the PI3K/AKT signaling through multiple molecular mechanisms in liver tissue of diabetic mice and glucosamine-stimulated HepG2 cells. The bioactive iridoid glucoside stimulates the AMPK activity by increasing its phosphorylation in hepatocytes that leads to downregulation of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), hence, enhanced glycogen synthesis and reduced

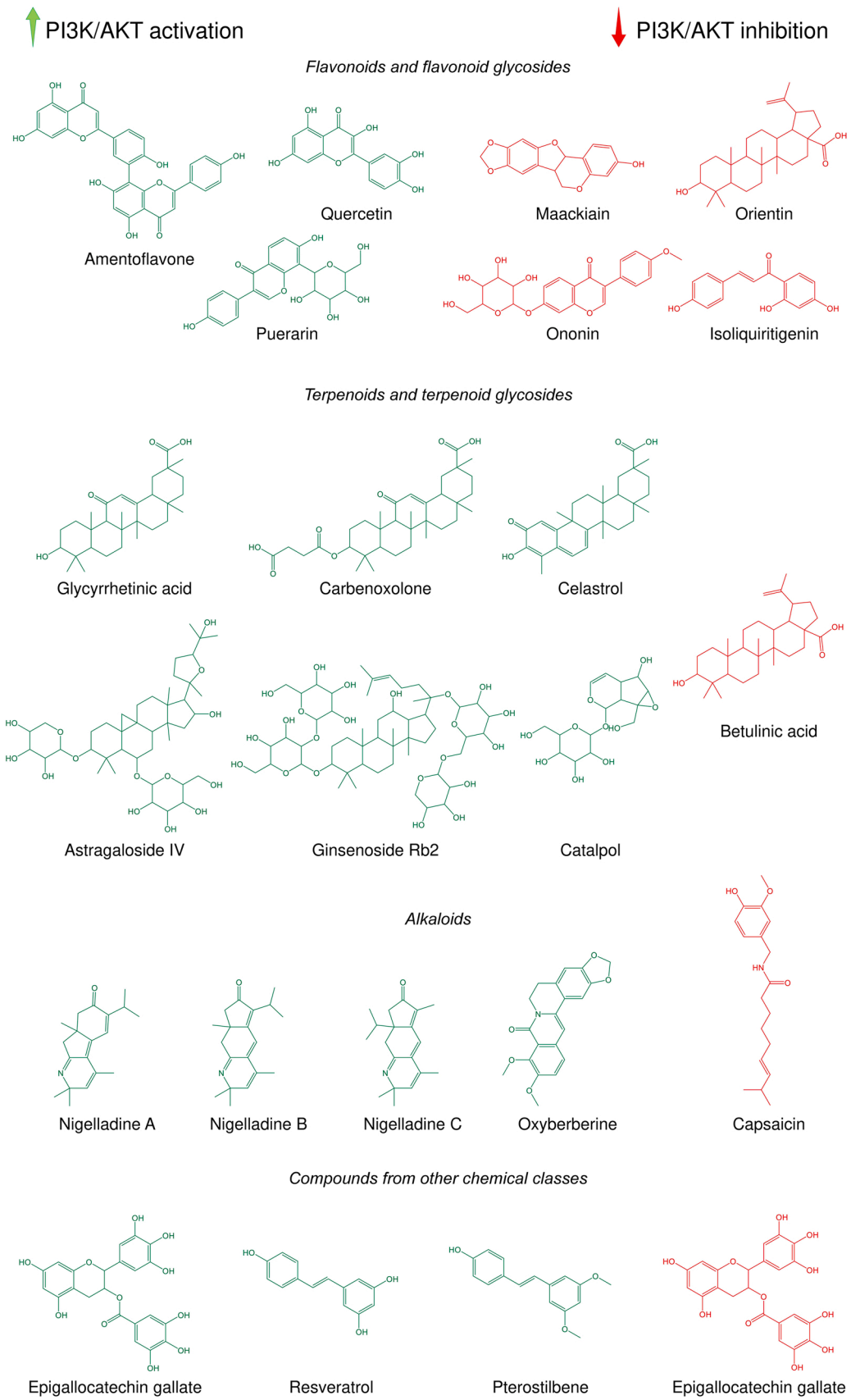

Fig. 2. Chemical structures of selected natural compounds that modulate the PI3K/AKT signaling pathway in preclinical models of obesity research. Color coding: green - activation; red - inhibition.

gluconeogenesis. Further, catalpol was reported to inhibit FOXO1 and GSK3 which aids the activation of AKT phosphorylation (at Ser473) and improves hepatic insulin signaling [117].

Insulin resistance induced by HFD feeding is positively correlated with pro-inflammatory factors. Activation of resident ATMs induces the NLR family pyrin domain containing 3 (NLRP3) inflammasome and the NFκB pathway in obesity that further aggravate the viscous cycle of obesity-related inflammation and disrupted insulin signaling in the adipose tissue, liver and skeletal muscle [124]. Glycyrrhetinic acid is a terpenoid saponin derived from the licorice root known to inhibit the lipid accumulation in adipocytes and to promote GLUT4 expression [118]. In addition, glycyrrhetinic acid prevents the development of IR induced by TNF-α and FFA stimulation in mice through activation of the PI3K/AKT/GSK3 pathway [118]. Similarly, its semi-synthetic derivative carbenoxolone was identified to regulate obesity-related inflammation and IR through the restriction of the NLRP3 inflammasome activity and stimulation of the PI3K/AKT phosphorylation in HFD-fed mice [124]. These two structurally similar compounds are examples of how in certain cases the bioactivity of the phytochemicals could be examined in detail and further intensified through minor chemical modulations. Celastrol is a pentacyclic triterpenoid known to act as a leptin sensitizer and to inhibit obesity-related inflammation that was reviewed in detail by Xu et al. [125]. The Bakar's group reported that celastrol activates the PI3K/AKT signaling in myotubes [58] and improves the mitochondrial function and glucose utilization in skeletal muscles of obese rats through AMPK/SIRT1 activation [126]. These studies suggest that the anti-obesogenic potential of celastrol is mediated at least in the muscle tissue through PI3K/AKT activation. Correspondingly, treatment with ginsenoside Rb2 (one of the most important saponins derived from the *Panax ginseng* roots) in insulin resistant murine adipocytes resulted in improved glucose uptake and activated AKT phosphorylation. The positive anti-obesogenic effect of this terpenoid was confirmed *in vivo* in HFD-fed mice. Ginsenoside Rb2 reduced the body weight and improved the glucose metabolism in adipose tissue and skeletal muscles of the experimental animals through activation in the PI3K/AKT signaling pathway [116].

Betulinic acid is a pentacyclic lupane-type triterpene that is abundantly distributed in medicinal and edible plants and is known for its hepatoprotective and anti-inflammatory properties. Recent investigation of ours has determined betulinic acid as the most potent anti-adipogenic compound in *Ziziphus jujuba* Mill. leaf extract. Betulinic acid hampered the process of adipogenic differentiation in human adipocytes through inhibition of the PI3K/AKT path-way and suppression of the major adipogenic transcription factors C/EBPα and PPARγ [6]. Furthermore, the modulation in the PPAR expression upon betulinic acid treatment was confirmed *in vivo* in glucose-induced lipid accumulation model of *Caenorhabditis elegans* [127].

In summary, the interaction of the terpenoids with the PI3K/AKT cascade members is not unidirectional. It varies from inhibition of the PI3K/AKT signaling that suppresses adipogenic differentiation and lipid biosynthesis by betulinic acid to activation of the PI3K/AKT pathway in an AMPK- and FOXO1-mediated manner in IR models by terpenoids like celastrol, ginsenoside Rb2 and astragaloside IV. Similarly to the flavonoid compounds discussed above, the terpenoids are also worthy of detailed exploration as PI3K modulators to identify the context-specific factors that drive their mode of action.

4.3. Alkaloids

Alkaloid compounds are nitrogen-containing secondary metabolites that are abundantly found in plants and function mainly as defense compounds against herbivores and pathogens. Alkaloids have great therapeutic potential, which is indicated by their significant pharmaceutical use, especially as anesthetics and cardioprotective agents, *e.g.*, morphine, strychnine, ephedrine, and nicotine [128,129].

Capsaicin is a bioactive alkaloid derived from the chili peppers that is commonly used as a dietary supplement to aid weight control. The molecular mechanism behind its anti-obesogenic effect is an object of intense investigation. Apart of being a selective exogenous agonist for the transient receptor potential vanilloid type 1, capsaicin was found to activate AMPK and thus preventing the lipogenic activity of SREBP-1c in hepatocytes. In addition, capsaicin suppresses AKT phosphorylation and that of its downstream effector mTORC1 leading to inhibition in DNL in HepG2 cells [53].

Berberine is a plant-derived secondary metabolite that is known to exert anti-adipogenic and anti-inflammatory effects and to induce browning in WAT [130]. However, the relatively low bioavailability of berberine is hence limiting its implementation in obesity management. Minor structural transformation of berberine such as that of its oxidized derivative oxyberberine significantly improves its pharmacokinetic profile *in vivo*, along with enhancement in the respective biological activity [119]. In a T2D murine model oxyberberine induced prevention of oxidative stress damage in pancreatic β-cells *via* GSK3 inhibition and thus activation of nuclear factor erythroid 2-related factor 2 (NRF2) and the PI3K/AKT signaling pathway that was superior to the effect on β-cells following metformin or berberine treatments [119]. Similarly, oxyberberine was found to activate the PI3K/AKT pathway through GSK3 inhibition in obese NAFLD rats [131]. Another investigation by Tang et al. [60] reported positive regulation in glucose utilization in L6 myotubes following treatment with three norditerpenoid alkaloids nigelladine A, B and C. The elevation in glucose consumption rates induced by the alkaloid compounds was found to be a result from PTP1B inhibition that activates the PI3K/AKT signaling cascade [60].

4.4. Compounds of other chemical classes

Among the selected studies targeting the PI3K/AKT signaling pathway in obesity models several report data involving natural compounds different from the abovementioned classes.

Epigallocatechin gallate (EGCG) is one of the most prominent dietary polyphenols abundantly found in green tea extract that promote pleiotropic health effect [132,133]. For instance, EGCG supplementation reduce WAT mass and induce hypoglycemic action in obesity and T2D models [133,134]. Several studies report that the metabolic effects of EGCG are mediated through the IRS1/PI3K/AKT signaling pathway [62,134,135]. Interestingly, depending on the cellular type and the pathological context EGCG could induce either activation [62,134] or inhibition [135] of PI3K phosphorylation and subsequently of its downstream effectors. Supplementation of the differentiation media with EGCG restrains adipogenic transformation of 3T3-L1 preadipocytes *via* inhibition of the PI3K/AKT signaling that leads to downregulation in PPARγ and FAS [135]. On the contrary, EGCG treatment induce PI3K phosphorylation and subsequently to an increase in GLUT4 translocation in myotubes [62] and FOXO1-mediated decrease in gluconeogenesis in hepatocytes [134]. These multidirectional actions of EGCG on PI3K/AKT signaling expose the demand of careful consideration of the treatment regimen and the individual degree of obesity before initiation of EGCG administration.

Resveratrol and its natural dimethylated analogue pterostilbene have been reported to re-activate PI3K/AKT signaling disturbed during obesity or T2D accompanied with IR [136,137]. Pterostilbene administration in diabetic rats resulted in decreased fasting blood glucose, alleviated inflammatory and oxidative stress markers (TNF-α, interleukin 6 and C reactive protein) and upregulation in the IRS1/PI3K/AKT/GLUT4 pathway in the adipose tissue [136]. Dapagliflozin is an anti-diabetic drug that acts as a selective sodium glucose transporter 2 antagonist that reduces the hyperglycemia through increase in renal glucose elimination. However, as a side effect, dapagliflozin administration leads to increase in renal and liver gluconeogenesis that neutralizes its efficacy. Resveratrol treatment counteracts the dapagliflozin-induced renal gluconeogenesis through increase in PI3K/AKT signaling activity in HFD-fed mice [137].

Honokiol is a bisphenol neolignan, naturally-occurring in the bark, seed cones and leaves of trees belonging to the genus Magnolia. It is reported for its beneficial medicinal properties, among which affecting the cell proliferation and apoptotic rate of cancer cells through modulation of the PI3K/AKT/mTOR signalling pathway [108]. Moreover, in a mouse model of obesity-related alcohol-induced acute pancreatitis chaiqin chengqi decoction (CQCQD) alleviated induced multi-organ dysfunction by decrease of AKT phosphorylation in pancreatic and adipose tissues. The network pharmacology analysis of all quality markers from the CQCQD revealed that six of them, among which is honokiol, possess high-affinity binding to AKT1 [138]. In a recent investigation, honokiol has stimulated adipocyte differentiation in murine adipocytes through SIRT3 activation. Along with upregulation in the adipogenic transcriptional profile, honokiol enhanced insulin signaling and promoted PI3K/AKT pathway [139]. Interestingly, despite the pro-adipogenic action of honokiol, its activation of insulin signaling could be beneficial when insulin sensitivity is impaired.

4.5. Critical assessment

Natural compounds possess the advantage of unique chemical scaffolds that frequently could be derived solely through a biosynthesis. This structural complexity permits the plant secondary metabolites to interact with major cellular signaling pathways *via* more than one mechanism and often synergistically through several protein targets [4,8,115,125].

The evaluated data from preclinical obesity models have revealed several modes of modulation of PI3K/AKT signaling through natural compounds. The insulin-dependent PI3K/AKT signaling pathway and the molecular targets that have mediated the respective effect of the selected natural compounds are outlined below and schematically presented in Fig. 3.

Direct modulation in the regulatory PI3K subunit or at the active phosphorylation sites of AKT are highlighted as the most frequently involved in the natural compound mechanism of anti-obesity action. Interaction between major downstream targets in the PI3K/AKT pathway such as GSK3, FOXO1 and mTORC1 and certain secondary metabolites represents another way of interference with the PI3K/AKT signaling. In addition, as PTP1B is a negative regulator of IRS1 that is critical for the insulin-dependent activation of PI3K, modification in this protein target results in fine-tuning of the PI3K/AKT pathway activity. Another pivotal for the energy balance molecular pathway is the AMPK/SIRT1 and its close communication with the PI3K/AKT pathway justifies its involvement in the molecular mechanism of action of various natural compounds.

5. Future perspectives for translation of natural PI3K/AKT modulators related to obesity into clinics: limitations and strategies

The ultimate accomplishment of a drug discovery project is to reach the development of a safe and effective medicine, which could not be fulfilled without human-based trials. At present the clinical data that concerns the druggability of PI3K as target against obesity are scarce. Although modulation of the PI3K/AKT signaling pathway appears effective in treating metabolic disorders in preclinical models, none have made it into clinical trials investigating their potential to treat obesity/obesity-related disorders so far. Correspondingly, investigations of the anti-obesity potential of natural compounds modulating the PI3K/AKT signaling in human subjects are missing. Possible reasons for this might be that still there are numerous limitations that should be overcome before initiation of such clinical trials. We could summarize them in two main groups: 1) related to the disease and 2) defined by the natural compound of interest.

Consensus whether the activation or inhibition of the PI3K/AKT signaling pathway mostly favors the metabolic health in obesity is not present, hence yet to be addressed. Thus, deeper understanding of the pathophysiological role of the PI3K/AKT signaling pathway in the development of obesity and its comorbidities would aid in identification of the appropriate direction in modulating this pathway as a therapeutic approach. As summarized from the preclinical investigations in the previous section, both activation and inhibition appeared beneficial, so

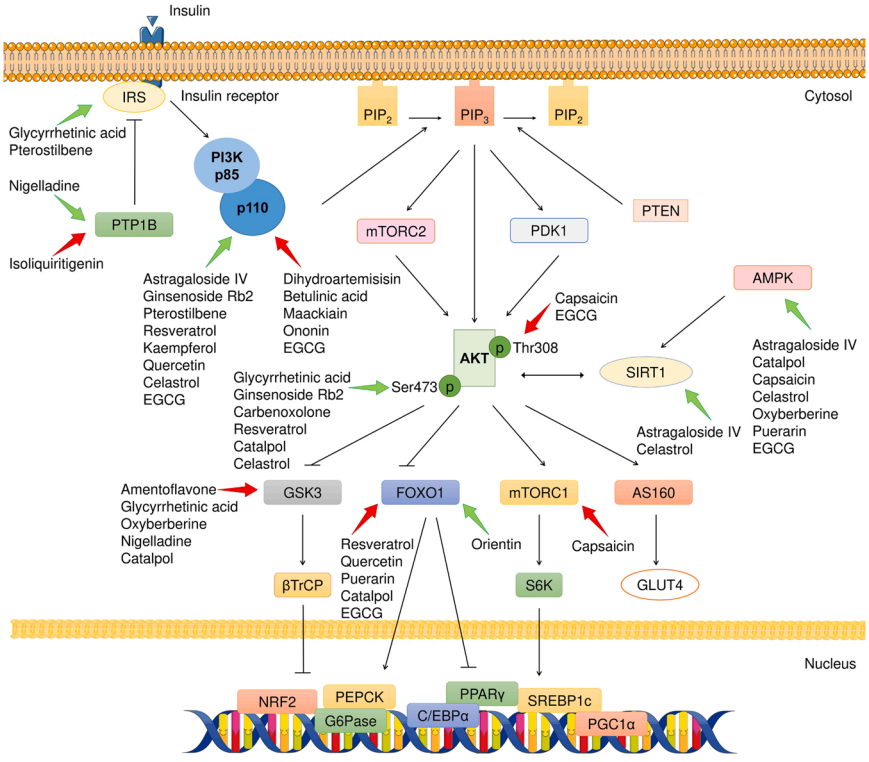

Fig. 3. Modulation of the PI3K/AKT signaling pathway targeting obesity through natural compounds. Evaluation of the molecular mechanisms of the selected natural compounds exposed several critical sites for interference on the PI3K/AKT pathway as follows: (i) direct targeting of PI3K subunits; (ii) direct interference with AKT phosphorylation; (iii) indirect PTP1B-mediated modulation of the PI3K/AKT signaling *via* IRS1; (iv) indirect FOXO1-mediated influence of the PI3K/AKT signaling; (v) indirect GSK3-mediated activation/inhibition; (vi) indirect mTORC1-mediated inhibition; (vi) indirect AMPK/SIRT1-mediated activation of the PI3K/AKT signaling. Color coding: green - activation; red - inhibition.

clear definition of the context where activation is required and *vice versa* is also of a great significance. Furthermore, most of the investigations that employ adipocyte cell lines and apply the treatments during adipogenic differentiation report inhibition of the PI3K/AKT pathway as mechanism that mediate the natural product anti-adipogenic effect [3,5,6112,135]. However, in obesity models that diet modifications are combined with inflammation, IR and/or T2D induction, the secondary metabolites treatments result predominantly in positive regulation of the PI3K/AKT signaling.

Another concern is that PI3K/AKT signaling mediates a wide spectrum of processes in the whole organism (special attention should be paid to oncogenesis), which additionally complicates development of an anti-obesity therapy that specifically targets at its modulation [26,33,36]. Finally, selective interaction with tissue specific isoforms of both PI3K and AKT could probably ensure tissue specific response [140].

Lessons can be learned from other diseases based on PI3K mutations such as cancer and rare syndromes such as the PROS where PI3K inhibitors have already been used [18,20]. The diverse group of overgrowth pathologies classified as PROS are caused by post-zygotic mosaic gain-of-function mutations in the *PIK3CA* gene (encoding PI3K p85), resulting in *PI3KCA* activation, which drives a variety of patient phenotypes, ranging from isolated macrodactyly to progressive and extensive lipomatous overgrowth associated with life-threatening vascular malformations as in congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome (CLOVES) [20,141,142]. Recently, the PI3K inhibitor Alpelisib (BYL719) had been applied to patients with severe PROS, who did not respond to any other treatment [141]. In these patients, Alpelisib treatment led to dramatic improvement of the disease, including reduction of vascular tumor size, reduced hemihypertrophy, attenuated scoliosis, and improved congestive heart failure [141]. Interestingly, some of the obese patients showed a marked reduction in body weight, which was not associated with a reduced food intake. Importantly, the treatment did not show severe side effects. In another case study, Alpelisib was given to a patient with a severe CLOVES syndrome with adipose tissue overgrowth at the lumbar and foot levels as well as multiple lipomas. After six months of therapy, lipomas appeared significantly reduced [142]. These interesting data render Alpelisib a promising targeted approach for patients with overgrowth syndromes caused by an overactivity of PI3K. Additionally, the results that correlate PI3K inhibitors treatment of PROS and body mass index are worth of further exploration with regard to identification of potential biomarkers to be verified in obese patients, which will guide to a more personalized approach in PI3K modulation.

Regarding natural compounds, the promising bioactivity in various *in vivo* and *in vitro* models is sufficient to motivate human studies investigating the activity of natural compounds targeting the PI3K/AKT signaling against obesity and obesity-related complications. However, several considerations should be taken into account prior to the initiation of a clinical study. Primary, there should be a sustainable and cost-effective mass (industrial) production of the secondary metabolite of interest. Another consideration is the relative low bioavailability of some of the natural compounds such as that of the flavonoids [112] or the narrow therapeutic window due to toxicity issues such as in the case of celastrol [125]. Given the relatively low selectivity towards specific molecular targets of many of the natural compounds, the druggability of PI3K as an anti-obesity target should be considered with caution. Therefore, experiments with chemically-modified metabolites in view of improved pharmacological and physicochemical properties could be conducted [119,124,131]. Potential combination between natural compounds and anti-obesity drugs that could lead to synergistic effect should be investigated. Development of appropriate pharmaceutical formulation (nano-carriers, nano/micro-capsules) for administration to overcome poor water solubility, poor bioavailability, stability and toxicity issues is another step in the translational process [115,125]. Further, targeted delivery, reduction of required dose and careful consideration whether the experimental *in vivo* doses are relevant/achievable in human studies is decisive.

Relevant illustration of the translation of natural compounds research from animal to human studies is that of the major steviol glycoside in the leaves of *Stevia rebaudiana* Bertoni stevioside [111,143]. Several human studies have confirmed the antidiabetic activity of the terpenoid compound used as natural sweetener that contains zero calorie, lacks glycemic response induction and has good safety profile [144]. For instance, acute oral administration of stevioside (1 g) reduced postprandial blood glucose, hyperlipidemia, and glucagon levels in overweight type 2 diabetic subjects, compared to the placebo group in a crossover randomized controlled trial [143]. The proposed mechanism of the antidiabetic action of stevioside includes: (i) induction of β-cell regeneration and increase in insulin release possible *via* increased glycolysis; (ii) increased expression of insulin receptor and activation of the IRS/PI3K/AKT pathway leading to GLUT4 translocation to the cytoplasmic membrane in the AT; (iii) decrease in inflammatory markers resulting in increased glucose sensitivity in AT; (iv) inhibition in liver gluconeogenesis through PEPCK downregulation that is also AKT-dependent. The overall effects of stevioside in the various tissues and organs act synergistically to activate insulin signaling and reduce glucagon level *via* modulation in the PI3K/AKT pathway [111,143,144]. Another example of a promising drug candidate for the treatment of obesity is the pentacyclic triterpenoid celastrol identified to act as a leptin sensitizer [145]. The pipeline for ERX-1000 (either celastrol or its derivative) clinical development is targeted to reach registration for weight control as an adjunct to a restricted-calorie diet and increased physical activity in patients with obesity. Preliminary data from this clinical trial (NCT04890873) have reported dose-dependent weight loss in a 4-week treatment period and improved glycemic control, thereby gaining initial proof of efficacy for ERX-1000 in obese patients [146]. Similarly, the promising preclinical bioactivity of the natural polyphenol resveratrol to induce energy expenditure and increase mitochondrial biogenesis has stimulated investigators to initiate clinical trial (NCT00998504) in patients with obesity. Treatment with resveratrol of 150 mg/day for 30 days was associated with decrease in postprandial glucagon secretion [147]. Despite that these clinical studies do not investigate the influence of the bioactive leads directly on the PI3K/AKT pathway in obese human, they provide a solid basis for future clinical developments. Nonetheless, the clinical application of natural compounds as PI3K modulators in the context of obesity still have a long way to go.

6. Conclusions

Natural compounds have shown a high therapeutic potential to various metabolic diseases including obesity and T2D in preclinical and clinical studies. However, their molecular targets and mechanisms of action are yet to be explained in sufficient details. Furthermore, the lack of conclusive statement whether activation or inhibition is beneficial when targeting the PI3K/AKT pathway in obesity is an important issue not only for the natural product research, but also for the mechanistic PI3K research. Despite of the controversy that is present regarding the context- and tissue-specific effects, preclinical obesity research that has investigated the modulation of the PI3K/AKT signaling pathway through bioactive phytochemicals provide reliable evidence to motivate initiation of human studies.

In conclusion, the effect of PI3K/AKT signaling in obesity and metabolic diseases is extensive and significant based on the reviewed preclinical studies, while the exact targets and mechanisms for obesity and diabetes therapy need further detailed clarification. Once the specific target and direction of modulation are verified and the above summarized limitations are overcome, clinical trials for investigating the anti-obesogenic effect of natural compounds could be initiated.

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CRediT authorship contribution statement

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Conflict of interest statement

The authors declare that the work on this review paper was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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